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REVIEW

Targeting CREBRF in Cancer: Mechanistic Insights and Future Directions

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Abstract: Luman/CREB3 recruitment factor (LRF), also known as CREBRF, was initially identified as a cellular binding protein of Luman through yeast two-hybrid screening of a human brain cDNA library. CREBRF plays a critical role in various biological processes, with its functions garnering significant attention in the field of oncology. Notably, CREBRF is involved in endoplasmic reticulum (ER) stress and regulates the unfolded protein response (UPR), leading to an accumulation of misfolded proteins. This can ultimately result in cellular dysfunction, apoptosis, and even tumorigenesis. In solid tumors, hypoxia is a common condition, and CREBRF has been implicated in hypoxia-induced autophagy, which promotes tumor cell proliferation. Depending on the tumor type and microenvironment, CREBRF exerts diverse effects by modulating distinct signaling pathways. This review summarizes CREBRF's involvement in ER stress, cell cycle regulation, autophagy, and the mechanisms through which it influences tumor initiation and progression across various cancer types. Furthermore, the potential of CREBRF as a therapeutic target in cancer treatment is discussed, providing insights into future research and clinical applications.

Keywords: CREBRF, ER, hypoxia, tumor, autophagy, therapeutic target

Introduction

Tumorigenesis and cancer progression are intricate processes governed by diverse biological mechanisms. Autophagy and endoplasmic reticulum (ER) stress are interconnected processes that serve dual roles in tumor biology, acting to either suppress or promote tumors depending on the context.[1] Autophagy is a cellular mechanism that degrades and recycles damaged organelles and proteins, maintaining cellular homeostasis.[2] During early tumorigenesis, autophagy acts as a tumor suppressor by removing damaged components and preventing genomic instability.[3] In established tumors, however, autophagy supports tumor survival by supplying nutrients during stress conditions like hypoxia or nutrient deprivation, commonly found in the tumor microenvironment.[4] ER stress occurs when the ER's protein-folding capacity is overwhelmed, triggering activation of the unfolded protein response (UPR). The UPR initially restores homeostasis by enhancing protein folding and degradation pathways.[5] Tumors frequently exploit the UPR to adapt to hostile microenvironments, fostering growth and therapeutic resistance.[5,6] Prolonged or unresolved ER stress can trigger apoptosis or activate additional mechanisms that foster tumorigenesis, such as the regulation of the PI3K/AKT/mTOR signaling pathway.[7] Autophagy and ER stress are interconnected. During ER stress, autophagy is activated as an adaptive mechanism to mitigate misfolded protein accumulation and relieve cellular stress.[8]

CREBRF (Luman/CREB3 Recruiting Factor, LRF) plays a pivotal role in regulating cellular stress responses and autophagy.[9,10] CREBRF mediates ER stress, initiating adaptive cellular changes. Prolonged ER stress may lead to cellular dysfunction, inflammation, apoptosis, and potentially drive tumorigenesis.[11] Under hypoxic conditions, CREBRF promotes autophagy through the CREB3/ATG5 pathway.[12] Aberrant CREBRF expression plays a crucial role in the development and progression of various cancers. This finding has been validated in studies on various tumor types, including gastric cancer,[13] acute myeloid leukemia (AML) and cervical cancer.[14] CREBRF exhibits diverse effects across tumor types, with its role varying depending on tumor type and microenvironment. In gastric cancer,[13] CREBRF

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promotes tumor progression; whereas in AML, it functions as a tumor suppressor.[15] In gliomas, under normal conditions, elevated CREBRF expression activates the AKT pathway, driving tumor cell proliferation.[16] Under hypoxic conditions, elevated CREBRF expression reduces autophagy levels, subsequently suppressing tumor cell proliferation.[12] Therefore, CREBRF's functional roles may be influenced by alterations in the tumor microenvironment. Additionally, a CREBRF mutation is associated with increased obesity and a significant reduction in type 2 diabetes risk, potentially influencing cancer risk.[17,18]

Research on the CREBRF gene is still in its early stages, and its exact role in tumor development and progression remains unclear. Evaluating its potential as a therapeutic target in cancer is essential. Exploring how this target can be effectively utilized for cancer diagnosis and treatment is equally critical. This review explores the biological functions of CREBRF, its role in tumor initiation and progression, and the molecular mechanisms driving its involvement in cancer development. It aims to provide a theoretical foundation for the development of CREBRF-targeted anti-cancer therapies.

Overview of CREBRF

Luman/CREB3 Recruiting Factor (LRF/CREBRF) is a Luman-associated protein activated during ER stress. It was first identified using yeast two-hybrid technology in a human brain cDNA library.[11] The CREBRF gene encodes a 639-amino-acid protein containing a highly acidic region, a bZIP domain, and a leucine zipper-like motif. This protein is highly conserved, sharing over 95% sequence homology with mouse and rat homologs (GenBank Gene IDs 77128 and 303016, respectively), underscoring its evolutionary and functional significance.[11]

cAMP response element-binding protein 3 (CREB3/Luman/CREB3/LZIP) is a central member of the CREB3 family, which includes CREB3L1/OASIS, CREB3L2/BBF2H7, CREB3L3/CREBH, and CREB3L4/AIbZIP.[19,20] These proteins exhibit substantial homology and conservation in their functional domains. CREB3 family members are single-pass transmembrane proteins localized to the ER membrane.[19] Their domains are arranged sequentially from the N-terminus (cytoplasmic side) to the C-terminus (luminal side), including: (1) Transactivation domain (TAD) – mediates sequence-specific DNA binding; (2) ATB domain – a conserved ~30-amino-acid region near the bZIP domain, unique to the CREB3 family; (3) bZIP domain – enables DNA binding and dimerization; and (4) Transmembrane domain (TMD) – anchors the protein to the ER membrane.[19,21]

During cellular stress, including endoplasmic reticulum (ER) stress, CREB3 family proteins move from the ER to the Golgi apparatus, where Site-1 protease (S1P) and Site-2 protease (S2P) sequentially cleave them.[19] This cleavage generates an N-terminal fragment with a bZIP domain that functions as a transcription factor. The N-terminal fragment is transported to the nucleus, where it binds to the cAMP response element (CRE) and activates the transcription of target genes.[19,22–24] CREBRF mainly acts as a negative regulator of CREB3. It does so by recruiting the CREB3 transcription factor to specific nuclear foci, suppressing its activity and promoting its degradation.[11] The biological functions of CREBRF are detailed in Figure 1.

CREBRF-Mediated Endoplasmic Reticulum Stress

Secretory and membrane proteins are synthesized on ribosomes attached to the ER membrane, where they fold and mature in the ER lumen.[25] Genetic mutations or changes in cellular conditions can disrupt this process, causing misfolded or unfolded proteins to accumulate in the ER lumen. The ER's limited capacity to handle proteins leads to their excessive accumulation, causing ER stress.[26] Three stress sensors—inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and protein kinase R-like ER kinase (PERK)-detect unfolded proteins during ER stress. These sensors activate the UPR, a mechanism that alleviates stress and restores ER homeostasis. If ER stress remains unresolved, the UPR may promote apoptosis, preventing prolonged cellular dysfunction.[5,19,27] In cancer cells, ER stress plays a dual role. ER stress helps tumor cells adapt to hypoxia and nutrient deprivation by activating the UPR or autophagy, promoting survival and growth. Conversely, excessive autophagy induces cell death, while prolonged severe ER stress triggers apoptosis in tumor cells.[5,28]

CREB3 family members, as ER stress transducers, share significant homology with ATF6, leading to similar mechanisms of transmembrane cleavage and transcriptional activation.[29] During ER stress, CREB3 moves to the Golgi apparatus from the ER, where it undergoes regulated intramembrane proteolysis (RIP). This activation enables

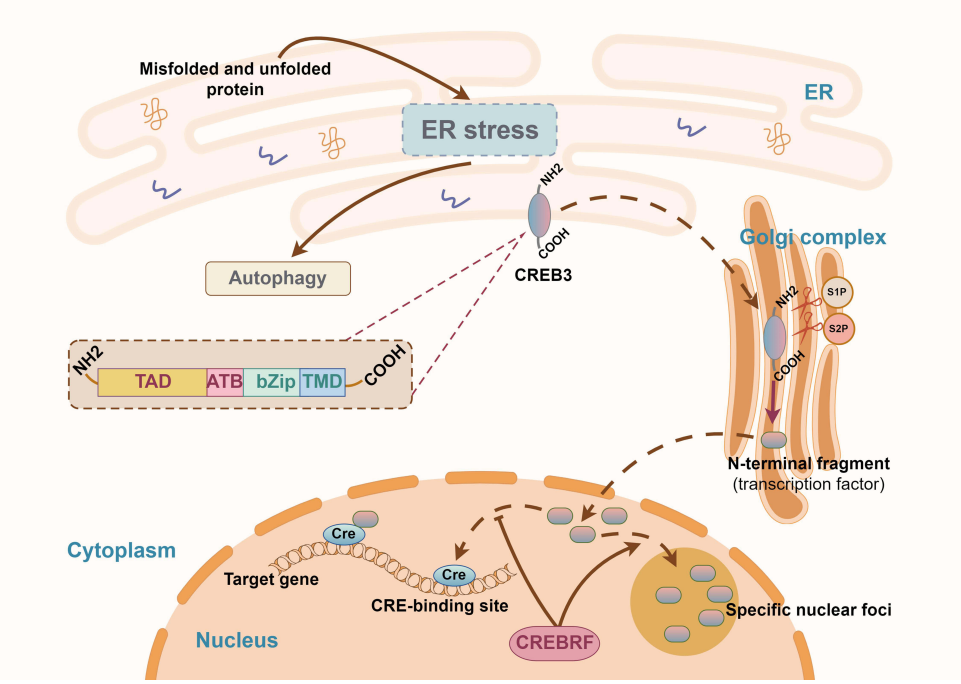

Figure 1 CREBRF as a Modulator of ER Stress Response Under ER stress conditions, CREB3 undergoes proteolytic cleavage and translocates to the nucleus, where it functions as a transcription factor. CREBRF plays a critical regulatory role by inhibiting CREB3 activity, recruiting it to distinct nuclear foci and modulating its transcriptional function. By Figdraw.

CREB3 to act as a transcription factor, regulating stress-responsive genes.[22] Similarly, CREBRF is UPR-sensitive and prone to proteasomal degradation. CREBRF primarily acts as a negative regulator of CREB3, suppressing its activity.[11] However, studies in Neuro2a cells indicate that CREBRF can also positively regulate CREB3, modulating ER stress.[30] This dual regulation underscores the intricate interplay between CREB3 family members and ER stress in diverse cellular contexts.

CREBRF and Cell Cycle Regulation

The eukaryotic cell cycle, consisting of G1, S, G2, and M phases, is stringently regulated by checkpoints that ensure DNA integrity and halt progression upon detecting damage.[31] The G1/S checkpoint inhibits CDK4/6-Cyclin D and CDK2-Cyclin E complexes to prevent damaged DNA replication. The G2/M checkpoint ensures DNA integrity and replication completeness, blocking mitotic entry if errors persist.[32] Malfunctioning checkpoints impair DNA repair, leading to genomic instability and an increased risk of cancer.[33]

Checkpoint dysregulation is a key feature of many cancers.[34–36] CREBRF regulates key cell cycle factors and transitions, playing a crucial role in biological processes like cancer progression and decidualization. In gastric cancer (GC), CREBRF activates the AKT pathway, upregulating CDK2, Cyclin D1, and Cyclin A to promote the G1/S transition and drive tumor cell proliferation.[13] CREBRF also influences decidualization by regulating the proliferation and differentiation of endometrial stromal cells (ESCs) into decidual cells. Silencing CREBRF downregulates Cyclin A and Cyclin B1, sparing Cyclin D3 and Cyclin E, causing S-phase arrest and reduced ESC proliferation.[37,38]

CREBRF and Autophagy

Autophagy degrades and recycles cellular components via the lysosomal system, selectively or non-selectively breaking down organelles and proteins to maintain metabolic balance and cellular homeostasis.[2] In tumor cells, autophagy supports metabolic demands, aiding their growth and survival.[3,39] Autophagy sustains cell survival during starvation, hypoxia, immune responses, and radio-chemotherapy by providing essential resources. Late-stage cancer cells heavily depend on autophagy to survive in the nutrient-deprived tumor microenvironment.[3,40–42]

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In breast cancer, CREBRF is significantly upregulated during drug-induced autophagy, and its high expression correlates with better clinical outcomes, suggesting its potential as an autophagy biomarker.[43] Moreover, FOXC1, a transcription factor frequently overexpressed in various cancers, has been shown to bind to the promoter region of CREBRF and suppress its expression in four distinct triple-negative breast cancer (TNBC) cell lines. This finding implies that CREBRF may function as a tumor suppressor in TNBC.[44] In endometrial epithelial cells, hormonal regulation upregulates CREBRF, which activates autophagy via the CREBRF-mTOR-autophagy pathway.[45] Human melanoma is characterized by constant MEK/ERK pathway activation.[46,47] CREB upregulates Noxa transcription through MEK/ERK signaling, inducing autophagy in melanoma cells and delaying apoptosis during nutrient starvation.[48] This indicates that CREBRF may be involved in regulating apoptosis in melanoma cells. In glioblastoma, the IL6-p-STAT3-miR155-3p-CREBRF-CREB3-ATG5 axis promotes hypoxia-induced autophagy, while IL6 receptor blockade suppresses this process.[10] Additionally, MicroRNA-124-3p promotes autophagy in gliomas by targeting CREBRF for downregulation.[16]

Solid tumors, especially malignant ones, commonly exhibit hypoxic conditions with oxygen levels significantly lower than their tissue of origin.[49–51] Hypoxic tumor regions exhibit extensive autophagy.[52] In glioblastoma, hypoxia downregulates CREBRF expression, correlating with elevated HIF-1α levels and promoting autophagy via the CREB3/ATG5 pathway.[12] Combined knockdown of CREB3 and inhibition of ATG5 suppresses hypoxia-induced autophagy.

CREBRF in Other Aspects

CREBRF is a versatile regulatory protein engaged in diverse physiological and pathological processes. In reproductive biology, CREBRF is crucial for hormonal signaling during pregnancy, influencing implantation and embryonic development.[53] It also affects maternal behavior by inhibiting the glucocorticoid receptor, which modulates the hypothalamic-pituitary-adrenal (HPA) axis and prolactin signaling.[54] MicroRNA miR-181d-5p targets CREBRF, influencing placental cell function and possibly contributing to pregnancy-related disorders.[55] Additionally, CREBRF is a critical regulator of muscle energy metabolism, and its dysfunction may affect tumor metabolic states.[56]

CREBRF and Tumors

Recently, the potential role of CREBRF in cancer therapy has gained attention (Figure 2), especially for its involvement in regulating tumor metabolism and improving therapeutic efficacy. CREBRF generally regulates tumors via the LncRNA/CircRNA-miR-CREBRF axis or the AKT signaling pathway.[57–59] CREBRF promotes tumorigenesis in cervical and gastric cancers but acts as a tumor suppressor in gallbladder cancer and AML. In gliomas, particularly glioblastomas, its role varies based on cellular physiological state and microenvironment, exhibiting dual biological functions.[13,14,16,60–65] Table 1 summarizes the dual roles of CREBRF in tumorigenesis, demonstrating both inhibitory and promotive effects across different cancer types.

Cervical Cancer (CC)

Cervical cancer (CC) is the most common gynecological malignancy and ranks as the fourth leading cause of cancer-related deaths among women. CREBRF, an essential transcription factor, is upregulated in CC and strongly associated with enhanced tumor proliferation, migration, and invasiveness. Numerous CircRNAs are upregulated in CC, functioning as miRNA sponges to suppress specific miRNAs and elevate CREBRF expression, thereby promoting CC progression. For example, circ_0009035 influences CC progression by regulating the miR-1305/CREBRF axis.[62] hsa_circ_0102171 targets the miR-4465/CREBRF axis, potentially promoting proliferation, reducing apoptosis, and enhancing invasion and migration in CC cells, thereby accelerating tumor progression and severity.[63] Additionally, the circ_0081723/miR-545-3p/CREBRF axis and CircVIRMA/miR-452-5p/CREBRF axis are implicated in CC progression.[14,60] These studies highlight the significant role of non-coding RNAs in regulating CREBRF expression and driving CC progression.

Head and Neck Squamous Cell Carcinoma (HNSCC)

Chemoradiotherapy failure is a significant contributor to recurrence, progression, and poor prognosis in head and neck squamous cell carcinoma (HNSCC).[66] MicroRNAs, particularly miR-124-3p, have been identified as critical mediators of drug resistance in HNSCC. A recent study showed that miR-124-3p is overexpressed in chemoradiotherapy-resistant

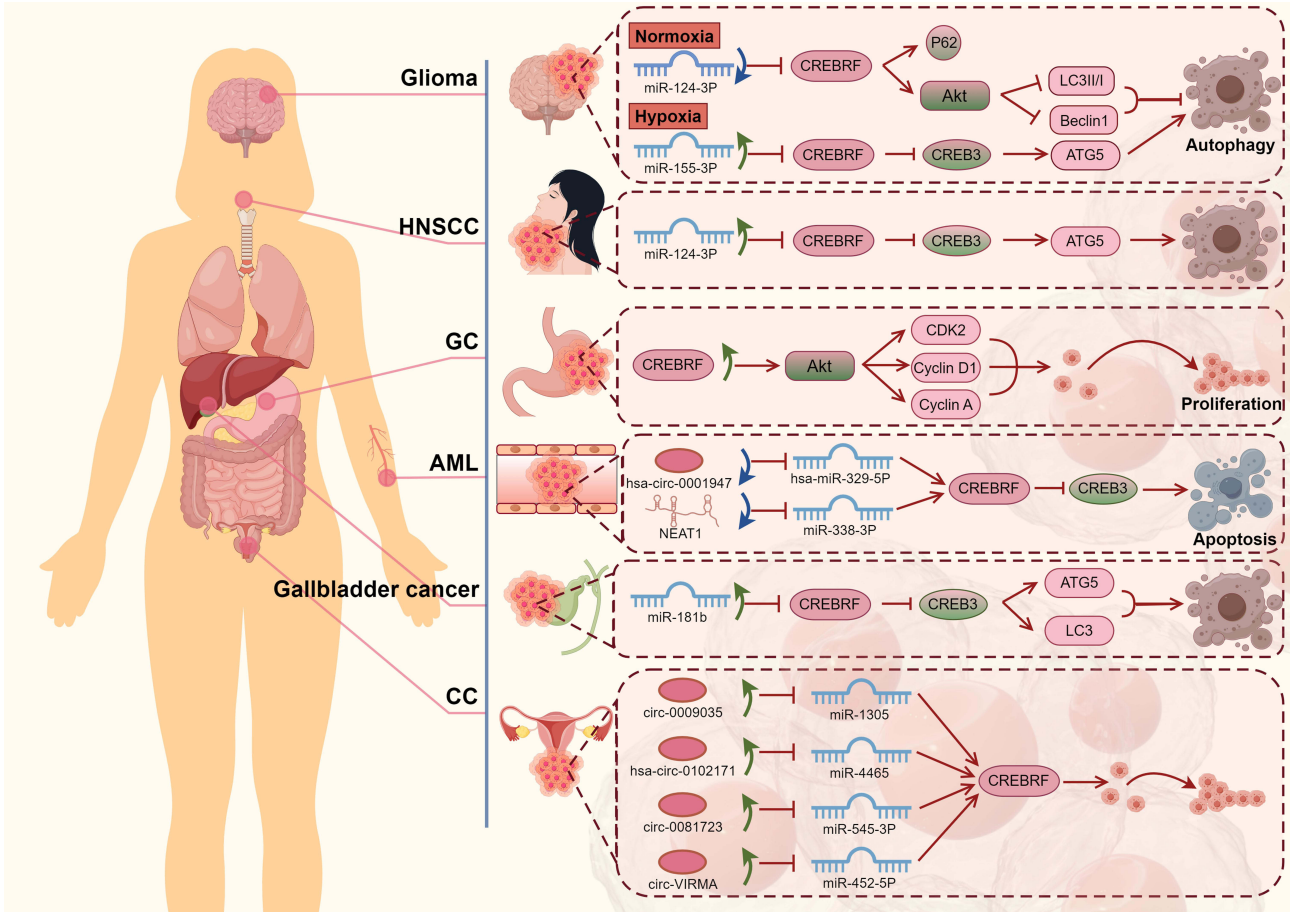

Figure 2 CREBRF plays a critical role in modulating regulatory pathways that influence the progression and therapeutic response of various cancers. By Figdraw.
Abbreviations: HNSCC, Head and neck squamous cell carcinoma; GC, Gastric cancer; AML, acute myeloid leukemia; CC, Cervical cancer.

HNSCC tumors compared to responsive tumors. Suppressing miR-124-3p improved the sensitivity of HNSCC cell lines to standard treatments, including 5-fluorouracil, cisplatin, and radiotherapy. MiR-124-3p downregulates the transcription factor CREBRF by directly targeting it. This downregulation activates the CREB3/ATG5 signaling axis, promoting aggressive tumor behavior. Inhibiting miR-124-3p restores CREBRF expression, which may reduce tumor invasiveness and migration, enhance chemoradiotherapy efficacy, and improve survival rates in HNSCC patients.[61] Therefore, targeting miR-124-3p and restoring CREBRF expression holds great promise for overcoming drug resistance in HNSCC.

Table 1 The Dual Roles of CREBRF in Tumorigenesis

Cancer Types	Expression Levels (Tumor vs Normal Tissue Comparison)	Biological Effects	Functional Impact on Tumor Progression
Glioma	Upregulation Downregulation (under hypoxic conditions)	Suppress autophagy Induce autophagy and promote cell proliferation	Promote Inhibit
HNSCC	Downregulation	Induce autophagy and enhance invasiveness and migratory capacity	Inhibit
GC	Upregulation	Stimulate cell proliferation	Promote
AML	Downregulation	Stimulate cell proliferation	Inhibit
Gallbladder cancer	Downregulation	Induce autophagy and stimulate cell proliferation	Inhibit
CC	Upregulation	Stimulate cell proliferation and enhance invasiveness and migration potential	Promote

Abbreviations: GC, Gastric cancer; CC, Cervical cancer.

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AML

AML is a hematological malignancy marked by the accumulation and impaired differentiation of clonal myeloid precursor cells in the bone marrow.[67] Studies have demonstrated that hsa_circ_0001947 is frequently downregulated in the bone marrow of AML patients. hsa_circ_0001947 acts as a molecular sponge for hsa-miR-329-5p, which directly targets and suppresses CREBRF mRNA expression. When hsa-miR-329-5p is sequestered by hsa_circ_0001947, CREBRF suppression is relieved, resulting in increased CREBRF expression and inhibition of AML cell proliferation.[64] Furthermore, lncRNAs can reduce the levels of free miRNAs, thereby increasing the expression of miRNA-repressed target proteins.[68] NEAT1 is a lncRNA downregulated in leukemia patients and cell lines, while miR-338-3p is overexpressed in AML.[69,70] NEAT1 binds to miR-338-3p, mitigating its suppression of CREBRF and thereby enhancing CREBRF expression. Elevated CREBRF expression may inhibit CREB3 activity, thereby suppressing AML cell proliferation and survival while promoting apoptosis.[15]

Gallbladder Cancer

Gallbladder cancer is a malignant tumor derived from the epithelial cells of the gallbladder, notable for its diverse metastatic pathways and poor prognosis.[71] miR-181b has demonstrated oncogenic roles in various cancers.[72–74] Research suggests that in gallbladder cancer, miR-181b directly targets and suppresses CREBRF, inhibiting CREB3 degradation and promoting the expression of autophagy-related genes, including LC3 and ATG5. This mechanism enables tumor cells to manage stress, thereby enhancing their survival and proliferation.[65] Rg3, a potential autophagy inhibitor, exhibits antitumor effects in several malignancies, such as colorectal and lung cancers.[75,76] In gallbladder cancer, Rg3 inhibits autophagic flux and suppresses tumor progression by blocking the miR-181b/CREBRF/CREB3 pathway. Exogenous overexpression of miR-181b diminishes the tumor-suppressive effects of ginsenoside Rg3, ultimately accelerating gallbladder cancer progression.[65]

Glioma

Glioma is the most common primary malignant brain tumor in adults.[77] In glioma cells, miR-124-3p is significantly downregulated, while CREBRF is upregulated. Overexpression of CREBRF increases p62 expression and activates the AKT pathway while suppressing autophagy-related proteins, including Beclin1 and LC3-II/I. These findings suggest that CREBRF promotes glioma cell survival by suppressing apoptosis and autophagy. Studies reveal that miR-124-3p directly targets CREBRF, inhibiting AKT activation and enhancing apoptosis and autophagy in glioma cells.[16] Under hypoxic conditions, the expression of CREBRF is diminished, while CREB3 levels are upregulated, thereby promoting autophagy, inhibiting apoptosis, and driving the proliferation of glioma cells.[12] Thus, understanding CREBRF function necessitates analyzing its expression levels in context with biophysiological conditions. This context-dependent regulation allows tumor cells to adapt to environmental changes, presenting potential opportunities for therapeutic intervention.

Gastric Cancer

Gastric cancer (GC) is a malignant tumor originating in the stomach and remains a major cause of cancer-related mortality worldwide.[78] CREBRF is highly upregulated in GC cells, activating the AKT pathway and significantly increasing the expression of cell cycle regulators CDK2, Cyclin D1, and Cyclin A. Cyclin D1, Cyclin A, and CDK2 are essential for the G1-to-S phase transition during the cell cycle.[79] Silencing CREBRF causes significant cell cycle arrest at the G1/G0 phase, thereby inhibiting GC cell proliferation. AKT pathway activation can counteract this effect and stimulate GC cell proliferation. These findings suggest that CREBRF may be a promising therapeutic target for gastric cancer.[13]

Future Directions of CREBRF in Cancer Treatment

CREBRF is pivotal in processes like ER stress, cell cycle regulation, and autophagy, underscoring its substantial impact on cancer progression. Its dual role as a tumor suppressor and oncogene highlights its complexity and therapeutic

potential. However, databases like the Drug Signatures Database on Enrichr reveal a lack of drugs targeting CREBRF, raising concerns about its druggability.

Further research is essential to clarify CREBRF's context-dependent roles in different tumor types. This involves studying how CREBRF regulates ER stress, cell cycle checkpoints, and autophagy in hypoxic or nutrient-deprived microenvironments. Exploring CREBRF's post-translational modifications and their effects on its tumor-promoting or suppressive functions may uncover new regulatory mechanisms and therapeutic opportunities.

Structural biology techniques like cryo-electron microscopy and molecular docking should be utilized to identify potential binding sites on CREBRF.[80] If direct targeting of CREBRF proves difficult, its upstream regulators or downstream effectors may serve as alternative therapeutic targets. For example, targeting pathways linked to ER stress or autophagy could indirectly modulate CREBRF activity. High-throughput screening of small molecules or peptides to modulate CREBRF function may identify promising candidates for therapy.[81]

CREBRF's context-dependent role, as a tumor suppressor in some cancers and an oncogene in others, highlights the need for patient stratification. Profiling CREBRF expression or functional status may facilitate precision medicine strategies. Integrating CREBRF-targeting strategies with therapies like immune checkpoint inhibitors, chemotherapy, or autophagy modulators could improve efficacy and overcome resistance. Relevant models like patient-derived organoids, xenografts, and genetically engineered mouse models are crucial for understanding CREBRF's role in cancer and its therapeutic potential.[82]

Despite the challenges in directly targeting CREBRF, its pivotal role in cancer biology, especially its potential function as a tumor suppressor, underscores the importance of further research on CREBRF. A thorough understanding of CREBRF's molecular functions, paired with innovative drug discovery and validation strategies, may unlock its potential as a cancer therapy target. Multidisciplinary collaboration will be essential to translate these insights into effective therapies.

Conclusion

CREBRF has been identified as a critical regulator in cancer biology, displaying both tumor-suppressive and tumor-promoting roles depending on the tumor type and microenvironment. These dual roles are governed by complex molecular mechanisms, emphasizing the importance of further research to elucidate CREBRF's context-specific contributions to cancer progression. Despite its considerable therapeutic potential, CREBRF remains relatively underexplored. Direct targeting is difficult because of the lack of clearly identified druggable sites. Alternative strategies, including targeting upstream regulators, downstream effectors, or related pathways, as well as employing advanced drug discovery technologies, present promising opportunities for intervention.

The context-specific roles of CREBRF underscore the importance of precision medicine. Patient stratification based on CREBRF expression profiles or functional states could facilitate personalized therapeutic strategies. Although challenges remain, CREBRF's crucial role in cancer biology makes it a promising target for therapeutic development. Expanding knowledge of CREBRF's molecular functions, regulatory networks, and druggability, supported by multidisciplinary collaboration, is vital for translating these findings into clinical applications. Addressing these gaps could lead to the development of innovative and effective cancer therapies targeting CREBRF.

Data Sharing Statement

The clinical data supporting the conclusions of this manuscript will be made available by the authors.

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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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Disclosure

The authors declare that they have no competing interests in this work.

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