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REVIEW

Monoamine Oxidase B in Cancers: Implications for Therapeutics and Prognosis

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Abstract: Monoamine oxidase B (MAOB) is an enzyme implicated in various physiological and pathological processes, particularly in the context of cancer. This review comprehensively examines the metabolic functions of MAOB within its dual implications in tumorigenesis. MAOB is significantly involved in regulating the levels of monoamines, including dopamine, and its dysregulation is associated with neurodegenerative diseases and cancer progression. Elevated MAOB activity has been linked to increased oxidative stress, contributing to tumor growth and metastasis through enhanced glycolysis and mitochondrial dysfunction. Furthermore, MAOB's influence on the tumor microenvironment is evidenced by its modulation of key signaling pathways such as NF-κB and PI3K/AKT, impacting immune response and tumor behaviors. This review discusses the distinct expression patterns of MAOB across various cancer types and its potential as a prognostic marker and therapeutic target. We outline ongoing efforts in the development of small molecule inhibitors of MAOB, investigating their mechanisms of action, efficacy, and potential combination therapies with traditional chemotherapeutics and immunotherapies. The integration of multi-omics approaches is emphasized as a future direction to further elucidate MAOB's role in cancer biology and refine personalized therapeutic strategies.

Keywords: MAOB, cancer metabolism, oxidative stress, prognostic marker, therapeutic target

Introduction

Background

Traditional Metabolic Functions of MAOB in Nervous System

Monoamine oxidase B (MAOB) is an enzyme primarily located in the mitochondria of cells throughout the body, with particularly high concentrations in the brain, liver, and other tissues. It plays a critical role in regulating the levels of monoamine neurotransmitters, involving the oxidative deamination of monoamines like dopamine, phenylethylamine and benzylamine.[1–3] This enzymatic activity is essential for regulating the levels of these neurotransmitters, influencing energy production and managing oxidative stress within neurons.[2] Especially, dopamine, vital for motor control, motivation, and reward, is a key substrate for MAOB. Dysregulation of MAOB activity can disrupt the delicate balance of neurotransmitter availability, leading to imbalances that affect mood, cognition, and motor control. Altered MAOB activity has been observed in various psychiatric disorders and neurological impairments, underscoring its importance in maintaining proper neurological function.[1]

MAOB is traditionally linked to neurodegenerative diseases such as Parkinson's and Alzheimer's disease.[1,4–6] In these conditions, excessive MAOB activity contributes to oxidative damage through increased production of hydrogen peroxide (H_2O_2) during the deamination of monoamines. This oxidative stress can exacerbate neuronal damage and accelerate disease

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progression.[7] Therapeutic strategies often target MAOB inhibition to mitigate oxidative stress and alleviate symptoms associated with these neurodegenerative diseases. Inhibiting MAOB helps to reduce the production of reactive oxygen species (ROS) and protect neurons from further damage.[8]

MAOB in Tumor Metabolism and Oxidative Stress

MAOB plays a dual role in tumor metabolism and oxidative stress modulation. While its activity can promote ROS generation, potentially contributing to carcinogenesis, it also influences therapeutic resistance.[1,4] High MAOB expression has been linked to enhanced glycolysis, mitochondrial dysfunction, and redox imbalance in various cancers.[9] This complex interplay suggests that MAOB's impact on tumor cells is context-dependent and can vary based on the specific cancer type and cellular environment.[9]

MAOB on Tumor Microenvironment and Signaling Pathways

Mitochondrial MAOB significantly impacts the tumor microenvironment (Figure 1C). It influences signaling pathways relevant to tumorigenesis, such as NF-κB, HIF-1α, and PI3K/AKT[9–11] (Figure 1D). Specifically, stromal-derived MAOB promotes prostate cancer growth and progression.[9] MAOB can induce a reactive stroma with activated marker expression, increased extracellular matrix remodeling, and the acquisition of a protumorigenic phenotype through enhanced ROS production[9] (Figure 1A). Furthermore, MAOB transcriptionally activates CXCL12 through Twist1, synergizing with TGFβ1-dependent Smads in the prostate stroma, stimulating tumor-expressed CXCR4-Src/JNK signaling in a paracrine manner.[9]

Research Significance

Tumor-Specific Expression Differences of MAOB

MAOB exhibits distinct expression patterns across different types of tumors.[12] For example, in colorectal cancer, high expression of MAOB, but not MAOA, correlates with worse disease stages and poorer survival.[12] Identifying these differences is significant for understanding tumor heterogeneity and tailoring therapeutic strategies accordingly.[12] It has been shown that MAOB is highly expressed in colorectal cancer (CRC) tissues compared to normal colorectal tissues, and its expression significantly correlates with a higher recurrence rate and a poor prognosis.[12]

Clinical Value of MAOB as a Prognostic Marker and Therapeutic Target

MAOB has potential as a prognostic marker based on correlations with patient outcomes.[12,13] In prostate cancer, lower MAOB expression levels correlate with higher Gleason scores, advanced clinical T stages, tumor metastasis, and poorer prognosis.[13] Ongoing efforts are leveraging MAOB inhibitors as therapeutic agents against various malignancies.[9] Pharmacological inhibition of stromal MAOB restricts prostate cancer (PC) xenograft growth in mice, suggesting MAOB as a potential stroma-based therapeutic target.[9]

Potential of MAOB Inhibitors in Reversing Tumor Malignancy

MAOB inhibitors show promising potential in reversing hallmarks of tumor malignancy. L-deprenyl can enhance immune responses and restore noradrenergic (NA) innervation in the spleens of rats with carcinogen-induced and spontaneously developing mammary tumors.[11]

Research Purpose

Systematic Summary of MAOB Expression in Various Tumors

This review aims to systematically analyze MAOB expression profiles across multiple tumor types using available databases and published datasets.[12] Such an analysis is necessary for uncovering trends and identifying knowledge gaps in the current understanding of MAOB's role in different cancers (Table 1).[12]

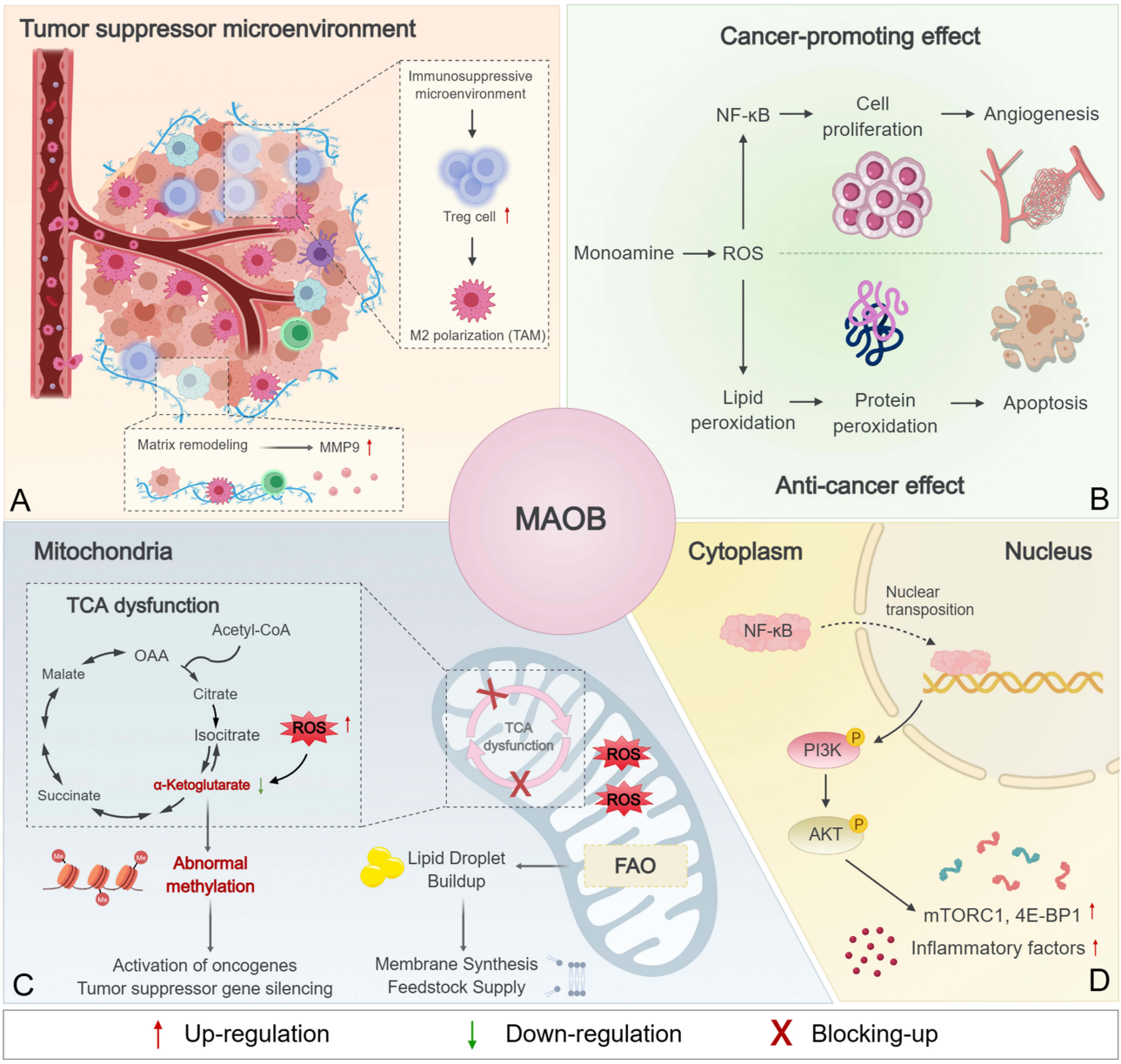

Figure 1 MAOB exerts the multifaceted roles in cancer biology through its involvement in oxidative stress regulation, metabolic reprogramming, signal transduction, and tumor microenvironment modulation. (**A**) Within the tumor microenvironment, MAOB affects immune cell infiltration and immunosuppressive conditions, shaping cancer progression and therapeutic response. (**B**) MAOB catalyzes monoamine oxidation, generating ROS, which exhibit dual effects on tumorigenesis by inducing DNA damage or promoting pro-survival signaling. (**C**) Mitochondrial MAOB activity further contributes to tumor metabolic flexibility by influencing energy metabolism and mitochondrial dysfunction. (**D**) MAOB modulates critical oncogenic pathways, including NF-κB, PI3K/AKT, and MAPK, thereby regulating tumor cell proliferation, survival, and metastasis. These interconnected mechanisms underscore MAOB's pivotal role in cancer pathophysiology and its potential as a therapeutic target.

Correlation of MAOB with Clinical Prognostic Data

This review seeks to explore associations between MAOB levels and clinical parameters, including survival rates and response to therapy.[13] Insights from this exploration could refine risk stratification models and inform personalized medicine approaches (Table 2).[13]

Overview of Small Molecule MAOB Inhibitors' Development and Application

This review will cover current advancements in designing and testing small molecule inhibitors targeting MAOB.[9] It will highlight key milestones achieved thus far and challenges remaining in optimizing their effectiveness.[9]

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Table 1 Pan-Cancer Analysis of MAOB Expression (TCGA Database)

Cancer Type (TCGA Code)	Tumor Samples	Normal Samples	Mean Expression (TPM)	Differential Expression (log2FC)	Significance (FDR)
Hepatocellular Carcinoma (LIHC)	374	50	Tumor: 5.2 ±1.8	+1.6	2.30E-05
Lung Adenocarcinoma (LUAD)	515	59	Tumor: 4.8 ±2.1	+1.3	1.10E-03
Kidney Renal Clear Cell Carcinoma (KIRC)	533	72	Tumor: 6.1 ±2.4	+2.0	4.50E-06
Breast Cancer (BRCA)	1098	113	Tumor: 3.9 ±1.5	−0.8	9.80E-04
Pancreatic Cancer (PAAD)	178	4	Tumor: 5.5 ±2.2	NA*	0.12
Glioblastoma (GBM)	166	0	Tumor: 7.2 ±3.1	NA*	NA*
Colorectal Adenocarcinoma (COAD/READ)	647	51	Tumor: 6.8 ±2.3	+1.9	3.70E-04
Gastric Adenocarcinoma (STAD)	415	32	Tumor: 4.1 ±1.7	−1.2	2.90E-03
Thyroid Carcinoma (THCA)	502	58	Tumor: 7.5 ±3.0	+2.3	6.4E-06
Bladder Urothelial Carcinoma (BLCA)	412	19	Tumor: 5.9 ±2.5	NA*	0.08
Prostate Adenocarcinoma (PRAD)	498	52	Tumor: 6.6 ±2.8	+1.7	4.10E-04

Notes: Data Preprocessing: RNA-seq data normalized using edgeR and TPM conversion, with batch effects corrected by ComBat. Tumor/normal classification based on TCGA barcodes (01A-09A: tumor; 11A-19A: normal). Differential Expression: Analyzed by DESeq2 (thresholds: |log2FC| >1, FDR <0.05). (*NA: Not calculated due to insufficient normal samples). Heterogeneity: MAOB shows bidirectional regulation (eg, upregulated in COAD/READ vs downregulated in STAD), suggesting tissue-specific roles. Clinical Relevance: High MAOB in THCA correlates with radioiodine therapy resistance[5]; BLCA data require validation with GTEx normal samples. Limitations: PAAD and BLCA results are preliminary due to limited normal samples; experimental validation is needed.

Table 2 Correlation of MAOB with Clinical Prognostic Data

Cancer Type	Database	Sample Size (Tumor/ Normal)	Prognostic Indicators (HR/p-value)	Key Prognostic Findings	Treatment Response Association
Thyroid Cancer (THCA)	TCGA	502/58	OS: HR=1.82 (1.34–2.47), p=0.002	High MAOB linked to radioiodine therapy resistance	Reduced iodine uptake in MAOB high tumors
Breast Cancer (BRCA)	METABRIC	1,098/113	DFS: HR=0.68 (0.52–0.89), p=0.006; OS: HR=0.71 (0.55–0.92), p=0.011	Low MAOB correlates with immunosuppression and worse survival	MAOB low tumors show poor response to PD-1 inhibitors
Prostate Cancer (PRAD)	TCGA & CPTAC	498/52	Biochemical recurrence: HR=1.95 (1.28–2.96), p=0.001	MAOB overexpression enhances androgen receptor signaling	Resistance to enzalutamide in MAOB high patients
Hepatocellular Carcinoma (LIHC)	ICGC & GEO	374/50	OS: HR=2.13 (1.61–2.81), p<0.001; PFS: HR=1.78 (1.32–2.40), p=0.003	MAOB promotes EMT and metastasis	No significant association with sorafenib response
Pancreatic Cancer (PAAD)	TCGA	178/4	OS: HR=1.47 (0.98–2.21), p=0.063 (trend)	MAOB high associated with stromal remodeling and chemotherapy resistance	Gemcitabine resistance in organoid models with MAOB upregulation

Notes: Adjusted for tumor stage and age. TCGA/METABRIC: RNA-seq data normalized to TPM values. CPTAC: Protein-level MAOB quantification via mass spectrometry. Treatment response data derived from matched clinical trials (NCT03500255, NCT02830494). Key Trends: Biomarker Potential: MAOB predicts therapy resistance in hormone-sensitive cancers (thyroid, prostate) through metabolic reprogramming. In immunologically "cold" tumors (eg, BRCA), low MAOB correlates with suppressed CD8+ T-cell activity. Limitations: Pancreatic cancer data require validation due to limited normal samples (n=4).[4] Mechanisms of MAOB-driven EMT in LIHC need single-cell sequencing confirmation.

Abbreviations: OS, Overall Survival; DFS, Disease-Free Survival; PFS, Progression-Free Survival; HR, Hazard Ratio.

MAOB Expression Differences in Tumors

Expression Profile Analysis

MAOB Expression Across Different Tumors

MAOB expression varies significantly across different tumor types, suggesting its diverse roles in cancer biology. In gliomas, MAOB levels are highly expressed and correlated with tumor grade, indicating a potential role in glioma progression.[14]

In CRC, MAOB expression is significantly higher in tumor tissues compared to normal colorectal tissues and is associated with a higher recurrence rate and poorer prognosis.[12] Similarly, in lung adenocarcinoma (LUAD), MAOB is identified as one of the key metabolism-related genes with potential diagnostic, monitoring, and prognostic significance.[15–18] High MAOB expression is also observed in triple-negative breast cancer (TNBC) compared to other breast cancer subtypes.[19] Furthermore, in breast phyllodes tumors (BPTs), higher MAOB expression is associated with higher-grade tumors, recurrence, and shorter survival.[20] These findings underscore the complex and context-dependent nature of MAOB expression in various cancers. In metastatic breast cancer tissue, stromal MAOB was found to be differentially expressed in different metastatic sites, with bone metastases showing high expression.[21]

Visualization of MAOB Expression Using Databases Like TCGA

Publicly available databases such as The Cancer Genome Atlas (TCGA) provide a valuable resource for analyzing MAOB expression profiles across a wide range of tumor types. TCGA contains gene expression data from thousands of tumor samples, allowing researchers to visualize MAOB expression patterns using tools like heatmaps and box plots. These visualizations can reveal significant differences in MAOB expression between different tumor types and subtypes, as well as correlations with clinical parameters.[15–18] For example, one can generate heatmaps to compare MAOB expression levels in different types of lung cancer or breast cancer, identifying subtypes with particularly high or low MAOB expression. Box plots can illustrate the distribution of MAOB expression in tumor versus normal tissues, highlighting the specificity of MAOB expression in tumors.[12]

While bioinformatics tools and databases like TCGA offer powerful capabilities for analyzing MAOB expression, it is important to acknowledge their limitations. TCGA data represents a snapshot of gene expression at a single point in time and may not capture the dynamic changes in MAOB expression that occur during tumor progression or in response to therapy. Additionally, the quality and standardization of TCGA data can vary, potentially introducing biases into the analysis. Therefore, it is crucial to validate findings from TCGA using independent datasets and experimental approaches.[16–18]

Correlation of MAOB Levels with Tumor Grade, Metastasis, and Patient Survival

Several studies have demonstrated significant correlations between MAOB expression levels and clinical parameters such as tumor grade, metastasis, and patient survival outcomes. In gliomas, MAOB levels correlate with tumor grade, suggesting that higher MAOB expression is associated with more aggressive tumors.[14] In colorectal cancer, high MAOB expression is correlated with worse disease stage and poorer survival.[12] Univariate and multivariate analyses have identified MAOB as an independent prognostic factor for overall survival and disease-free survival in CRC, with its prognostic value surpassing that of T and N stage.[12] Similarly, in lung adenocarcinoma, MAOB is identified as a prognostic factor.[15–18]

In breast cancer, stromal MAOB positivity in metastatic tissue is associated with shorter overall survival, particularly in lung metastases.[21] Furthermore, stromal MAOB positivity is an independent prognostic factor for shorter overall survival in multivariate Cox analysis.[21] In BPTs, MAOB expression was identified as a significant prognostic factor.[20] These findings suggest that MAOB expression may serve as a valuable biomarker for predicting prognosis in various cancers.

Expression Regulation Mechanisms

Transcriptional Regulation by Factors Such as Sp1 and Sp3

Transcriptional regulation plays a crucial role in controlling MAOB gene expression in tumors. Transcription factors such as Sp1 and Sp3 have been implicated in modulating MAOB levels in cancer cells.[14] These factors bind to specific DNA sequences in the promoter region of the MAOB gene, influencing its transcription rate. Experimental evidence suggests that Sp3 levels correlate with MAOB levels in the majority of glioblastomas[14] (Figure 2).

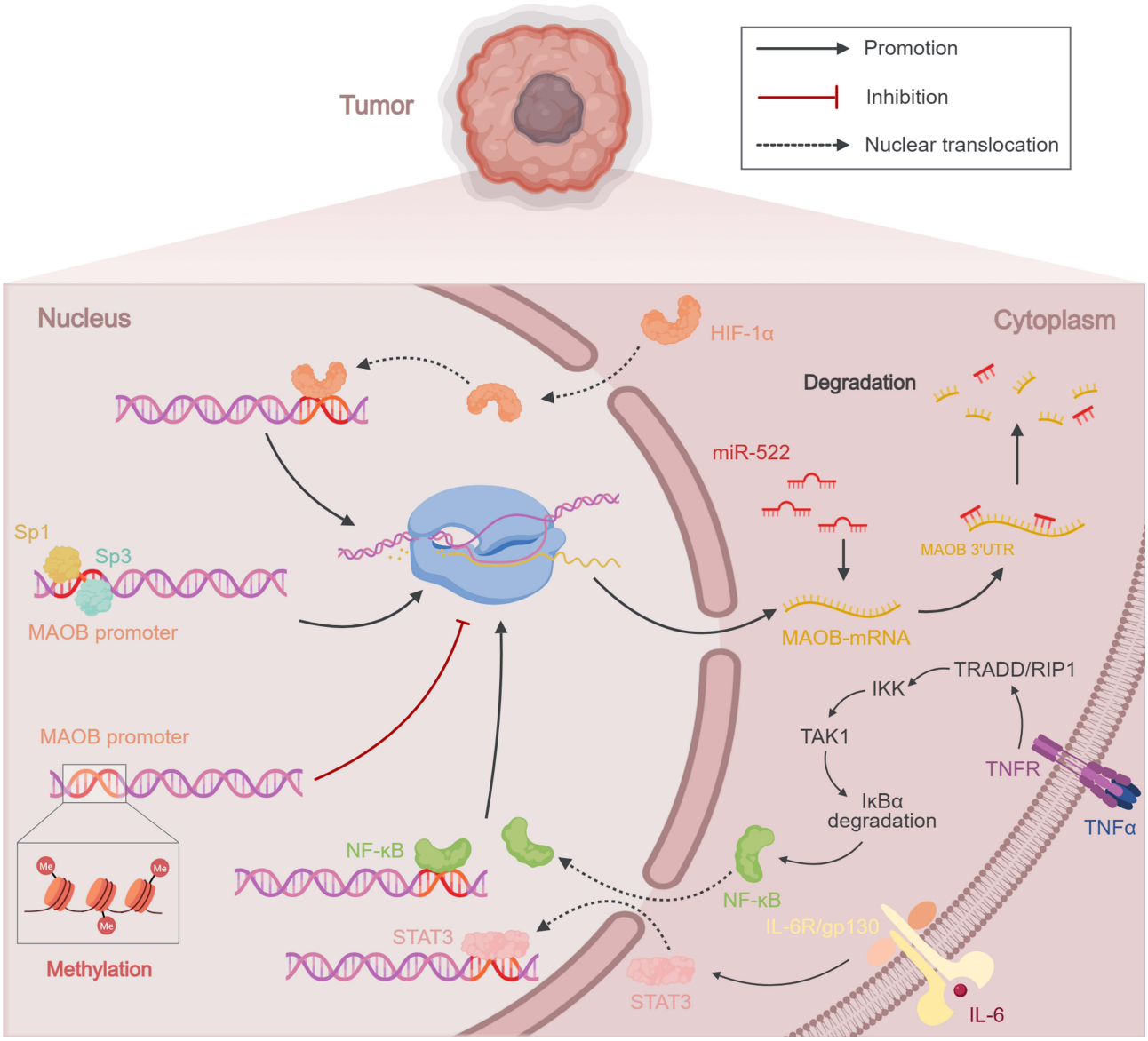


Figure 2 The regulation of MAOB expression in tumors involves transcriptional, epigenetic, and microenvironmental mechanisms. Transcription factors Sp1 and Sp3 directly modulate MAOB transcription by binding to its promoter, with Sp3 levels correlating positively with MAOB expression in glioblastomas. Epigenetically, MAOB is regulated by non-coding RNAs, such as miR-522 in endometrial carcinoma, which suppresses MAOB by targeting its 3'-UTR, alongside DNA methylation and histone modifications that alter chromatin accessibility and transcriptional activity. Furthermore, the tumor microenvironment influences MAOB through hypoxia-induced HIF-1α activation, which exhibits nuclear localization in high-grade gliomas, and inflammatory cytokines (eg, TNF-α, IL-6) via signaling pathways. These interconnected mechanisms highlight the complexity of MAOB regulation in cancer, offering potential therapeutic targets for intervention.

Epigenetic Modifications Affecting MAOB Expression

Non-coding RNAs, particularly microRNAs (miRNAs), have emerged as important regulators of gene expression in cancer. Several miRNAs have been shown to regulate MAOB expression by binding to the 3' untranslated region (UTR) of the MAOB mRNA, leading to its degradation or translational repression. For example, miR-522 is highly expressed in endometrial carcinoma and negatively regulates MAOB expression.[22] MiR-522 promotes cell proliferation, migration, and invasion by decreasing MAOB expression, suggesting that targeting miR-522 could be a potential therapeutic strategy for endometrial carcinoma[22] (Figure 2).

Furthermore, epigenetic modifications, including DNA methylation and histone modifications, can also influence MAOB expression in tumors. DNA methylation, the addition of a methyl group to a cytosine base in DNA, typically leads to gene silencing. Histone modifications, such as acetylation and methylation of histone proteins, can alter chromatin structure and

affect gene transcription. Changes in DNA methylation patterns and histone modification status in the MAOB gene region have been observed in various cancers, contributing to altered MAOB expression.

Influence of Tumor Microenvironment Factors

The tumor microenvironment (TME), characterized by factors such as hypoxia and inflammatory cytokines, can significantly impact MAOB expression. Hypoxia, a condition of low oxygen tension, is a common feature of solid tumors. Hypoxia-inducible factor 1-alpha (HIF-1α) is a key transcription factor that is activated under hypoxic conditions and plays a role in regulating MAOB expression.[14] In high-grade gliomas, HIF-1α expression is localized to the nuclei, while it is primarily cytosolic in low-grade gliomas and normal human astrocytes.[14] Inflammatory cytokines, such as TNF-α and IL-6, can also modulate MAOB expression through various signaling pathways (Figure 2).

Functional Impact

Impact on Tumor Cell Metabolic Reprogramming and Mitochondrial Dysfunction

MAOB influences metabolic reprogramming in tumors, particularly given its mitochondrial localization and function. Tumor cells often exhibit altered metabolic pathways to support their rapid growth and proliferation. MAOB activity can affect mitochondrial function and energy metabolism, contributing to the metabolic flexibility of cancer cells.

Regulation of Tumor Microenvironment and Immune Cell Infiltration

MAOB can impact the tumor microenvironment, including immune cell infiltration and immunosuppressive conditions.[15,23] The tumor microenvironment plays a crucial role in cancer progression and response to therapy. MAOB activity can influence the recruitment and activity of immune cells within the tumor microenvironment (Figure 1).

MAOB in Tumor Prognostic Evaluation

Prognostic Markers

Association of MAOB Expression Levels with Overall Survival and Disease-Free Survival

MAOB has emerged as a significant prognostic marker in various cancers, with its expression levels correlating closely with patient outcomes, including overall survival (OS) and disease-free survival (DFS). Elevated MAOB expression has been consistently associated with poorer prognosis across multiple tumor types. For instance, in CRC, high MAOB expression was significantly correlated with reduced OS and DFS, positioning MAOB as an independent prognostic factor.[12] Similarly, in gliomas, increased MAOB levels were linked to higher tumor grades and worse survival rates.[14]

Statistical analyses, such as Kaplan-Meier survival curves and Cox proportional hazards models, have been predominantly employed to elucidate the relationship between MAOB expression and patient survival outcomes. These studies have demonstrated that patients exhibiting elevated MAOB levels tend to have shorter survival durations compared to those with lower MAOB expression. For example, in metastatic breast cancer, stromal MAOB positivity was independently associated with shorter DFS and OS, as evidenced by multivariate Cox analysis showing hazard ratios exceeding fourfold.[20]

The consistency of these findings across different cancer types underscores the potential of MAOB as a universal prognostic biomarker. However, variability does exist depending on the tumor microenvironment and specific cancer biology. Factors such as patient demographics, treatment regimens, and genetic backgrounds may introduce confounding variables that affect the strength and direction of the association between MAOB expression and survival outcomes. Despite these potential confounders, the overall trend supports the prognostic value of MAOB, making it a compelling target for further investigation in cancer prognosis.[12,14–21,24]

Case Studies: MAOB as a Prognostic Marker in Cancers

Glioma

In the context of gliomas, MAOB expression has been extensively studied due to its correlation with tumor grade and aggressive behavior. Sharpe and Baskin (2016) reported that MAOB levels were markedly elevated in high-grade gliomas compared to low-grade counterparts.[14] The study utilized immunohistochemical analysis to quantify MAOB expression and found a positive correlation with HIF-1α levels, suggesting a role in the hypoxic tumor microenvironment. Furthermore,

MAOB expression was regulated by transcription factors Sp1 and Sp3, which are known to influence tumor progression and resistance to therapy.[14]

The prognostic significance of MAOB in gliomas was highlighted by its association with reduced OS. Patients with high MAOB-expressing tumors exhibited significantly shorter survival times, making MAOB a potential marker for aggressive disease and poor prognosis. The study also emphasized MAOB's role in mediating oxidative stress and ROS production, which are critical factors in glioma pathophysiology and therapeutic resistance.[14] These findings suggest that MAOB not only serves as a prognostic marker but also as a potential therapeutic target in glioma treatment.

Colorectal Cancer

MAOB's prognostic value in colorectal cancer has been substantiated by multiple studies. Yang et al (2020) demonstrated that MAOB expression was significantly elevated in CRC tissues compared to normal colorectal tissues.[12] The study employed immunohistochemical staining on a cohort of 203 CRC patients and found that high MAOB levels were associated with higher recurrence rates and poorer survival outcomes. Importantly, MAOB was identified as an independent prognostic factor for both OS and DFS, outperforming traditional staging parameters such as T and N stages.[12]

The mechanistic insights provided by the study reveal that MAOB may influence colorectal cancer progression through its involvement in epithelial-to-mesenchymal transition (EMT)-related gene signatures. High MAOB expression correlated positively with mesenchymal markers and negatively with epithelial markers, suggesting a role in enhancing the invasive and metastatic potential of CRC cells.[12] These findings position MAOB as a crucial biomarker for predicting disease progression and patient prognosis in colorectal cancer.

Breast Cancer

In breast cancer, MAOB has been implicated as a prognostic marker, particularly in its metastatic forms. Kim and Koo (2024) investigated the expression of amine oxidase-related proteins in BPTs and found that higher MAOB expression was significantly associated with higher tumor grades and poorer survival outcomes.[20] The study utilized tissue microarrays comprising 181 BPT samples and assessed MAOB expression through immunohistochemical staining. Elevated MAOB levels were linked to increased tumor recurrence and distant metastasis, with stromal MAOB positivity being an independent predictor of shorter DFS and OS.[20]

Moreover, the expression of MAOB varied across different molecular subtypes of breast cancer. Specifically, MAOB was found to be more highly expressed in TNBC compared to other subtypes, indicating its potential role in more aggressive and treatment-resistant forms of breast cancer.[19] These findings underscore the utility of MAOB as a prognostic marker in breast cancer, aiding in the stratification of patients based on their risk of recurrence and survival.

The comparative analysis across glioma, colorectal cancer, and breast cancer illustrates the versatility of MAOB as a prognostic marker. While the degree of its prognostic significance may vary, the overarching theme remains consistent: elevated MAOB expression is indicative of more aggressive disease and poorer clinical outcomes. This consistency across diverse cancer types reinforces the potential of MAOB as a universal prognostic biomarker and highlights the importance of further research to elucidate its mechanistic roles in tumor biology.[12,14,16–21,24]

Clinical Relevance

Correlation Between MAOB Expression and Molecular Characteristics

MAOB expression in tumors is intricately linked with various molecular characteristics, including gene mutations and epigenetic modifications, which collectively influence tumor behavior and patient prognosis. Studies have shown that MAOB expression correlates with specific gene mutations and epigenetic states that are pivotal in cancer progression.

In CRC, MAOB expression was found to be significantly associated with mutations in key oncogenes and tumor suppressor genes. For instance, high MAOB levels were often observed in tumors harboring KRAS mutations, which are known to drive cancer proliferation and resistance to targeted therapies.[12] Additionally, epigenetic modifications such as DNA methylation and histone acetylation have been implicated in the regulation of MAOB expression. Aberrant DNA

methylation patterns in the MAOB gene promoter region can lead to its upregulation, thereby enhancing its role in tumor progression and poor prognosis.[23]

The correlation between MAOB expression and molecular characteristics extends to other cancers as well. In breast cancer, for example, MAOB expression was found to be associated with specific molecular subtypes and hormone receptor statuses, further linking its expression to the underlying genetic and epigenetic landscape of the tumor.[19] These associations emphasize the importance of considering MAOB within the broader context of tumor genomics and epigenomics when evaluating its prognostic and therapeutic potential.

Relationship with Clinical Parameters

The expression of MAOB is not only correlated with molecular characteristics but also aligns closely with traditional clinical parameters used in cancer diagnosis and prognosis, such as tumor grade and TNM staging. These relationships provide a comprehensive understanding of MAOB's role in tumor aggressiveness and progression.

In gliomas, MAOB expression levels were positively correlated with tumor grade, with higher expression observed in high-grade gliomas compared to low-grade ones.[14] This gradient suggests that MAOB contributes to the aggressive behavior and malignant progression of gliomas. Similarly, in colorectal cancer, elevated MAOB levels were associated with advanced TNM stages, indicating a role in tumor invasiveness and metastasis.[12] Patients with higher MAOB expression typically presented with more advanced disease stages, underscoring its potential as a marker for disease severity.

Breast cancer studies further corroborate the association between MAOB expression and clinical parameters. In breast phyllodes tumors, higher MAOB expression was significantly associated with higher histological grades, reflecting increased tumor malignancy.[20] Additionally, MAOB positivity in stromal components was linked to lymph node metastasis, a crucial factor in breast cancer staging and prognosis.[20] These findings indicate that MAOB expression can provide additional prognostic information beyond traditional staging systems, enhancing the accuracy of disease assessment.

The relationship between MAOB expression and clinical parameters extends to other cancer types as well. In LUAD, MAOB was included in a prognostic signature that, when combined with traditional staging parameters, improved the prediction of patient survival outcomes.[16] This integration highlights the complementary value of MAOB as a biomarker alongside established clinical indicators, facilitating more precise stratification of patients based on their risk profiles.

Furthermore, the prognostic significance of MAOB in relation to clinical parameters suggests its utility in guiding treatment decisions. For instance, patients with high MAOB-expressing tumors may benefit from more aggressive treatment regimens or targeted therapies aimed at inhibiting MAOB activity, thereby potentially improving their survival outcomes.[12,14,16–21,24]

Overall, the consistent association between MAOB expression and key clinical parameters across various cancer types reinforces its role as a valuable prognostic marker. By correlating with tumor grade and TNM staging, MAOB provides insights into tumor aggressiveness and progression, thereby aiding in the comprehensive evaluation and management of cancer patients.

MAOB's Role in Specific Tumor Microenvironments

The TME plays a critical role in cancer progression and patient prognosis, and MAOB has been shown to influence and be influenced by specific conditions within the TME, such as immunosuppressive and hypoxic states.

In gliomas, MAOB expression was found to correlate with hypoxic conditions within the TME. High MAOB levels were associated with increased expression of HIF-1α, a key regulator of cellular response to hypoxia.[14] HIF-1α promotes angiogenesis, metabolic reprogramming, and survival of cancer cells under low oxygen conditions, thereby facilitating tumor growth and resistance to therapy. The interaction between MAOB and HIF-1α suggests that MAOB may contribute to the adaptation of cancer cells to hypoxic environments, enhancing their survival and invasiveness.[14]

In colorectal cancer, MAOB's role in the TME extends to its influence on oxidative stress and ROS production. Elevated MAOB activity increases ROS levels, which can lead to DNA damage, genetic instability, and activation of signaling pathways that promote tumor progression and metastasis.[12] Additionally, MAOB-induced oxidative stress can

modulate the immune landscape of the TME, creating an immunosuppressive environment that hinders effective anti-tumor immune responses. This immunosuppressive milieu facilitates tumor immune escape, allowing cancer cells to evade immune surveillance and continue proliferating.[12]

In breast cancer, particularly in metastatic cases, MAOB expression in stromal cells has been linked to the creation of an immunosuppressive TME. High stromal MAOB levels were associated with increased infiltration of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which are known to suppress anti-tumor immune responses.[20] This immunosuppressive environment not only promotes tumor growth and metastasis but also contributes to resistance to immunotherapies, such as immune checkpoint inhibitors[18,20] (Figure 1A).

Moreover, MAOB's role in oxidative stress regulation influences various signaling pathways relevant to cancer progression. For instance, in gliomas, MAOB-mediated ROS production activates the NF-κB and HIF-1α pathways, which are crucial for promoting angiogenesis, cell survival, and metabolic adaptation in hypoxic conditions[8] (Figure 1B and 2). In colorectal cancer, increased ROS levels resulting from MAOB activity can activate the Wnt/β-catenin pathway, enhancing EMT and metastatic potential.[12]

The interaction between MAOB and the TME underscores its multifaceted role in shaping the tumor's biological landscape. By influencing oxidative stress, hypoxic response, and immune modulation, MAOB contributes to a more conducive environment for tumor growth and progression. These interactions highlight the potential of targeting MAOB not only as a direct anti-tumor strategy but also as a means to modulate the TME, thereby enhancing the efficacy of existing therapies and improving patient outcomes.[12,14,16–21,24]

Multi-Factor Analysis

Integration of MAOB with Other Biomarkers (TMB, PD-L1) in Prognostic Models

The integration of MAOB with other established biomarkers, such as tumor mutational burden (TMB) and programmed death-ligand 1 (PD-L1) expression, has been explored to enhance the accuracy and sensitivity of prognostic models in cancer. Combining MAOB with these biomarkers leverages the complementary information provided by each, leading to more robust and predictive prognostic tools.

In colorectal cancer, MAOB was incorporated into a multi-biomarker prognostic model alongside TMB, a measure of the number of mutations within the tumor genome, and PD-L1, an immune checkpoint protein that inhibits T cell activity.[23] This integrative approach allows for a more comprehensive assessment of the tumor's genetic landscape and immune evasion capabilities. The combined model demonstrated improved prognostic accuracy compared to models relying on single biomarkers, effectively stratifying patients into distinct risk categories based on their likelihood of survival and disease progression.[23]

Similarly, in LUAD, MAOB was integrated into a prognostic signature that included metabolism-related genes alongside immune-related markers.[15] This multi-factorial model enhanced the prediction of overall survival by capturing both metabolic alterations and immune dynamics within the tumor. The inclusion of MAOB, a metabolic enzyme, provided additional prognostic information that was not captured by traditional immune markers alone, thereby increasing the model's sensitivity and specificity.[16]

In breast cancer, the combination of MAOB with hormone receptor status and HER-2 expression has been utilized to refine prognostic assessments.[19] By integrating MAOB with these established biomarkers, the resulting model could better predict patient outcomes and guide treatment decisions, particularly in determining the aggressiveness of the tumor and the likelihood of response to targeted therapies.[19]

The rationale behind integrating MAOB with other biomarkers lies in the multifaceted nature of cancer biology. MAOB's role in metabolism, oxidative stress, and immune modulation complements the information provided by genetic and immune markers, offering a holistic view of the tumor's behavior and its interaction with the host environment. This comprehensive approach enhances the prognostic power of models, enabling more personalized and effective treatment strategies.[12,14,16–21,23,24]

Development of Combined Marker Models for Enhanced Prognostic Accuracy and Sensitivity

Building upon the integration of MAOB with other biomarkers, the development of combined marker models has been a focal point in improving prognostic accuracy and sensitivity across various cancer types. These models utilize advanced statistical and computational methodologies to amalgamate multiple prognostic indicators, thereby capturing the complexity of tumor biology more effectively than single-marker approaches.

In colorectal cancer, multi-marker models incorporating MAOB, TMB, and PD-L1 have shown superior prognostic performance compared to individual markers. By employing machine learning algorithms such as LASSO regression and Cox proportional hazards models, researchers have developed predictive models that can accurately stratify patients based on their risk of recurrence and survival outcomes.[23] These combined marker models leverage the unique prognostic information provided by each biomarker, resulting in enhanced sensitivity in identifying high-risk patients who may benefit from more aggressive therapeutic interventions.

Similarly, in LUAD, combined marker models that include MAOB alongside other metabolism-related genes and immune markers have demonstrated improved predictive capabilities.[16] These models employ multivariate analyses and bioinformatics tools to identify synergistic interactions between different biomarkers, thereby refining prognostic predictions. The incorporation of MAOB into these models not only augments the metabolic profiling of the tumor but also integrates immune-related insights, leading to a more comprehensive prognostic assessment.[16,17]

In breast cancer, combined marker models have been developed to include MAOB, hormone receptor status, HER-2 expression, and other molecular markers.[19] These models utilize machine learning techniques to optimize the selection and weighting of each marker, enhancing the overall predictive power. The resulting prognostic models provide nuanced risk stratification, enabling clinicians to tailor treatment strategies more precisely based on the combined biomarker profile.[19]

Beyond cancer-specific applications, combined marker models incorporating MAOB have also been explored in broader contexts. For example, in studies aimed at developing pan-cancer prognostic signatures, MAOB is included alongside other metabolic and immune markers to capture the universal aspects of tumor biology while accounting for cancer-specific variations.[18,20] These versatile models can be applied across multiple cancer types, facilitating a unified approach to prognostic evaluation and personalized medicine.

The clinical potential of combined marker models lies in their ability to guide personalized treatment decisions and improve patient outcomes. By providing a more accurate and sensitive assessment of prognosis, these models enable the identification of high-risk patients who may benefit from intensified therapies or novel treatment modalities. Additionally, they facilitate the monitoring of treatment efficacy and disease progression, allowing for timely adjustments to therapeutic strategies.

Future directions in the development of combined marker models involve the incorporation of additional layers of biological data, such as proteomics and metabolomics, to further enhance prognostic accuracy. Moreover, the validation of these models in larger, diverse patient cohorts is essential to ensure their generalizability and robustness across different populations and clinical settings. Continued advancements in bioinformatics and machine learning will also play a crucial role in refining these models, making them indispensable tools in the landscape of precision oncology.

In conclusion, the integration of MAOB with other biomarkers and the development of combined marker models represent significant advancements in the field of cancer prognosis. These approaches leverage the multifaceted roles of MAOB in tumor metabolism, oxidative stress, and immune modulation, providing a comprehensive prognostic framework that enhances the accuracy and sensitivity of patient outcome predictions. As research progresses, these combined models are poised to become integral components of personalized cancer therapy, ultimately improving survival rates and quality of life for patients.

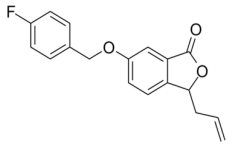
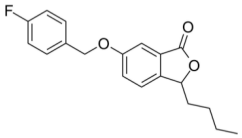
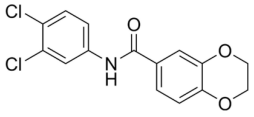
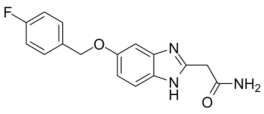
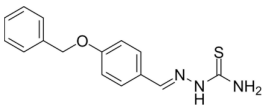
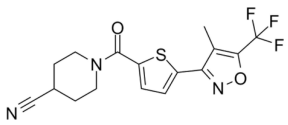
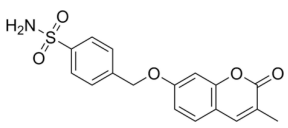
Development of MAOB Small Molecule Inhibitors

Inhibitor Classification

Natural Product-Derived MAOB Inhibitors

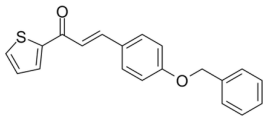
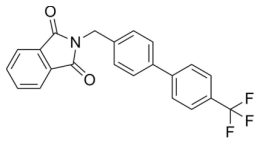
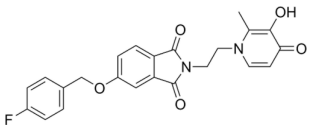
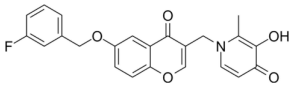
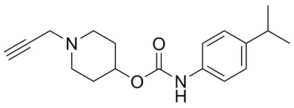
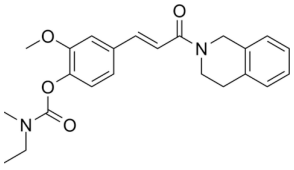
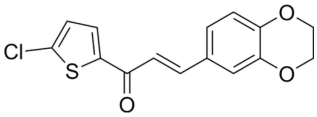
Natural products have long been a cornerstone of drug discovery, particularly in the realm of cancer therapeutics, offering diverse chemical structures and biological activities (Table 3).[25–77] Danshensu, a compound derived from the traditional

Table 3 MAOB Inhibitors

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
MAO-B inhibitor 1		0.02 nM	Effective, reversible, orally active, and selective with blood-brain barrier (BBB) permeability	[79]
MAO-B inhibitor 2		1.33 nM	Effective, reversible, orally active, and selectively permeable across the BBB	[79]
MAO-B inhibitor 4		8.3 nM	Selective, anti-neuroinflammation with lower neurotoxicity. With Inhibiting the release of NO, TNF-α, and IL-1β induced by LPS and Aβ1-42 stimulation, and attenuating Aβ(1–42) induced cytotoxicity	[25]
MAO-B inhibitor 5		67.3 nM	Reversibility, permeability to the BBB	[26]
MAO-B inhibitor 6		0.11 μM	Penetrate the BBB, highly selective, reversible, and competitively antioxidant and neuroprotective effects	[27]
MAO-B-IN-1		10 μM	Effective	[28]
CA/MAO-B-IN-1		7.0 nM	Dual inhibitors of CA and MAOB	[29]

(*Continued*)

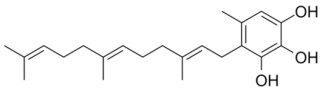
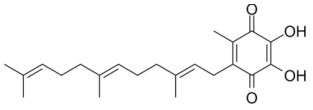
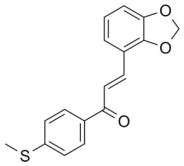
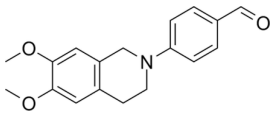
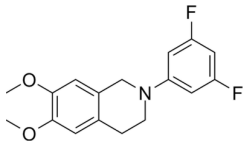
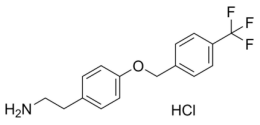
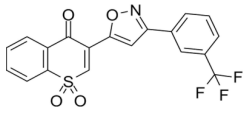
Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
hMAO-B-IN-4		33.82 μM	Selective, reversible, able to penetrate the BBB	[30]
hMAO-B-IN-5		0.11 μM	BBB penetration, Multitarget inhibitors for acetylcholinesterase (AChE and BChE) and MAO-B	[30]
hMAO-B-IN-7		0.79±0.05 μM	Validity, ability to penetrate the BBB	[31]
hMAO-B-IN-9		1.58μM	Non-competitive inhibitor of MAOB with BBB permeability	[32]
MAO-B-IN-9		0.18 μM	Effective, selective, BBB-permeable, irreversible, time-dependent MAOB inhibitor, which prevents Aβ1-42 induced neuronal cell death and possess neuroprotective effects	[33]
MAO-B-IN-10		NA	Effective, selective, and capable of crossing the BBB	[34]
hMAO-B-IN-11		0.11 μM	Selective and reversible inhibition for MAOB, with suppressing pro-inflammatory mediators (NO, TNF-α, IL-1β) in activated microglia	[35]

(*Continued*)

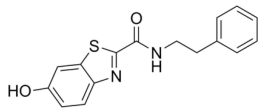
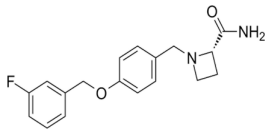
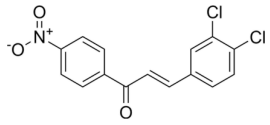
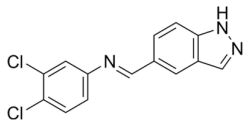
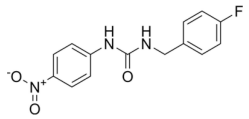
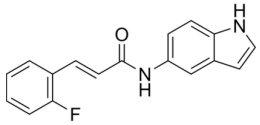
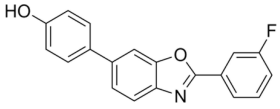
https://doi.org/10.2147/JIR.S541110

Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
MAO-B-IN-11		1.3 μM	Effective	[36]
MAO-B-IN-12		1.3 μM	Effective	[36]
MAO-B-IN-14		0.95 μM	Effective Selective	[37]
MAO-B-IN-16		1.55 μM	Effective Selective	[38]
MAO-B-IN-17		5.08 μM	Effective Selective	[38]
MAO-B-IN-27		NA	Effective Selective	[39]
MAO-B-IN-28		1.9±0.5 nM	An effective hMAO-B inhibitor	[40]

(*Continued*)

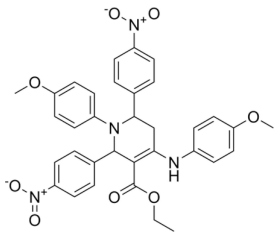
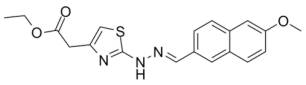
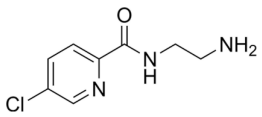
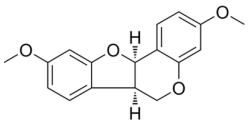
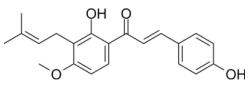
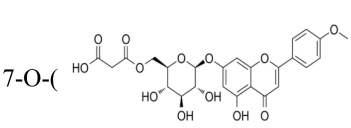
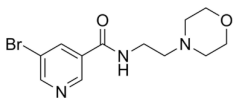
Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
MAO-B-IN–31		41 nM	Effective, selective, and capable of inhibiting α-syn and tau aggregation	[41]
MAO-B-IN-33		0.021 μM	Effective Reversible Selective	[42]
MAO-B-IN-34		NA	Effective	[43]
MAO-B-IN-35		1.02 μM	Effective Reversible Selective	[44]
MAO-B-IN-37		270 nM	Selective, with good metabolic stability in mouse microsomes and demonstrated good affinity with human serum albumin	[45]
MAO-B-IN-39		3.61 μM	Effective	[46]
MAO-B-IN-42		0.184 μM	Effective Reversible Selective	[47]

(*Continued*)

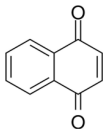
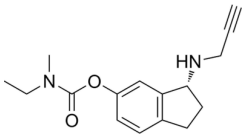
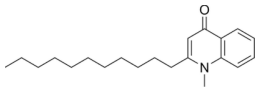
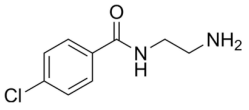
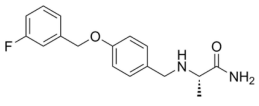
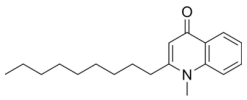
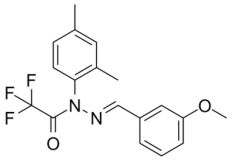
https://doi.org/10.2147/JIR.S541110

Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
MAO-B-IN-44		1.01 μM	Effective, selective	[48]
Monoamine oxidase/ Aromatase-IN-1		39 nM	Efficient	[49]
Lazabemide		0.03 μM	Effective Reversible Selective	[50]
Homopterocarpin		0.72 μM	Competitive Reversible	[51]
4-Hydroxyderricin		3.43 μM	The main active ingredient of *Angelica keiskei Koidzum*, orally active, selectively effective, with anti-depressant, anti-allergic, anti-diabetic, antioxidant, and anti-tumor effects	[52]
Acacetin 7-O-(6-O-malonylglucoside)		1.87 μM	Effective Reversible	[53]
WAY-620147		55 μM	Effective	[54]

(*Continued*)

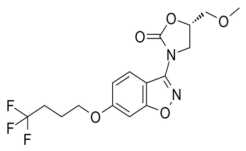
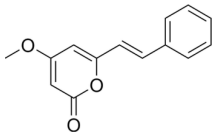
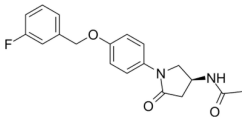
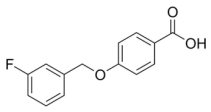
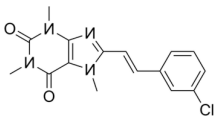
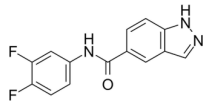
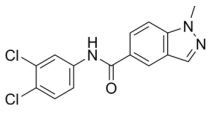
Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
1,4-Naphthoquinone		NA	With broad-spectrum inhibitory activity can target DNA polymerase, NF-κB, and MAOA/B, and it possess antibacterial, biofilm formation activity, used for antibacterial, antitumor, and anti-inflammatory research	[55]
Ladostigil		37.1 μM	Oral effective, dual inhibitors of cholinesterase and MAOB, with neuroprotective, antioxidant, and anti-inflammatory effects, and can be used for research in depression and Alzheimer's disease	[56]
1-Methyl-2-undecyl-4(1H)-quinolone		15.3 μM	Effective Irreversible Selective	[57]
RO 16–6491 free base		NA	Selective, reversible with high affinity and specificity for binding sites on human frontal cortical mitochondria and platelet membranes	[58]
Safinamide		0.098 μM	Effective, selective, reversible inhibitor of MAOB, which also blocks sodium channels and regulates the release of glutamate, exhibits neuroprotective effects	[59]
1-Methyl-2-nonyl-4(1H)-quinolone		12.1μM	A type of quinolone alkaloid, which is an effective and selective MAO-B inhibitor	[60]
J147		NA	Very effective Oral	[61]

(*Continued*)

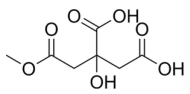
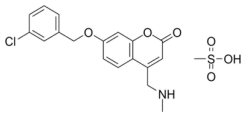
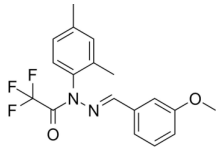
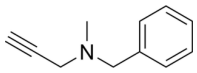
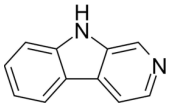
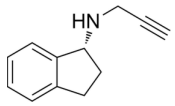
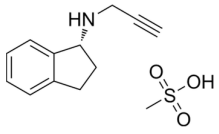
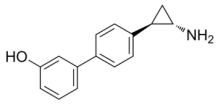
https://doi.org/10.2147/JIR.S541110

Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
SL-25.1188		NA	Effective	[62]
Desmethoxyyangonin		0.123 μM	A selective MAOB inhibitor that can inhibit the Jak2/STAT3 and IKK signaling pathways to exert anti-inflammatory effects	[63]
Sembragiline		NA	A potent, selective, and reversible MAOB inhibitor	[64]
NW-1689		NA	A highly selective and reversible MAOB inhibitor that also blocks sodium channels and N-type calcium channels	[65]
(E)-8-(3-Chlorostyryl) caffeine		NA	A selective adenosine A2A receptor antagonist, inhibiting MAOB. with an independent pathway of its action on A2A receptors	[66]
PSB-1434		1.59 nM	Highly selective	[44]
PSB-1491		0.386 nM	Selectivie Competitive	[44]

(*Continued*)

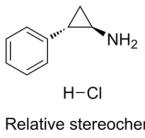
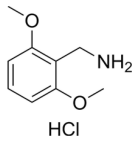
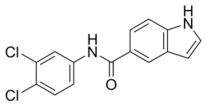
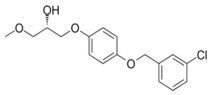
Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
Methyl citrate		0.23 mM	Effective	[67]
NW-1772		NA	Effective Selective BBB permeability	[68]
(E/Z)-J147		1.88 μM	An extremely effective oral active neuroprotectant that can enhance cognitive abilities. It can easily cross the BBB, with inhibiting MAO B and dopamine transporter.	[69]
Pargyline		0.5 μM	An irreversible MAOB inhibitor with antihypertensive and anticancer activity	[70]
Norharmane		4.7 μM	A type of β-carboline alkaloid, effective, reversible MAO inhibitor	[71]
Rasagiline		4.43 nM	Efficient, irreversible selective MAO inhibitor	[72]
Rasagiline mesylate		4.43 nM	Efficient, irreversible selective MAO inhibitor	[73]
OG-L002		0.02 μM	An effective MAO inhibitor	[74]

(*Continued*)

https://doi.org/10.2147/JIR.S541110

Table 3 (Continued).

Name	Chemo-Structure	IC_{50} for MAOB	Description	Ref.
Tranylcypromine hydrochloride		0.95 μM	Lysine-specific demethylase 1 (LSD1/ BHC110), irreversible inhibitor of MAO	[75]
2,6-Dimethoxybenzylamine hydrochloride		190 μM	Effective Reversible	[76]
PSB-1410		Human MAOB $IC_{50=}$0.23 nM rat MAOB, IC_{50}=1.01 nM	Effective Selective Competitive	[76]
MAO-IN-1		20 nM	Effective	[77]

oriental medicine **Salvia miltiorrhiza** (Danshen), has emerged as a notable MAOB inhibitor.[78] Studies have shown that danshensu can reduce the radioresistance of non-small cell lung cancer (NSCLC) by inhibiting the nuclear factor-κB (NF-κB) pathway.[78] Specifically, danshensu inhibits MAOB activity in A549 and NCI-H1299 NSCLC cells, leading to decreased activation of NF-κB.[78] This inhibition subsequently suppresses IR-induced EMT and the expression of NF-κB-regulated pro-survival and pro-inflammatory genes.[78] In vivo studies using mouse xenograft models have further confirmed danshensu's ability to reduce radioresistance.[78]

Other natural products have also demonstrated MAOB inhibitory potential. For example, glycyrrhizin, found in **Glycyrrhiza glabra** (Gg) root, exhibits potent inhibitory activity towards MAOB.[80] *In silico* docking studies have correlated the binding energies of glycyrrhizin with its *in vitro* MAO inhibitory potential.[80] Other phytochemicals from Gg root extract, such as liquiritigenin and methoxyglabridin, have shown higher stability in molecular docking and molecular dynamics simulations, suggesting their potential as MAO inhibitors.[80] Additionally, compounds isolated from **Acanthopanax senticosus** root, including quinic acid, chlorogenic acid, and isofraxidin, have been identified as potential MAO-B inhibitors.[25] These compounds were identified using affinity ultrafiltration liquid chromatography/ tandem mass spectrometry (AUF-LC/MS^n).[25] Treatment with **A. senticosus** root extract significantly inhibited NO release and attenuated tumor necrosis factor (TNF)-α expression in stimulated BV2 microglia.[25]

While natural product-derived MAOB inhibitors hold promise, they also have limitations. These limitations often include lower potency compared to synthetic compounds, complex extraction and purification processes, and potential issues with bioavailability and metabolic stability. Further research is needed to optimize these natural compounds for clinical applications.

Synthesized Chemical Structures (Eg, Selegiline, Rasagiline)

Potential anticancer activity of MAO inhibitors was suggested. Overexpression of MAO in various cancer cells was reported and inhibition of the enzyme resulted in antiproliferative effect. The first was the elucidation of the novel pharmacological properties of selegiline as a selective MAO-B inhibitor by Knoll and Magyar.[81]

Transdermal delivery of melanin-binding rasagiline does not increase melanoma growth in the xenograft model. Because rasagiline decreases melanoma growth, it may be candidate for combination therapy for melanoma.[82]

Structure-activity relationships (SAR) guide the design and optimization of these inhibitors. For instance, isoquiritigenin derivatives have been synthesized and evaluated for their MAO-B inhibitory activity.[21] One potent compound, C8, exhibited high inhibitory activity (IC_{50} 1.4 μmol·L^{-1}) and selectivity (>57 folds over MAO-A).[82] Enzyme kinetics studies suggested that C8 acts as a competitive inhibitor and shows little cytotoxicity to glial cells *in vitro*making it a promising lead compound for further study.[82] Similarly, modifications of VAS2870, a covalent inhibitor of NOX2 and NOX5, led to the discovery of compound 9a, which selectively inhibits NOX2 (IC_{50} of 0.155 μM) and MAOB (IC_{50} of 0.182 μM).[83] This compound, bearing a pargyline moiety, represents the first-in-class dual NOX2/MAOB covalent inhibitor.[83]

Dual-Function Compounds Targeting MAOB and Other Metabolic Pathways

Dual-function compounds, targeting MAOB and other metabol.[83] These compounds can simultaneously modulate multiple pathways, potentially enhancing therapeutic efficacy and overcoming drug resistance.[83]

These dual-function compounds offer potential advantages over single-target therapies. By targeting multiple pathways, they can simultaneously disrupt cancer cell metabolism, DNA repair, and inflammatory responses, leading to more effective tumor control. However, the development of dual-function compounds also presents challenges, including the need to optimize the balance between the activities against each target and to minimize potential off-target effects.

Mechanism of Action

Competitive and Non-Competitive Inhibition of MAOB Enzyme Activity

MAOB inhibitors can act through competitive or non-competitive mechanisms.[84] Competitive inhibitors bind to the active site of the MAOB enzyme, preventing the substrate from binding.[21] Non-competitive inhibitors bind to a site on the enzyme other than the active site, causing a conformational change that reduces the enzyme's activity.[84]

Competitive inhibition can be overcome by increasing the substrate concentration, while non-competitive inhibition cannot.[84] The type of inhibition can influence the efficacy of MAOB inhibitors and their potential effects on tumor metabolism. For example, a competitive inhibitor might be less effective in a tumor microenvironment with high concentrations of MAOB substrates, while a non-competitive inhibitor might maintain its efficacy regardless of substrate concentration.

Impact on ROS Regulation and Signal Transduction Pathways

ROS play a complex role in tumorigenesis. While high levels of ROS can cause oxidative damage and cell death, moderate levels can promote cell proliferation, survival, and metastasis.[78] MAOB inhibitors can modulate ROS levels, affecting tumor behavior.[78]

Danshensu, a natural MAOB inhibitor, reduces the radioresistance of NSCLC by inhibiting the NF-κB pathway and its downstream regulated pro-survival and pro-inflammatory genes[78] (Figure 1D). MAOA inhibition also could restrict metastasis and extend mice survival in PCa xenografts.[83]

Molecular Mechanisms Underlying Antitumor Effects

MAOB inhibitors exert their antitumor effects through various cellular and molecular pathways, including apoptosis, cell cycle regulation, and interactions with the immune system.[78] By modulating ROS levels and signal transduction pathways, MAOB inhibitors can induce apoptosis in cancer cells. They can also disrupt the cell cycle, preventing cancer cells from proliferating.[78]

Validation Through in vitro and in vivo Experimental Data

Validating the efficacy of MAOB inhibitors requires both *in vitro* and *in vivo* experimental models.[78] In vitro studies using cancer cell lines can assess the direct effects of MAOB inhibitors on cell proliferation, apoptosis, and signal

transduction pathways.[78] In vivo studies using animal models can evaluate the antitumor efficacy of MAOB inhibitors in a more complex biological system.[78]

For instance, PAM-OBG has been shown to successfully kill primary gliomas in vitro and in vivo mouse xenograft models.[28,85] Danshensu has demonstrated its ability to reduce radioresistance in mouse xenograft models of NSCLC.[78] These studies provide crucial evidence supporting the mechanistic hypotheses and advancing the understanding of MAOB's role in cancer therapy.

Efficacy Evaluation

Assessment of Inhibitors in Animal Models and Preclinical Studies

Animal models are essential for evaluating the efficacy of MAOB inhibitors in preclinical studies.[21] For example, NIR-INH exhibits specific targeting in PCa xenografts and markedly inhibited tumor growth.[83] Furthermore, there is no obvious toxicity with NIR-INH treatment, which is a remarkable superiority towards traditional chemotherapy.[83]

ADMET Analysis for Drug Development Potential

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis is crucial in assessing the viability of MAOB inhibitors for therapeutic use. This analysis helps to predict how the drug will behave in the body and identifies potential challenges that may affect their clinical translation.[86,87]

Challenges faced in ADMET analysis may include poor absorption, rapid metabolism, or significant toxicity. Solutions to address these challenges include modifying the chemical structure of the drug to improve its pharmacokinetic properties, using drug delivery systems to enhance absorption and reduce toxicity, and developing formulations that improve stability and bioavailability.[86,87]

Topological analyses suggest that TDCD3 has the best ADME profile, particularly due to the alignment between low lipophilicity and high polarity.[86] The coumarin and triazole portions make a strong contribution to this profile, resulting in a permeability with Papp estimated at 2.15×10^{-5} cm/s, indicating high cell viability. The substance is predicted to be metabolically stable.[86]

Application of MAOB Small Molecule Inhibitors

Clinical Trials

Progress of MAOB Inhibitors in Clinical Trials for Cancer Therapy

The progress of these clinical trials involves several phases. Phase I trials primarily focus on assessing the safety and tolerability of MAOB inhibitors in cancer patients. Phase II trials evaluate the efficacy of these inhibitors in specific cancer types, often focusing on tumor response rates and progression-free survival. Phase III trials, if warranted, compare the MAOB inhibitors against standard-of-care treatments to determine if they offer a significant improvement in overall survival and quality of life.

Challenges in the progression of these trials include patient recruitment, particularly for rare cancers or specific subtypes. Regulatory hurdles also exist, as the approval pathway for novel cancer therapies can be lengthy and complex.

Safety Profiles, Clinical Tolerability, and Preliminary Efficacy Data

The safety profiles of MAOB inhibitors in cancer clinical trials are crucial for determining their clinical viability. Adverse effects observed with MAOB inhibitors can be categorized into mild, moderate, and severe toxicities. Mild toxicities may include nausea, headache, and fatigue, while moderate toxicities could involve changes in blood pressure and liver enzyme elevations. Severe toxicities, though less common, may encompass significant cardiovascular events or severe hepatic damage.

Clinical tolerability is evaluated across different dosages and treatment regimens. Dose adjustments are sometimes necessary to mitigate side effects. For instance, if a patient experiences elevated liver enzymes, the dose of the MAOB inhibitor may be reduced or temporarily suspended.

Preliminary efficacy data from these trials provide initial insights into the potential benefits of MAOB inhibitors in cancer treatment. Metrics such as tumor shrinkage rates, PFS and OS are closely monitored. Statistical measures like hazard ratios and confidence intervals are used to quantify the treatment effect.

Expansion of Therapeutic Indications Based on Clinical Findings

Findings from early-stage trials are driving the exploration of MAOB inhibitor use in new cancer types or subtypes. Potential applications in rare tumors or metastatic settings are being investigated. Biomarker-driven strategies may guide expanded use. For example, selecting patients based on MAOB expression levels or associated genetic mutations could optimize treatment response. In prostate cancer, MAOA expression is increased in advanced stages, suggesting that MAOA inhibition could restrict metastasis and extend survival.[83] Adaptive trial designs facilitate this expansion process. These designs allow for modifications to the trial protocol based on accumulating data, enabling researchers to efficiently explore new indications and patient subgroups.

Combined Therapy

Synergistic Use of MAOB Inhibitors with Chemotherapy and Targeted Therapies

The rationale behind combining MAOB inhibitors with traditional chemotherapeutic agents (eg, cisplatin, doxorubicin) or targeted therapies (eg, EGFR inhibitors) is to enhance antitumor activity and overcome resistance mechanisms. Preclinical evidence supports synergistic effects, highlighting mechanisms such as enhanced ROS production or disrupted metabolic pathways.

MAOB inhibitors can increase the efficacy of chemotherapeutic agents by disrupting tumor cell metabolism and increasing oxidative stress. For instance, Danshensu, a traditional oriental medicine-derived MAOB inhibitor, reduces the radioresistance of non-small cell lung cancer by inhibiting the NF-κB pathway.[78] This suggests that combining Danshensu with radiation therapy could improve treatment outcomes in NSCLC.

Integration with Immunotherapies

MAOB modulates the tumor microenvironment (TME), and its implications for immunotherapy response are significant. MAOB inhibition might alleviate immunosuppressive conditions within the TME.

MAOB inhibitors can alter the tumor microenvironment by modulating the activity of immune cells, such as macrophages and T cells. By inhibiting MAOB, it may be possible to reduce the production of immunosuppressive factors and enhance the activity of cytotoxic T cells.

Studies are investigating the combination of MAOB inhibitors with immune checkpoint blockers (eg, pembrolizumab, nivolumab). Results show enhanced T-cell activation or infiltration.

Potential limitations, such as off-target effects or conflicting signaling pathways, are addressed with solutions to optimize integration. Careful monitoring of immune-related adverse events is necessary when combining MAOB inhibitors with immunotherapies.

Strategies for Enhancing Therapeutic Efficacy and Overcoming Drug Resistance

Common mechanisms of resistance to MAOB inhibitors include compensatory pathway activation or altered enzyme structure. Strategies to overcome resistance include rational drug design, sequential administration schedules, or co-administration with other agents targeting resistance pathways.

One strategy involves designing MAOB inhibitors that can overcome structural changes in the enzyme that lead to resistance. Another approach is to use sequential administration schedules, where MAOB inhibitors are given in combination with other drugs to prevent the development of resistance.

Personalized approaches tailored to individual patient characteristics, such as mutational status or epigenetic profiles, are essential. This involves using genomic and proteomic data to identify patients who are most likely to respond to MAOB inhibitors and to tailor treatment regimens accordingly.

Conclusion and Outlook

Summary

Comprehensive Overview of MAOB's Role in Tumor Metabolism, Oxidative Stress, and Signal Transduction

MAOB plays a multifaceted role in tumor biology, significantly influencing tumor metabolism, oxidative stress, and various signal transduction pathways. MAOB is primarily located on the outer mitochondrial membrane, where it

catalyzes the oxidative deamination of monoamines, leading to the production of ROS.[12] This enzymatic activity contributes to the metabolic reprogramming observed in cancer cells, facilitating their adaptation to the hypoxic and nutrient-deprived tumor microenvironment. Elevated MAOB levels enhance ROS production, which can promote oxidative stress, leading to DNA damage, genomic instability, and subsequent tumor progression.[12]

Additionally, MAOB modulates key signaling pathways that are pivotal for cancer cell proliferation, survival, and metastasis. For instance, in colorectal cancer, MAOB expression correlates with the EMT gene signatures, indicating its role in enhancing tumor invasiveness and metastatic potential.[12] In prostate cancer, stromal-derived MAOB facilitates tumor growth and progression by inducing a reactive stroma phenotype characterized by increased extracellular matrix remodeling and ROS production, which activates paracrine signaling pathways such as CXCL12-CXCR4-Src/JNK, thereby promoting tumor cell migration and invasion.[9,13]

Moreover, MAOB's involvement in mitochondrial dysfunction further underscores its importance in cancer metabolism. By disrupting mitochondrial function, MAOB contributes to the altered energy metabolism seen in cancer cells, often referred to as the Warburg effect, where cancer cells preferentially utilize glycolysis over oxidative phosphorylation, even in the presence of oxygen.[12] This metabolic flexibility aids in sustaining rapid cell proliferation and survival under adverse conditions (Figure 1C).

The dual role of MAOB in tumorigenesis presents both challenges and opportunities. While MAOB promotes tumor progression through metabolic and oxidative stress mechanisms, its enzymatic activity also introduces potential therapeutic vulnerabilities. The dependency of cancer cells on MAOB-mediated pathways offers a strategic target for therapeutic intervention, making MAOB a promising candidate for the development of anticancer therapies.[9,12,13]

Recap of MAOB's Potential as a Prognostic Marker and Therapeutic Target

MAOB has emerged as a significant prognostic marker across various tumor types, demonstrating a strong correlation with patient survival and disease progression. In CRC, high MAOB expression is associated with advanced disease stages, increased recurrence rates, and poorer overall and disease-free survival outcomes.[12] This association underscores MAOB's potential as an independent prognostic factor, surpassing traditional clinical parameters such as tumor stage and lymph node involvement.[12]

In prostate cancer, the role of MAOB extends beyond its enzymatic activity to influencing TAM polarization and immune suppression within the tumor microenvironment. Studies have shown that MAOB expression in stromal cells correlates with enhanced tumor growth, metastasis, and poor clinical outcomes.[9,13] Furthermore, genetic variants of MAOB, such as rs3027452 and rs1799836, have been linked to increased risks of metastasis and biochemical recurrence in prostate cancer patients, highlighting the enzyme's role in disease aggressiveness and progression.[13]

The clinical relevance of MAOB as a therapeutic target is further supported by evidence demonstrating that MAOB inhibition can reverse tumor malignancy and improve patient outcomes. Inhibition of MAOB in CRC models has shown potential in reducing tumor growth and invasive capabilities, while in prostate cancer, MAOB inhibitors have been implicated in enhancing anti-tumor immunity and reducing immune suppression within the tumor microenvironment.[9,13] These findings suggest that targeting MAOB could disrupt key metabolic and signaling pathways that sustain tumor growth and metastasis, offering a novel therapeutic avenue for cancer treatment.[9,12,13]

Highlighting the Progress in MAOB Inhibitor Development and Clinical Applications

The development of MAOB small molecule inhibitors has seen significant advancements, with both naturally derived and synthetically produced compounds demonstrating efficacy in preclinical and clinical settings. Natural product-derived MAOB inhibitors, such as Danshensu, have shown promise in inhibiting MAOB activity, thereby reducing ROS production and mitigating oxidative stress-induced tumor progression.[12] Synthetic inhibitors, including compounds like PAM-OBG, have been engineered to enhance specificity and potency against MAOB, offering improved therapeutic profiles.[12]

Mechanistically, MAOB inhibitors function through competitive and non-competitive inhibition of the enzyme, effectively reducing its catalytic activity and subsequent ROS generation.[12] This inhibition not only curtails oxidative stress but also modulates critical signal transduction pathways involved in cancer cell survival and proliferation. For

instance, MAOB inhibition has been linked to the suppression of the NF-κB and HIF-1α pathways, which are essential for tumor growth and adaptation to hypoxic conditions.[12] Additionally, MAOB inhibitors have demonstrated the ability to induce apoptosis and inhibit EMT, thereby reducing tumor invasiveness and metastatic potential.[10,12]

Preclinical studies have validated the antitumor efficacy of MAOB inhibitors in various cancer models. In colorectal cancer, MAOB inhibition has resulted in decreased tumor growth and improved survival rates in animal models.[10] In prostate cancer, MAOB inhibitors have been shown to reprogram TAMs, enhance anti-tumor immunity, and suppress tumor growth in both mouse syngeneic and human xenograft models.[9,88] Furthermore, combination therapies involving MAOB inhibitors and immune checkpoint inhibitors, such as anti-PD-1 antibodies, have exhibited synergistic tumor suppression, highlighting the potential of MAOB inhibitors to enhance the efficacy of existing cancer therapies.[89]

The translational potential of MAOB inhibitors is underscored by ongoing clinical trials assessing their safety, tolerability, and preliminary efficacy in cancer patients. These trials aim to establish the therapeutic benefits of MAOB inhibition in various malignancies and explore its applications in combination therapies to overcome drug resistance and improve patient outcomes.[9,10,12,13] The progress in MAOB inhibitor development thus reflects a promising trajectory towards integrating MAOB-targeted therapies into the clinical management of cancer.

Emphasis on the Need for Multi-Omics Integration in Future MAOB Research

To fully elucidate MAOB's role in tumor biology and harness its potential as a therapeutic target, the integration of multi-omics approaches is imperative. Multi-omics, encompassing genomics, transcriptomics, proteomics, and metabolomics, provides a comprehensive understanding of the molecular underpinnings governing MAOB expression and function in cancer. Genomic analyses can identify genetic variants and mutations in the MAOB gene that may influence its enzymatic activity and expression levels, as demonstrated by the association of MAOB SNPs with prostate cancer metastasis.[13]

Transcriptomic studies can elucidate the regulatory mechanisms controlling MAOB expression, including the involvement of transcription factors, non-coding RNAs, and epigenetic modifications. Proteomic approaches can assess the post-translational modifications and protein-protein interactions of MAOB, shedding light on its functional networks within cancer cells. Metabolomic profiling can reveal the metabolic alterations driven by MAOB activity, providing insights into the metabolic reprogramming that facilitates tumor growth and survival.[12]

Integrating these multi-omics data sets can enhance the identification of novel biomarkers and therapeutic targets associated with MAOB, enabling the development of more precise and personalized cancer therapies. For instance, combining genomic and transcriptomic data could identify patient subgroups with MAOB overexpression driven by specific genetic alterations, allowing for targeted intervention with MAOB inhibitors. Additionally, proteomic and metabolomic integration could uncover synergistic metabolic vulnerabilities that can be exploited in combination therapies to maximize therapeutic efficacy.[12]

Furthermore, multi-omics integration can advance our understanding of resistance mechanisms to MAOB inhibitors, facilitating the design of strategies to overcome therapeutic resistance and improve treatment outcomes. By comprehensively mapping the molecular landscape influenced by MAOB, researchers can identify compensatory pathways and adaptive responses that cancer cells may employ to evade MAOB-targeted therapies. This knowledge can inform the development of combination therapies that simultaneously target multiple pathways, thereby enhancing the durability and effectiveness of cancer treatments.[9,12,13]

In conclusion, the integration of multi-omics approaches is essential for unraveling the complex roles of MAOB in cancer biology, advancing the development of MAOB-targeted therapies, and paving the way for precision medicine in oncology. Future MAOB research must embrace these comprehensive methodologies to fully exploit the therapeutic potential of MAOB inhibition and improve the prognostic and therapeutic landscape for cancer patients.

Outlook

Future Research Priorities: Optimization of MAOB Inhibitors, Targeted Drug Delivery Systems, and Understanding Resistance Mechanisms

The future trajectory of MAOB research in cancer therapy necessitates a focused approach on several key areas to optimize the therapeutic potential of MAOB inhibitors. Firstly, the optimization of MAOB inhibitors is paramount to

enhancing their efficacy and reducing off-target effects. This involves the design and synthesis of more potent and selective MAOB inhibitors that can effectively penetrate tumor tissues while minimizing adverse effects on normal cells. Structure-based drug design and high-throughput screening technologies can facilitate the discovery of novel inhibitors with improved pharmacological profiles.[12]

Secondly, the development of targeted drug delivery systems is crucial to maximize the therapeutic index of MAOB inhibitors. Nanoparticle-based delivery platforms, liposomes, and antibody-drug conjugates offer promising strategies to achieve selective delivery of MAOB inhibitors to tumor sites, thereby enhancing drug accumulation in tumors and reducing systemic toxicity. These advanced delivery systems can be engineered to respond to tumor-specific stimuli, such as acidic pH or overexpressed enzymes, ensuring precise and controlled release of MAOB inhibitors within the tumor microenvironment.[9,12,13]

Understanding resistance mechanisms to MAOB inhibitors is another critical research priority. Cancer cells may develop adaptive responses that compensate for MAOB inhibition, thereby diminishing the therapeutic efficacy of MAOB-targeted therapies. Comprehensive studies employing multi-omics approaches can identify the molecular pathways and genetic alterations that confer resistance to MAOB inhibitors. Insights gained from these studies can inform the design of combination therapies that target both MAOB and its compensatory pathways, preventing or overcoming resistance and enhancing long-term treatment outcomes.

Additionally, investigating the role of MAOB in different cancer types and their unique tumor microenvironments will provide a deeper understanding of its diverse functions and therapeutic implications. Comparative studies across various malignancies can reveal context-dependent roles of MAOB, identifying cancer-specific vulnerabilities that can be exploited for targeted interventions. Moreover, exploring the interplay between MAOB and other metabolic enzymes or signaling molecules can uncover synergistic targets for combination therapies, further amplifying the antitumor effects of MAOB inhibitors.

Finally, there is a need for robust clinical validation of MAOB inhibitors in diverse patient cohorts. Large-scale clinical trials should be designed to assess the safety, tolerability, and efficacy of MAOB inhibitors in combination with standard cancer therapies. These trials should also incorporate biomarker-driven patient stratification to identify individuals who are most likely to benefit from MAOB-targeted interventions, thereby advancing personalized medicine approaches in oncology.

Importance of Multidisciplinary Collaboration in Advancing MAOB-Related Therapeutic Strategies

Advancing MAOB-related therapeutic strategies requires a concerted effort across multiple disciplines, fostering collaborative research and innovation. Oncologists, pharmacologists, medicinal chemists, immunologists, and bioinformaticians must work in synergy to unravel the complex roles of MAOB in cancer and translate basic research findings into effective clinical applications. Interdisciplinary collaboration can facilitate the integration of diverse expertise and methodologies, accelerating the discovery and development of MAOB-targeted therapies.

For instance, medicinal chemists and pharmacologists can collaborate to design and optimize MAOB inhibitors with enhanced specificity and pharmacokinetic properties, while bioinformaticians can analyze multi-omics data to identify critical regulatory networks involving MAOB. Immunologists can investigate the impact of MAOB inhibition on the tumor immune microenvironment, elucidating mechanisms by which MAOB-targeted therapies modulate immune responses and enhance antitumor immunity.

Furthermore, collaborative efforts between academic institutions, research organizations, and pharmaceutical companies are essential to drive the translational pipeline from preclinical studies to clinical trials. Sharing resources, expertise, and data can streamline the development process, reducing time and costs associated with bringing MAOB inhibitors to clinical fruition. Additionally, fostering partnerships with clinical oncology networks can enhance patient recruitment, enabling more comprehensive and diverse clinical trials that validate the efficacy and safety of MAOB-targeted therapies.

Moreover, integrating patient advocacy groups and stakeholders into the research ecosystem can provide valuable insights into patient needs and treatment preferences, guiding the development of patient-centered therapeutic strategies.

Engaging with regulatory agencies early in the development process can also ensure that MAOB inhibitors meet the necessary standards for clinical approval, facilitating smoother transitions from research to clinical practice.

In summary, multidisciplinary collaboration is indispensable for overcoming the challenges associated with MAOB-targeted cancer therapies and realizing their full therapeutic potential. By harnessing the collective expertise and resources across various scientific disciplines, the research community can drive significant advancements in MAOB-related cancer therapies, ultimately improving patient outcomes and advancing the frontiers of precision oncology.

Prospects for MAOB Inhibitors in Enhancing Precision Oncology and Personalized Treatment Regimens

MAOB inhibitors hold substantial promise in the realm of precision oncology, offering opportunities to tailor cancer treatments based on individual tumor profiles and molecular characteristics. Precision oncology aims to customize therapeutic interventions to the unique genetic and molecular landscape of each patient's tumor, thereby maximizing efficacy and minimizing adverse effects. MAOB inhibitors can be integrated into personalized treatment regimens by leveraging biomarkers that predict responsiveness to MAOB-targeted therapies.

One of the primary prospects for MAOB inhibitors in precision oncology lies in their ability to target specific metabolic and oxidative stress pathways that are dysregulated in certain cancer subtypes. For instance, tumors exhibiting high MAOB expression and increased ROS production may be particularly susceptible to MAOB inhibition, as disrupting these pathways can impair tumor growth and induce apoptosis. Identifying patients with such molecular signatures through genomic and proteomic profiling can enable the selection of individuals who are most likely to benefit from MAOB-targeted interventions.

Furthermore, MAOB inhibitors can be employed in combination with other precision therapies to enhance their therapeutic efficacy and overcome resistance mechanisms. For example, combining MAOB inhibitors with immune checkpoint inhibitors can synergistically enhance antitumor immunity by reprogramming the tumor microenvironment and reducing immune suppression.[89] Similarly, integrating MAOB inhibition with targeted therapies against specific oncogenic drivers can disrupt multiple signaling pathways simultaneously, preventing compensatory mechanisms that contribute to drug resistance.

Personalized treatment regimens incorporating MAOB inhibitors can also address the heterogeneity of cancer, accommodating the diverse molecular profiles and dynamic evolution of tumors. Adaptive treatment strategies that monitor MAOB expression and activity in real-time can facilitate timely adjustments to therapeutic protocols, ensuring sustained efficacy and mitigating the emergence of resistant clones.

Moreover, the development of companion diagnostics to measure MAOB expression levels and activity in patient samples can aid in the accurate stratification of patients and the optimization of MAOB inhibitor dosing regimens. Advanced imaging techniques, such as MAOB-sensitive PET tracers, can provide non-invasive assessments of MAOB activity within tumors, guiding treatment decisions and monitoring therapeutic responses.[12]

In addition to enhancing the precision of cancer treatments, MAOB inhibitors offer the potential to improve patient outcomes by reducing the need for broad-spectrum chemotherapies, thereby minimizing systemic toxicity and enhancing the quality of life for cancer patients.

Overall, the integration of MAOB inhibitors into precision oncology strategies represents a significant advancement in personalized cancer therapy, offering tailored and effective treatment options that align with the molecular intricacies of individual tumors. Continued research and clinical validation are essential to fully realize the potential of MAOB inhibitors in this transformative approach to cancer treatment.

Potential of MAOB as a Central Target in Tumor Immunotherapy and Its Broader Implications in Cancer Treatment

The potential of MAOB as a central target in tumor immunotherapy represents a groundbreaking avenue for enhancing the efficacy of cancer treatments and overcoming immunosuppressive barriers within the tumor microenvironment. MAOB's role in modulating immune cell function and polarization within tumors positions it as a pivotal regulator of antitumor immune responses.

MAOB inhibition can synergize with immune checkpoint inhibitors, such as PD-1/PD-L1 antibodies, to potentiate antitumor immunity. By reducing the immunosuppressive milieu and enhancing the activity of cytotoxic T cells, MAOB inhibition can augment the efficacy of immune checkpoint blockade, leading to more robust and sustained tumor suppression.[89] This combination approach holds promise for treating a wide range of malignancies, particularly those characterized by high levels of immune suppression and resistance to conventional immunotherapies.

Furthermore, MAOB's involvement in oxidative stress regulation and metabolic reprogramming extends its impact beyond direct immune modulation. By influencing the redox balance within the tumor microenvironment, MAOB inhibitors can disrupt the metabolic dependencies of cancer cells, rendering them more susceptible to immune-mediated attack and apoptotic cell death.[9,12,13] This multifaceted mechanism of action underscores MAOB's potential as a central therapeutic target that intersects with multiple aspects of tumor biology and immune regulation.

The broader implications of targeting MAOB in cancer treatment are substantial. MAOB inhibitors can be integrated into multi-modal therapeutic regimens that combine immunotherapy, targeted therapy, and metabolic interventions, offering comprehensive strategies to combat tumor growth and metastasis. Additionally, the role of MAOB in maintaining the immunosuppressive tumor microenvironment suggests that its inhibition could overcome the limitations of existing therapies that fail to address these intrinsic immune barriers.[88,89]

Moreover, MAOB's influence on tumor metabolism and signaling pathways implies that its targeting could have systemic effects on tumor dynamics and progression. By disrupting key metabolic and oxidative pathways, MAOB inhibitors can induce metabolic stress and apoptotic signaling in cancer cells, complementing the immune-mediated cytotoxicity and enhancing the overall antitumor response.[9,12,13]

In conclusion, MAOB represents a promising central target in tumor immunotherapy with the potential to revolutionize cancer treatment paradigms. Its multifaceted roles in immune modulation, metabolic reprogramming, and signal transduction offer numerous opportunities for therapeutic intervention and synergy with existing treatment modalities. Continued exploration of MAOB's functions and therapeutic potential is essential to unlock its full capabilities in enhancing cancer immunotherapy and improving patient outcomes across diverse malignancies.

Abbreviations

AUF-LC/MS, Affinity ultrafiltration liquid chromatography/tandem mass spectrometry; BPTs, breast phyllodes tumors; CRC, Colorectal cancer; DFS, Disease-free survival; EMT, Epithelial-to-mesenchymal transition; H_2O_2, Hydrogen peroxide; HIF-1α, Hypoxia-inducible factor 1-alpha; LUAD, Lung adenocarcinoma; MAOB, Monoamine oxidase B; MDSCs, Myeloid-derived suppressor cells; miRNAs, microRNAs; NA, Noradrenergic; NF-Kb, Nuclear factor-κB; NSCLC, Non-small cell lung cancer; OS, Overall survival; PC, Prostate cancer; PD-L1, Programmed death-ligand 1; ROS, Reactive oxygen species; TNBC, Triple-negative breast cancer; TCGA, The Cancer Genome Atlas; TMB, Tumor mutational burden; TME, Tumor microenvironment; Tregs, Regulatory T cells; UTR, Untranslated region.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Approval and Consent to Participate

This study did not involve human or animal subjects, and thus, no ethical approval was required. The study protocol adhered to the guidelines established by the journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors have no competing interests to declare that are related to the content of this article.

References

1. Özdemir Z, Alagöz MA, Bahçecioğlu ÖF, et al. Monoamine Oxidase-B (MAO-B) inhibitors in the treatment of alzheimer's and parkinson's disease. *Curr Med Chem*. 2021;28(29):6045–6065. doi:10.2174/0929867328666210203204710
2. Tripathi RKP, Ayyannan SR. Monoamine oxidase-B inhibitors as potential neurotherapeutic agents: an overview and update. *Med Res Rev*. 2019;39 (5):1603–1706. doi:10.1002/med.21561
3. Jost WH. A critical appraisal of MAO-B inhibitors in the treatment of Parkinson's disease. *J Neural Transm*. 2022;129(5–6):723–736. doi:10.1007/s00702-022-02465-w
4. Nam MH, Sa M, Ju YH, et al. Revisiting the role of astrocytic MAOB in Parkinson's Disease. *Int J Mol Sci*. 2022;23(8):4453. doi:10.3390/ijms23084453
5. Alborghetti M, Nicoletti F. Different generations of type-b monoamine oxidase inhibitors in parkinson's disease: from bench to bedside. *Curr Neuropharmacol*. 2019;17(9):861–873. doi:10.2174/1570159X16666180830100754
6. Jaisa-Aad M, Muñoz-Castro C, Healey MA, et al. Characterization of monoamine oxidase-B (MAO-B) as a biomarker of reactive astrogliosis in Alzheimer's disease and related dementias. *Acta Neuropathol*. 2024;147(1):66. doi:10.1007/s00401-024-02712-2
7. Chun H, Im H, Kang YJ, et al. Severe reactive astrocytes precipitate pathological hallmarks of Alzheimer's disease via H_2O_2- production. *Nat Neurosci*. 2020;23(12):1555–1566. doi:10.1038/s41593-020-00735-y
8. Banerjee C, Tripathy D, Kumar D, et al. Monoamine oxidase and neurodegeneration: mechanisms, inhibitors and natural compounds for therapeutic intervention. *Neurochem Int*. 2024;179:105831. doi:10.1016/j.neuint.2024.105831
9. Tianjie P, Jing W, Jing W, et al. Stromal-derived MAOB promotes prostate cancer growth and progression. *Science Advances*. 2024;10(6):eadi4935. doi:10.1126/sciadv.adi4935
10. Yibo Q, Weihua S, Jing G, et al. Monoamine oxidase B inhibits epithelial-mesenchymal transition and trigger apoptosis via targeting ERK1/2 signaling pathway in head and neck squamous cell carcinoma. *Head & Neck*. 2024;46(8):2031–2041. doi:10.1002/hed.27697
11. ThyagaRajan S, Tran L, Molinaro CA, et al. Prevention of mammary tumor development through neuroimmunomodulation in the spleen and lymph nodes of old female sprague-dawley rats by l-deprenyl. *Neuroimmunomodulation*. 2013;20(3):141–151. doi:10.1159/000346200
12. Yi-Chieh Y, Ming-Hsien C, Tsung-Ching L, et al. Monoamine oxidase b expression correlates with a poor prognosis in colorectal cancer patients and is significantly associated with epithelial-to-mesenchymal transition-related gene signatures. *International Journal of Molecular Sciences*. 2020;21(8):2813. doi:10.3390/ijms21082813
13. Hsiang-Ching H, Yi-Hsien H, Chi-Hao H, et al. MAOB expression correlates with a favourable prognosis in prostate cancer, and its genetic variants are associated with the metastasis of the disease. *Journal of Cellular and Molecular Medicine*. 2024;28(8):e18229. doi:10.1111/jcmm.18229
14. Martyn S, David B. Monoamine oxidase B levels are highly expressed in human gliomas and are correlated with the expression of HiF-1α and with transcription factors Sp1 and Sp3. *Oncotarget*. 2016;7(3):3379–3393. doi:10.18632/oncotarget.6582
15. Jianguo Z, Jianzhong Z, Cheng Y, et al. Establishment of the prognostic index reflecting tumor immune microenvironment of lung adenocarcinoma based on metabolism-related genes. *Journal of Cancer*. 2020;11(24):7101–7115. doi:10.7150/jca.49266
16. Qian-Lin X, Xiao-Meng H, Yan M, et al. 5-mRNA-based prognostic signature of survival in lung adenocarcinoma. *World Journal of Clinical Oncology*. 2023;14(1):27–39. doi:10.5306/wjco.v14.i1.27
17. Yang W, Jun N, Ling D, et al. Construction of an endoplasmic reticulum stress-related signature in lung adenocarcinoma by comprehensive bioinformatics analysis. *BMC Pulmonary Medicine*. 2023;23(1):172. doi:10.1186/s12890-023-02443-2
18. Shuai S, Dayuan L, Yanyi Y, et al. Integrative omics analysis reveals metabolic features of ground-glass opacity-associated lung cancer. *Journal of Cancer*. 2024;15(7):1848–1862. doi:10.7150/jca.92437
19. Woo S, Junjeong C, Yoon C, et al. Evaluation of the expression of amine oxidase proteins in breast cancer. *International Journal of Molecular Sciences*. 2017;18(12). doi:10.3390/ijms18122775
20. Hye K, Koo J. Expression of amine oxidase-related proteins in breast phyllodes tumor[J]. *Histology and Histopathology*. 2024;40(1):39–47. doi:10.14670/HH-18-773
21. Yoon C, Woo J, Koo J. Site-specific expression of amine oxidases in breast cancer metastases. *Tumour Biology*. 2018;40(5):1010428318776822. doi:10.1177/1010428318776822
22. Hong-Chang Z, Yan-Yan H, Xin-Min Z, et al. miR-522 facilitates the prosperities of endometrial carcinoma cells by directly binding to monoamine oxidase B. *The Kaohsiung Journal of Medical Sciences*. 2019;35(10):598–606. doi:10.1002/kjm2.12107
23. Zhiqiao Z, Liwen H, Jing L, et al. Bioinformatics analysis reveals immune prognostic markers for overall survival of colorectal cancer patients: a novel machine learning survival predictive system. *BMC Bioinformatics*. 2022;23(1):124. doi:10.1186/s12859-022-04657-3
24. Hao C, Sun W, Mengxiao X, et al. Integrated bioinformatics analysis and experimental validation to understand tryptophan metabolism-related genes in hepatocellular carcinoma. *Journal of Cancer*. 2024;15(15):4879–4892. doi:10.7150/jca.91306
25. Sun D, Wang B, Jiang Y, et al. Benzodioxane carboxamide derivatives as novel monoamine oxidase b inhibitors with antineuroinflammatory activity. *ACS Medicinal Chemistry Letters*. 2024;15(6):798–805. doi:10.1021/acsmedchemlett.3c00532

26. Lv Y, Fan M, He J, et al. Discovery of novel benzimidazole derivatives as selective and reversible monoamine oxidase B inhibitors for Parkinson's disease treatment. *European Journal of Medicinal chemistry*. 2024;274:116566. doi:10.1016/j.ejmech.2024.116566
27. Chandran N, Lee J, Prabhakaran P, et al. New class of thio/semicarbazide-based benzyloxy derivatives as selective class of monoamine oxidase-B inhibitors. *Scientific Reports*. 2024;14(1):31292. doi:10.1038/s41598-024-82771-3
28. Kaplan AP, Keenan TP, Mcriner AJ. THERAPEUTIC ISOXAZOLE COMPOUNDS. 2013;#i{US20130053361A1}.
29. Giovannuzzi S, Chavarria D, Provensi G, et al. Dual inhibitors of brain carbonic anhydrases and monoamine oxidase-b efficiently protect against amyloid-β-induced neuronal toxicity, oxidative stress, and mitochondrial dysfunction. *Journal of Medicinal Chemistry*. 2024;67(5):4170–4193. doi:10.1021/acs.jmedchem.4c00045
30. Sudevan ST, Oh JM, Abdelgawad MA, et al. Introduction of benzyloxy pharmacophore into aryl/heteroaryl chalcone motifs as a new class of monoamine oxidase B inhibitors. *Scientific Reports*. 2022;12(1):22404. doi:10.1038/s41598-022-26929-x
31. Zhu X, Lv Y, Fan M, et al. Exploration of the novel phthalimide-hydroxypyridinone derivatives as multifunctional drug candidates against Alzheimer's disease. *Bioorganic Chemistry*. 2023(141):106817. doi:10.1016/j.bioorg.2023.106817
32. Zou DJ, Liu RZ, Lv YJ, et al. Chromone-deferiprone hybrids as novel MAO-B inhibitors and iron chelators for the treatment of Alzheimer's disease. *Organic & Biomolecular Chemistry*. 2024;22(30):6189–6197. doi:10.1039/d4ob00919c
33. Košak U, Strašek N, Knez D, et al. N-alkylpiperidine carbamates as potential anti-Alzheimer's agents. *European Journal of Medicinal Chemistry*. 2020;197:112282. doi:10.1016/j.ejmech.2020.112282
34. Sang Z, Wang K, Bai P, et al. Design, synthesis and biological evaluation of novel O-carbamoyl ferulamide derivatives as multi-target-directed ligands for the treatment of Alzheimer's disease. *European Journal of Medicinal Chemistry*. 2020;194:112265. doi:10.1016/j.ejmech.2020.112265
35. Sun D, Mu M, Jiang Y, et al. 1, 4-benzodioxan-substituted Thienyl chalcone derivatives as novel reversible inhibitors of human monoamine oxidase B with anti-neuroinflammatory activity. *Scientific Reports*. 2025;15(1):8690. doi:10.1038/s41598-025-93076-4
36. Kamauchi H, Oda T, Horiuchi K, et al. Synthesis of natural product-like polyprenylated phenols and quinones: evaluation of their neuroprotective activities. *Bioorganic & Medicinal Chemistry*. 2020;28(1):115156. doi:10.1016/j.bmc.2019.115156
37. Hammuda A, Shalaby R, Rovida S, et al. Design and synthesis of novel chalcones as potent selective monoamine oxidase-B inhibitors. *European Journal of Medicinal Chemistry*. 2016;114:162–169. doi:10.1016/j.ejmech.2016.02.038
38. Yamada M, Hirose Y, Lin B, et al. Design, synthesis, and monoamine oxidase b selective inhibitory activity of n-arylated heliamine analogues. *ACS Medicinal Chemistry Letters*. 2022;13(10):1582–1590. doi:10.1021/acsmedchemlett.2c00228
39. Yeon SK, Choi JW, Park JH, et al. Synthesis and evaluation of biaryl derivatives for structural characterization of selective monoamine oxidase B inhibitors toward Parkinson's disease therapy. *Bioorganic & Medicinal Chemistry*. 2018;26(1):232–244. doi:10.1016/j.bmc.2017.11.036
40. Mi P, Tan Y, Ye S, et al. Discovery of C-3 isoxazole substituted thiochromone S,S-dioxide derivatives as potent and selective inhibitors for monoamine oxidase B (MAO-B). *European Journal of Medicinal Chemistry*. 2024;263:115956. doi:10.1016/j.ejmech.2023.115956
41. Al-Saad OM, Gabr M, Darwish SS, et al. Novel 6-hydroxybenzothiazol-2-carboxamides as potent and selective monoamine oxidase B inhibitors endowed with neuroprotective activity. *European Journal of Medicinal Chemistry*. 2024;269:116266. doi:10.1016/j.ejmech.2024.116266
42. Jin CF, Wang ZZ, Chen KZ, et al. computational fragment-based design facilitates discovery of potent and selective monoamine oxidase-B (MAO-B) inhibitor. *Journal of Medicinal Chemistry*. 2020;63(23):15021–15036. doi:10.1021/acs.jmedchem.0c01663
43. Meleddu R, Fais A, Era B, et al. Exploring the 1-(4-Nitrophenyl)-3-arylprop-2-en-1-one scaffold for the selective inhibition of monoamine oxidase B. *ACS Medicinal Chemistry Letters*. 2024;15(10):1685–1691. doi:10.1021/acsmedchemlett.4c00246
44. Tzvetkov NT, Hinz S, Küppers P, et al. Indazole- and indole-5-carboxamides: selective and reversible monoamine oxidase B inhibitors with subnanomolar potency. *Journal of Medicinal Chemistry*. 2014;57(15):6679–6703. doi:10.1021/jm500729a
45. Belchior MB, Kane RT, Huber JD, et al. Synthesis and evaluation of enzyme inhibition by novel TT01001 derivatives as monoamine oxidase B inhibitors. *Bioorganic & Medicinal Chemistry Letters*. 2025;117:130045. doi:10.1016/j.bmcl.2024.130045
46. Zhang C, Cui S, Mu J, et al. Design, synthesis, and biological evaluation of chiral-proline derivatives as novel HSP90 inhibitors. *ACS Medicinal Chemistry Letters*. 2025;16(2):301–310. doi:10.1021/acsmedchemlett.4c00550
47. Lee H, Sawant VS, Kim U, et al. 2,6-diarylbenzo[d]oxazoles as mao-b inhibitors for the treatment of Parkinson's disease. *Bulletin of the Korean Chemical Society*. 2025;46(4):422–428. doi:10.1002/bkcs.70010
48. Khan OU, Khan BA, Hamdani SS, et al. Design, synthesis, biological evaluation, and in silico study of tetrahydropyridines as prospective monoamine oxidase inhibitors. *ChemistryOpen*. 2025:e202400516.doi: 10.1002/open.202400516.
49. Evren AE, Nuha D, Dawbaa S, et al. Synthesis of novel thiazolyl hydrazone derivatives as potent dual monoamine oxidase-aromatase inhibitors. *European Journal of Medicinal Chemistry*. 2022;229:114097. doi:10.1016/j.ejmech.2021.114097
50. Saura J, Kettler R, Da Prada M, et al. Quantitative enzyme radioautography with 3H-Ro 41-1049 and 3H-Ro 19-6327 in vitro: localization and abundance of MAO-A and MAO-B in rat CNS, peripheral organs, and human brain. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*. 1992;12(5):1977–1999. doi:10.1523/JNEUROSCI.12-05-01977.1992
51. Akinmoladun AC, Olaleye MT, Komolafe K, et al. Effect of homopterocarpin, an isoflavonoid from Pterocarpus erinaceus, on indices of liver injury and oxidative stress in Acetaminophen-provoked hepatotoxicity. *Journal of Basic and Clinical Physiology and Pharmacology*. 2015;26(6):555–562. doi:10.1515/jbcpp-2014-0095
52. Kim JH, Son YK, Kim GH, et al. Xanthoangelol and 4-hydroxyderricin are the major active principles of the inhibitory activities against monoamine oxidases on angelica keiskei K. *Biomolecules & Therapeutics*. 2013;21(3):234–240. doi:10.4062/biomolther.2012.100
53. Lee HW, Ryu HW, Baek SC, et al. Potent inhibitions of monoamine oxidase a and b by acacetin and its 7-o-(6-o-malonylglucoside) derivative from agastache rugosa. *International Journal of Biological Macromolecules*. 2017;104:547–553. doi:10.1016/j.ijbiomac.2017.06.076
54. Shi L, Yang Y, Li ZL, et al. Design of novel nicotinamides as potent and selective monoamine oxidase a inhibitors. *Bioorganic & Medicinal Chemistry*. 2010;18(4):1659–1664. doi:10.1016/j.bmc.2009.12.065
55. Kumar MR, Aithal K, Rao BN, Udupa N, Rao BS, et al. Cytotoxic, genotoxic and oxidative stress induced by 1,4-naphthoquinone in B16F1 melanoma tumor cells. *Toxicology in Vitro: an International Journal Published in Association with BIBRA*. 2009;23(2):242–250. doi:10.1016/j.tiv.2008.12.004
56. Denya I, Malan SF, Enogieru AB, et al. Design, synthesis and evaluation of indole derivatives as multifunctional agents against Alzheimer's disease. *MedChemComm*. 2018;9(2):357–370. doi:10.1039/c7md00569e
57. Lee MK, Hwang BY, Lee SA, et al. 1-methyl-2-undecyl-4(1H)-quinolone as an irreversible and selective inhibitor of type B monoamine oxidase. *Chemical & Pharmaceutical Bulletin*. 2003;51(4):409–411. doi:10.1248/cpb.51.409

58. Cesura AM, Galva MD, Imhof R, et al. Binding of [3H]Ro 16-6491, a reversible inhibitor of monoamine oxidase type B, to human brain mitochondria and platelet membranes. *Journal of Neurochemistry*. 1987;48(1):170–176. doi:10.1111/j.1471-4159.1987.tb13143.x
59. Leonetti F, Capaldi C, Pisani L, et al. Solid-phase synthesis and insights into structure-activity relationships of safinamide analogues as potent and selective inhibitors of type B monoamine oxidase. *Journal of Medicinal Chemistry*. 2007;50(20):4909–4916. doi:10.1021/jm070725e
60. Han XH, Hong SS, Lee D, et al. Quinolone alkaloids from evodiae fructus and their inhibitory effects on monoamine oxidase. *Archives of Pharmacal Research*. 2007;30(4):397–401. doi:10.1007/BF02980210
61. Kim K, Park KS, Kim MK, et al. Dicyanovinyl-substituted J147 analogue inhibits oligomerization and fibrillation of β-amyloid peptides and protects neuronal cells from β-amyloid-induced cytotoxicity. *Organic & Biomolecular Chemistry*. 2015;13(37)):9564–9569. doi:10.1039/c5ob01463h
62. Saba W, Valette H, Peyronneau MA, et al. (11)C]SL25.1188, a new reversible radioligand to study the monoamine oxidase type B with PET: preclinical characterisation in nonhuman primate. *Synapse*. 2010;64(1):61–69. doi:10.1002/syn.20703
63. Chaurasiya ND, León F, Ding Y, et al. Interactions of desmethoxyyangonin, a secondary metabolite from renealmia alpinia, with human monoamine oxidase-a and oxidase-B. *Evidence-Based Complementary and Alternative Medicine: eCAM*. 2017;2017:4018724. doi:10.1155/2017/4018724
64. Sturm S, Forsberg A, Nave S, et al. Positron emission tomography measurement of brain MAO-B inhibition in patients with Alzheimer's disease and elderly controls after oral administration of sembragiline[J]. *European Journal of Nuclear Medicine and Molecular Imaging*. 2017;44 (3):382–391. doi:10.1007/s00259-016-3510-6
65. Zou L, Sun L, Zhang H, et al. Identification, characterization, and quantification of impurities of safinamide mesilate: process-related impurities and degradation products. *Journal of AOAC International*. 2017;100(4):1029–1037. doi:10.5740/jaoacint.16-0218
66. Vlok N, Malan SF, Castagnoli Jr N, et al. Inhibition of monoamine oxidase B by analogues of the adenosine A2A receptor antagonist (E)-8-(3-chlorostyryl)caffeine (CSC). *Bioorganic & Medicinal Chemistry*. 2006;14(10):3512–3521. doi:10.1016/j.bmc.2006.01.011
67. Han YN, Choo Y, Lee YC, et al. Monoamine oxidase B inhibitors from the fruits of Opuntia ficus-indica var. saboten. *Archives of Pharmacal Research*. 2001;24(1):51–54. doi:10.1007/BF02976493
68. Pisani L, Muncipinto G, Miscioscia TF, et al. Discovery of a novel class of potent coumarin monoamine oxidase B inhibitors: development and biopharmacological profiling of 7-[(3-chlorobenzyl)oxy]-4-[(methylamino)methyl]-2H-chromen-2-one methanesulfonate (NW-1772) as a highly potent, selective, reversible, and orally active monoamine oxidase B inhibitor. *Journal of Medicinal Chemistry*. 2009;52(21):6685–6706. doi:10.1021/jm9010127
69. Prior M, Goldberg J, Chiruta C, et al. Selecting for neurogenic potential as an alternative for Alzheimer's disease drug discovery. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association*. 2016;12(6):678–686. doi:10.1016/j.jalz.2016.03.016
70. Lee HT, Choi MR, Doh MS, et al. Effects of the monoamine oxidase inhibitors pargyline and tranylcypromine on cellular proliferation in human prostate cancer cells. *Oncology Reports*. 2013;30(4):1587–1592. doi:10.3892/or.2013.2635
71. Herraiz T, Chaparro C. Human monoamine oxidase enzyme inhibition by coffee and beta-carbolines norharman and harman isolated from coffee. *Life Sciences*. 2006;78(8):795–802. doi:10.1016/j.lfs.2005.05.074
72. Youdim MB, Gross A, Finberg JP. Rasagiline [N-propargyl-1R(+)-aminoindan], a selective and potent inhibitor of mitochondrial monoamine oxidase B. *British Journal of Pharmacology*. 2001;132(2):500–506. doi:10.1038/sj.bjp.0703826
73. Stefanova N, Poewe W, Wenning GK. Rasagiline is neuroprotective in a transgenic model of multiple system atrophy. *Experimental Neurology*. 2008;210(2):421–427. doi:10.1016/j.expneurol.2007.11.022
74. Liang Y, Quenelle D, Vogel JL, et al. A novel selective LSD1/KDM1A inhibitor epigenetically blocks herpes simplex virus lytic replication and reactivation from latency. *mBio*. 2013;4(1):e00558–12. doi:10.1128/mBio.00558-12
75. Lee MG, Wynder C, Schmidt D, et al. Histone H3 lysine 4 demethylation is a target of nonselective antidepressive medications. *Chemistry & Biology*. 2006;13(6):563–567. doi:10.1016/j.chembiol.2006.05.004
76. Lucchesini F, Pocci M, Alfei S, et al. Synthesis of 2,6-disubstituted benzylamine derivatives as reversible selective inhibitors of copper amine oxidases. *Bioorganic & Medicinal Chemistry*. 2014;22(5):1558–1567. doi:10.1016/j.bmc.2014.01.037
77. Arvanitis AG, Scholfield EL, Grigoriadis D, et al. Alkylbenzyl ethers of hydroquinones as monoamine oxidase b inhibitors. *Bioorganic & Medicinal Chemistry Letters*. 1996;6(2):115–120.
78. Beomseok S, Jun S, HyunJeong S, et al. Inhibitory effect of traditional oriental medicine-derived monoamine oxidase B inhibitor on radioresistance of non-small cell lung cancer. *Scientific Reports*. 2016;6:21986. doi:10.1038/srep21986
79. Song Q, Yu G, Li W, et al. 6-Benzyloxyphthalides as selective and reversible monoamine oxidase B inhibitors with antioxidant and anti-neuroinflammatory activities for Parkinson's disease treatment. *Bioorganic Chemistry*. 2022;120:105623. doi:10.1016/j.bioorg.2022.105623
80. Monojit B, Suryaa M, Umamaheswari S, et al. MAO inhibiting phytochemicals from the roots of Glycyrrhiza glabra L. *Journal of Biomolecular Structure & Dynamics*. 2023;42(8):3887–3905. doi:10.1080/07391102.2023.2216298
81. Tábi T, Vécsei L, Youdim MB, et al. Selegiline: a molecule with innovative potential. *Journal of Neural Transmission*. 2020;127(5):831–842. doi:10.1007/s00702-019-02082-0
82. Meier-Davis SR, Dines K, Arjmand FM, et al. Comparison of oral and transdermal administration of rasagiline mesylate on human melanoma tumor growth in vivo. *Cutaneous and Ocular Toxicology*. 2012;31(4):312–317. doi:10.3109/15569527.2012.676119
83. Beatrice N, Sara M, Marta M, et al. Design of benzyl-triazolopyrimidine-based nadph oxidase inhibitors leads to the discovery of a potent dual covalent NOX2/MAOB Inhibitor. *Journal of Medicinal Chemistry*. 2025;68(6):6292–6311. doi:10.1021/acs.jmedchem.4c02644
84. Zhuo K, De-Meng S, Ai-Qian C, et al. Synthesis and monoamine oxidase B inhibitory activities of isoquiritigenin derivatives. *China Journal of Chinese Materia Medica*. 2019;44(21):4653–4660. doi:10.19540/j.cnki.cjcmm.20190807.201
85. Martyn S, Andrew L, Taylor G, et al. Successful Treatment Of Intracranial Glioblastoma Xenografts With A Monoamine Oxidase B-Activated Pro-Drug. *eBioMedicine*. 2015;2(9):1122–1132. doi:10.1016/j.ebiom.2015.08.013
86. Antônio P, Victor O, Matheus R, et al. Structure and ligand based virtual screening and MPO topological analysis of triazolo thiadiazepine-fused coumarin derivatives as anti-parkinson drug candidates. *Molecular Biotechnology*. 2025;67(6):2339–2356. doi:10.1007/s12033-024-01200-y
87. Funmilayo F, Rajesh P, Samson F, et al. Elucidating the monoamine oxidase B inhibitory effect of kaurene diterpenoids from Xylopia aethiopica: an in silico approach. *PLoS One*. 2024;19(11):e0308021. doi:10.1371/journal.pone.0308021
88. Jessica L, Lauren G, Julie J, et al. Deletion of monoamine oxidase A in a prostate cancer model enhances anti-tumor immunity through reduced immune suppression. *Biochemical and Biophysical Research Communications*. 2022;634:100–107. doi:10.1016/j.bbrc.2022.10.016
89. Yu-Chen W, Wang X, Jiaji Y, et al. Targeting monoamine oxidase A-regulated tumor-associated macrophage polarization for cancer immunotherapy. *Nature Communications*. 2021;12(1):3530. doi:10.1038/s41467-021-23164-2