

Biological Mechanisms of Microwave Ablation in Thyroid Tumors and Its Induced Immunomodulatory Effects

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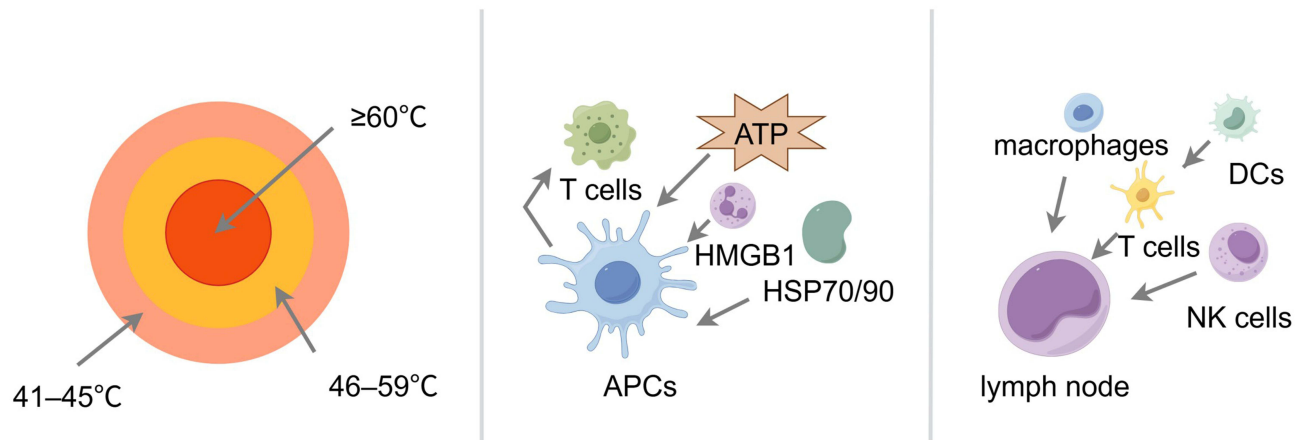
Abstract: Microwave ablation (MWA) is a minimally invasive thermal ablation technique that eradicates thyroid tumors by rapidly increasing tissue temperature to 60–100 degrees Celsius (°C) through dielectric hysteresis. This focused electromagnetic heating leads to irreversible protein denaturation, cell membrane disruption, and coagulative necrosis. Within the ablation zone, mitochondria and the endoplasmic reticulum sustain severe thermal injury accompanied by DNA double-strand breaks. The resulting cell death occurs via apoptosis, pyroptosis, and ferroptosis, while necrotic tissue triggers a robust inflammatory response that facilitates debris clearance and tissue remodeling. Damage-associated molecular patterns (DAMPs) and heat shock proteins (HSPs), released from dying cells, mediate immunogenic cell death (ICD) and promote dendritic cell activation and cytotoxic T lymphocyte (CTL) responses, leading to systemic antitumor immunity. Moreover, thermal injury disrupts the local vasculature, resulting in transient ischemia and hypoxia that activate the hypoxia-inducible factor-1 alpha (HIF-1 α) pathway and stimulate vascular repair and fibrosis through transforming growth factor-beta (TGF- β) and vascular endothelial growth factor (VEGF) signaling. In addition, peripheral immune alterations and immune-related gene activation suggest potential synergy between MWA and immune checkpoint blockade. Collectively, MWA not only provides effective local tumor destruction but also reshapes the tumor immune microenvironment, offering a rationale for combined thermal and immunotherapeutic strategies in thyroid oncology.

Keywords: microwave ablation, thyroid tumors, papillary thyroid carcinoma, biological mechanisms, immunomodulation

Introduction

Thyroid cancer is the most common malignancy of the endocrine system and accounts for approximately 3.1% of all cancer cases worldwide.¹ Among its subtypes, papillary thyroid carcinoma (PTC) is the predominant form of differentiated thyroid cancer, representing 80 to 85% of all thyroid malignancies.^{2,3} Papillary thyroid microcarcinoma (PTMC) has emerged as a major subtype and now represents nearly half of all PTC cases.⁴ With the global increase in PTMC incidence, ultrasound-guided minimally invasive therapies (MITs) have become effective alternatives to conventional thyroidectomy. Compared with surgery, these image-guided approaches are associated with favorable safety profiles, cosmetic outcomes, and quality-of-life advantages, and have been increasingly adopted for local tumor control.^{4,5} Microwave ablation (MWA), one of the most common MIT techniques, has been validated as a safe and effective treatment for PTMC. Clinical studies have reported complication rates as low as 1.2% during long-term follow-up with a mean duration of nearly 68 months.^{6–8} In a retrospective analysis of 1029 patients with solitary T1N0M0 PTC, disease progression showed no significant difference between the MWA and surgical groups, while MWA demonstrated fewer intraoperative and postoperative complications. T1b tumors exhibited a slightly slower absorption rate than T1a lesions.² A prospective study with 461 participants also found no difference in recurrence or shrinkage rates between PTMCs with or without capsular invasion.⁹ Microwave ablation has further shown

Graphical Abstract



value in treating multifocal PTMCs.^{10,11} In addition, its use in benign thyroid nodules (BTNs) has been well documented. Lin et al reported favorable therapeutic and cosmetic outcomes in 87 patients with large BTNs of 4 centimeters or more treated with MWA.¹² Similarly, a 48-month study involving 148 patients demonstrated a mean reduction of 96.9% in nodule volume, with a recurrence rate of only 1.35% and no significant alteration in thyroid function.¹³ Collectively, these findings support MWA as a safe and minimally invasive option for both benign and low-risk malignant thyroid nodules. Despite its proven clinical efficacy, the biological mechanisms underlying MWA remain poorly characterized. The processes within the ablation zone—including coagulative necrosis, stress response, immune activation, and tissue remodeling—are incompletely understood.

Local Biological and Cellular Responses to Microwave Ablation

Thermal Injury and Coagulative Necrosis

Microwave ablation (MWA) generates localized high temperature that irreversibly destroys thyroid tumor cells, leading to the release of tumor-specific and tumor-associated antigens (TSA, TAA) as well as intracellular danger signals. The technique relies on the dielectric hysteresis effect, in which an oscillating electromagnetic field between 900 and 2500 megahertz drives polar molecules, mainly water, to continuously reorient with the alternating field. This movement increases molecular kinetic energy, rapidly raising tissue temperature to 60 to 100 °C. At these levels, proteins denature, membranes lose integrity, and the cells undergo coagulation and dehydration, leading to necrosis.^{14–16} The mechanism of thermal injury occurs at both the membrane and subcellular levels and is influenced by the tumor microenvironment.¹⁷ The ablation area can be divided into three zones: a central region of coagulative necrosis, a surrounding margin of reversible sublethal damage, and adjacent unaffected thyroid tissue.¹⁸ Cellular injury arises from both direct heat effects and secondary ischemia. The extent of destruction depends on power, exposure time, and the thermal tolerance of the target tissue. Continuous exposure to 40 to 45 °C for 30 to 60 minutes can cause irreversible damage, while exposure above 60 °C results in cell death within seconds.¹⁹ At temperatures between approximately 41 and 59 °C, cells experience sublethal heat stress resulting in reversible or delayed injury, whereas above 60 °C, coagulative necrosis occurs almost instantaneously.²⁰ This temperature range reflects the steep gradient immediately outside the central necrotic zone, where perfusion-mediated heat dissipation causes a rapid temperature drop, forming a narrow but biologically active transitional zone. Thermal coagulation represents an irreversible process that involves the denaturation of proteins, organelle destruction, and breakdown of cellular and extracellular structures.²¹ Denatured proteins expose hydrophobic residues, lose their alpha-helical and beta-sheet configurations, and eventually unfold into random

coil conformations above 80 °C.²² These molecular alterations cause cytoplasmic homogenization, nuclear shrinkage, and membrane rupture, which are the histological hallmarks of coagulative necrosis.

In the peripheral zone, sublethal exposure between 45 and 60 °C can trigger delayed apoptosis or ferroptosis over several days. Beyond this boundary, transient physiological changes such as increased blood flow, permeability, and oxygenation may occur.²³ Importantly, coagulative necrosis exposes intracellular antigens, damage-associated molecular patterns (DAMPs), and heat shock proteins (HSPs). These molecules recruit and activate antigen-presenting cells, bridging local tissue destruction with systemic antitumor immune activation. This link between thermal injury and immune stimulation provides a biological foundation for combining MWA with immunotherapy in thyroid cancer.

Cell Membrane Rupture and Structural Damage

Disruption of cell membrane integrity is one of the primary mechanisms through which MWA induces cell death.^{19,24} When exposed to heat, the lipid structure becomes unstable. Thermally induced “superfluidity” alters the function of membrane-associated proteins, even under moderate stress conditions.²⁵ Even mild heating beyond 37 °C can enhance membrane fluidity and permeability.²⁶ The cytoskeleton also contributes significantly to membrane stability. Alterations in actin filaments and microtubules often accompany increased membrane permeability. Such structural changes compromise diffusion and transmembrane transport, ultimately leading to cellular rupture and death.

In thyroid tumor MWA, membrane rupture represents a key event in tumor cell destruction. This breakdown also triggers innate immune activation by releasing intracellular components such as adenosine triphosphate (ATP), high-mobility group box 1 protein (HMGB1), and other DAMPs, which promote immunogenic cell death.²⁷ Studies have shown that multiple ablation techniques can induce the exposure of calreticulin, ATP, and HMGB1, which are essential for dendritic cell activation and subsequent adaptive immune responses.²⁸ Ferroptosis, another immunogenic cell death pathway, is associated with DAMP release and inflammation.²⁹ These processes are closely linked to mitochondrial injury, endoplasmic reticulum stress, DNA fragmentation, and pyroptosis, indicating that membrane damage serves as the initiating event within the post-ablation immunoregulatory cascade. Although extensive studies have explored how heat disrupts cellular lipids and structural proteins, systematic research on thyroid-specific membrane alterations remains limited.³⁰ Future investigations combining real-time imaging, multi-omics analysis, and animal models may clarify how membrane injury interacts with immune responses. Understanding this dynamic relationship will help refine ablation parameters and support the rational design of MWA-based immunotherapy strategies.

Mitochondrial and Endoplasmic Reticulum Damage

Papillary thyroid carcinoma cells have been observed to exhibit a characteristic increase in mitochondrial number.³¹ Heat treatment has been demonstrated to induce significant alterations in mitochondrial membrane permeability, resulting in impaired electron transport within the respiratory chain. This phenomenon is accompanied by excessive production of reactive oxygen species (ROS) and a substantial decline in ATP synthesis, consequently leading to disruption of energy metabolism.³² These functional alterations emerge early, with mitochondrial ultrastructural abnormalities typically observable within minutes. These include the premature appearance of inner dense granules, vesiculation and swelling of cristae, expansion of cristae spaces, and myelin-like degeneration.³³ The structural integrity of the endoplasmic reticulum (ER) is similarly susceptible to thermal damage. The molecular oscillations induced by microwave ablation have been shown to disrupt ER function, trigger ER stress responses, and cause marked ER dilation. Given that thyroid cancer cells typically exist in a microenvironment characterized by nutrient deprivation and high metabolic stress, their ER is more fragile than that of normal cells, making it more susceptible to irreversible damage under thermal stress.^{34,35} Damage to the mitochondria and the ER has been demonstrated to disrupt not only energy metabolism and protein folding, but also to induce programmed cell death, such as apoptosis and pyroptosis. This process has been shown to occur through calcium signaling disruption, excessive ROS production, and activation of stress pathways.^{36–39} The present state of research on mitochondrial—ER interactions following thyroid tumor microwave ablation and their role in induced immune regulation remains limited. Future studies integrating real-time imaging, multi-omics analyses, and immunological experiments may help clarify how microwave ablation modulates immunogenic cell death, inflammatory

responses, and tumor immune microenvironment remodeling, thereby providing a more rigorous mechanistic basis for combination strategies involving MWA and immunotherapy.

DNA Double-Strand Breaks (DSBs)

DNA double-strand breaks (DSBs) represent one of the most severe forms of genetic injury. The phosphorylated histone variant histone H2A.X phosphorylated on serine 139 (γ H2AX) is widely used as a biomarker for DSB formation. Elevated temperature during MWA can directly induce DNA strand scission and impair repair capacity in thyroid tumor cells. Heat exposure rapidly increases γ H2AX foci formation in mammalian cells, signifying the accumulation of DNA strand breaks.⁴⁰ At the same time, hyperthermia disrupts key DNA repair pathways, producing transient repair defects and promoting the persistence of DSBs.⁴¹ Two main mechanisms are implicated in heat-induced DSB formation. First, elevated temperature denatures thermosensitive DNA repair enzymes, particularly DNA polymerase alpha and beta, which are essential for strand resynthesis.^{42–45} Loss of polymerase activity compromises the accuracy of base excision and recombination repair. Second, heat induces abnormal condensation of chromatin and matrix proteins, distorting chromatin organization and restricting access of repair complexes.^{26,46} Experimental data demonstrate a clear time- and dose-dependent relationship between temperature elevation and DSB persistence, with γ H2AX signal intensity correlating with both exposure duration and thermal dose.⁴⁷

Altered γ H2AX and DNA damage response (DDR) signaling have been identified in thyroid tumors, suggesting that DSBs may serve as quantifiable biomarkers of thermal injury.⁴⁸ Although direct visualization of DSB kinetics following MWA remains limited, current evidence indicates that heat-induced enzyme inactivation, oxidative stress, and chromatin disruption collectively contribute to DSB accumulation in both tumor and adjacent thyroid tissue.

Importantly, DSBs can act as potent triggers of immunogenic cell death (ICD). Persistent or improperly repaired DNA fragments that leak into the cytoplasm can activate the cyclic guanosine monophosphate–adenosine monophosphate (cyclic GMP–AMP, cGAMP) synthase (cGAS)–stimulator of interferon genes (STING) signaling pathway, initiating type I interferon and chemokine responses.^{49,50} This signaling cascade enhances dendritic cell maturation and T-cell priming, linking genotoxic injury to immune activation. Persistent or improperly repaired DNA fragments can activate the cGAS–STING pathway, initiating type I interferon and pro-inflammatory responses. Moreover, DNA repair factors such as ataxia telangiectasia mutated (ATM) and BRCA1/2 (DNA repair–associated genes) have been shown to modulate cGAS–STING signaling under DNA damage conditions, further influencing innate immune activation.⁵⁰ To clarify these processes in MWA, systematic quantification of γ H2AX foci and assessment of cGAS–STING pathway activation will help delineate the immune consequences of DNA injury. Understanding this interplay between DNA repair and innate immunity may guide optimized combinations of MWA and immunotherapy to enhance antitumor.

Inflammatory Response and Absorption Processes Within the Ablated Zone

MWA induces rapid coagulative necrosis of thyroid follicles and follicular epithelium, leading to the release of tumor antigens and damage-associated molecular patterns (DAMPs). This inflammatory milieu recruits macrophages, dendritic cells (DCs), and natural killer (NK) cells that orchestrate innate immune responses and link local tissue damage with systemic immune activation. This cellular disruption initiates an aseptic inflammatory cascade characterized by increased vascular permeability, upregulation of adhesion molecules, and recruitment of macrophages, neutrophils, and dendritic cells.^{32,51–53} Histological examination typically reveals a fibrous capsule encircling necrotic tissue, containing inflammatory infiltrates and degenerative cells that exhibit nuclear enlargement and focal chromatin dispersion.⁵⁴ Over time, necrotic tissue is degraded and cleared through lymphatic drainage and phagocytic activity.^{55,56} As macrophages infiltrate the ablation zone, they release cytokines and growth factors that promote angiogenesis, extracellular matrix deposition, and debris clearance.⁵⁷ Notably, this acute sterile inflammation engenders conducive conditions for adaptive immune responses (eg, dendritic cell maturation and cross-priming of CD8⁺ T cells), which may elucidate the local–systemic (abscopal) immune effects observed following thermal ablation.^{32,51,58} This cascade bridges local tissue destruction with systemic antitumor immunity and may underlie the abscopal effect observed in various ablation models.

However, the balance between immune activation and pro-tumor remodeling remains complex. While inflammatory signaling can enhance immune surveillance, persistent activation of growth and angiogenic factors may favor recurrence

or residual tumor proliferation. Therefore, delineating the temporal dynamics of inflammation—from acute immune activation to late tissue repair—is essential for identifying therapeutic windows for immunomodulation. Future research should focus on integrating cytokine profiling, immune cell tracking, and imaging-based monitoring to clarify how MWA-induced inflammation influences long-term outcomes. Understanding these pathways could inform strategies to enhance beneficial immune effects while minimizing pro-tumor remodeling, thereby improving both local control and systemic response to therapy.

Cell Death Modes: Apoptosis and Pyroptosis

MWA induces various forms of programmed cell death depending on temperature and exposure duration. When thermal stress is moderate, apoptosis predominates, whereas exposure to higher temperatures (typically above 50 °C) shifts the mechanism toward necrosis.⁵⁹ MWA generates substantial oxidative stress, resulting in excessive ROS production and depletion of intracellular glutathione (GSH). These biochemical alterations sensitize cells to heat-induced injury and activate intrinsic apoptotic pathways.⁶⁰ During this process, phosphatidylserine (PS) translocates to the outer plasma membrane, serving as an “eat-me” signal that promotes macrophage-mediated clearance of dying cells while limiting the release of proinflammatory molecules.^{61,62} The controlled nature of apoptosis thus allows tissue remodeling to proceed with minimal inflammatory spillover. In contrast, pyroptosis is a proinflammatory form of programmed cell death, in which membrane pore formation leads to cellular swelling and promotes the release of inflammatory cytokines.^{61,63} MWA also promotes lipid peroxidation through ROS accumulation and iron-dependent Fenton reactions, triggering ferroptosis, another regulated death pathway distinct from apoptosis.³² This process links oxidative stress to lipid damage and underscores the complexity of cell death regulation under hyperthermic conditions. Collectively, apoptosis, pyroptosis, and ferroptosis form an interconnected network that dictates the balance between tumor eradication, inflammation, and immune activation.

While apoptosis contributes to orderly cell clearance, pyroptosis and ferroptosis enhance the immunogenic potential of ablated tissue by releasing DAMPs and inflammatory mediators. These signals activate dendritic cells and cytotoxic T lymphocytes, thereby facilitating adaptive immune responses. However, the relative contribution of each cell death pathway in thyroid tumor ablation remains largely undefined. Future studies integrating molecular profiling, live imaging, and immunologic assays may elucidate how different death modes coordinate local cytotoxicity and systemic immunity. Understanding these mechanisms will be essential for refining MWA protocols and developing combination strategies that leverage cell death–driven immunogenicity to improve clinical outcomes.⁶⁴

Damage-Associated Molecular Patterns and Heat Shock Proteins Mediate Immunogenic Cell Death

Following the process of MWA, a significant release of tumor-specific and associated antigens occurs, along with DAMPs—including DNA, RNA, HMGB1, ATP, and heat shock proteins HSP70/HSP90—into the microenvironment.⁶⁵ These molecules act as danger signals that activate antigen-presenting cells (APCs) through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs).^{58,66} Activated DCs internalize these antigens, upregulate costimulatory molecules (CD80/CD86), and present them via major histocompatibility complex (MHC) pathways to CD4⁺ and CD8⁺ T cells. These activated DCs subsequently prime CD4⁺ helper T cells and CD8⁺ cytotoxic T lymphocytes (CTLs), forming the core of adaptive immune activation following MWA. NK cells may also participate by eliminating residual tumor cells (Figure 1).^{67–69} This process characterizes immunogenic cell death (ICD), linking physical tumor destruction to immune activation. Released HMGB1 and ATP not only promote DC maturation but also stimulate cytokine production and effector T-cell activation. Moreover, HMGB1 supports tissue repair by recruiting stem cells and promoting angiogenesis.^{70,71} Heat shock proteins (HSPs) play dual roles in this process.⁷² Exposure to thermal stress markedly increases expression of HSP25/27, HSP70, and HSP90.^{45,60,73} Acting as ATP-dependent chaperones, they assist protein refolding, prevent aggregation, and modulate apoptosis through regulation of p53 and Bax.⁷⁴ HSP27 and HSP70 can translocate into the nucleus, enhancing DNA polymerase beta activity, while HSP90 stabilizes oncogenic proteins and promotes angiogenesis, contributing to tumor resilience.^{45,60,75} Inhibition of HSP90 has been shown to

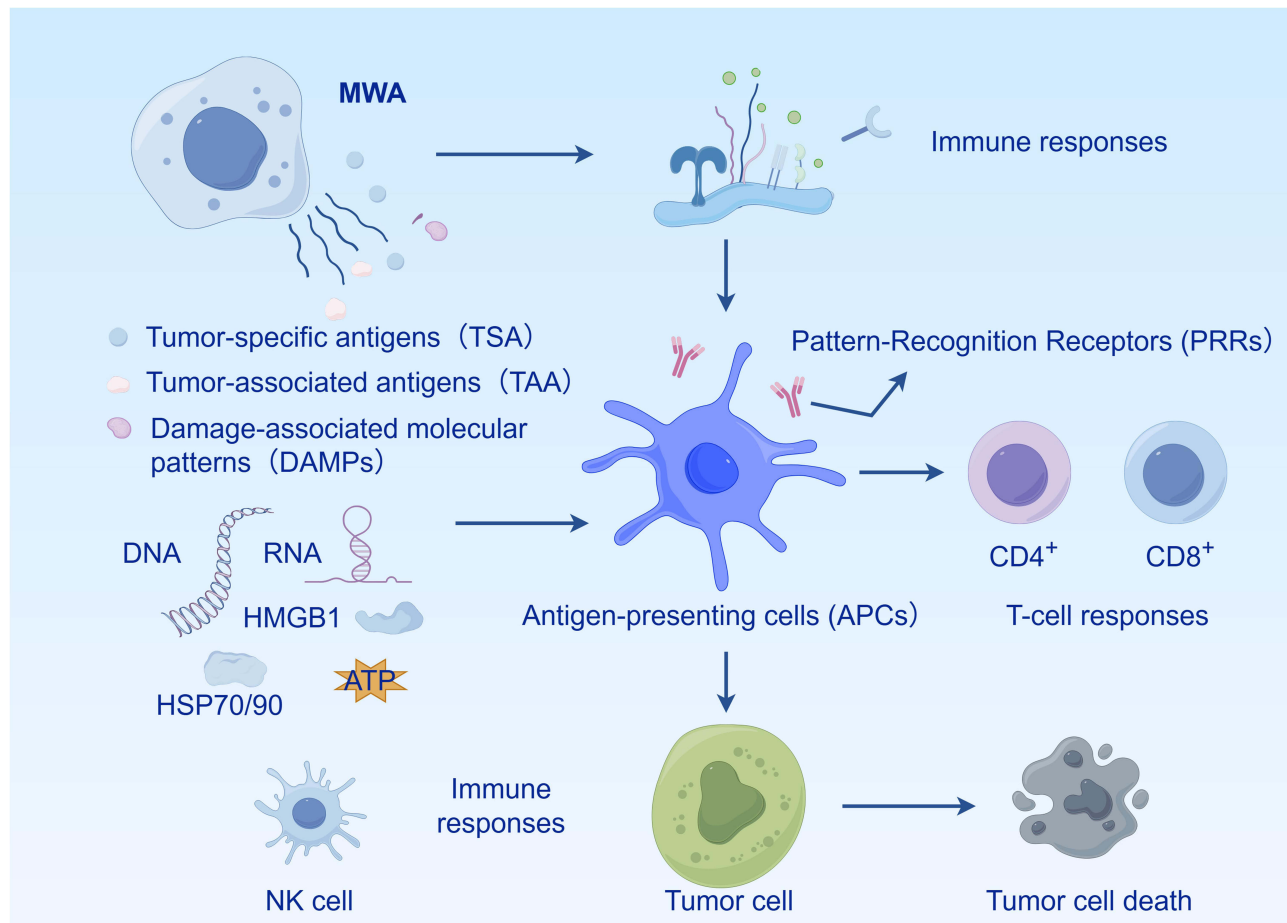


Figure 1 Immunogenic cell death induced by microwave ablation of thyroid tumor cells. MWA induces the release of TSA, TAA, and DAMPs, including DNA, RNA, high-mobility group box I (HMGB1), ATP, and HSP70 and HSP90. These molecules activate PRRs on APCs, such as dendritic cells and macrophages. Activated APCs stimulate CD4⁺ and CD8⁺ T-cell responses and NK cell activation, ultimately leading to tumor cell death and systemic antitumor immunity.

increase thermal sensitivity and strengthen ICD responses, suggesting a potential strategy for combining MWA with molecular chaperone inhibitors.^{76,77} Overall, DAMPs and HSPs bridge thermal cytotoxicity and immune activation. Their coordinated release transforms ablated tumor tissue into an in-situ vaccine that activates both innate and adaptive immunity, providing a mechanistic foundation for integrating MWA with immunotherapy.

Vascular Injury, Hypoxic Response, and Tissue Fibrosis/Remodeling

Vascular disruption is one of the earliest and most critical biological effects of MWA. Local heating increases vascular permeability and causes thermal collapse of small blood vessels, leading to microvascular occlusion and ischemia.^{78,79} This process amplifies tumor hypoxia and metabolic stress, enhancing thermal sensitivity of the ablated tissue.^{80,81} Compared with other ablation modalities, MWA effectively reduces the “heat-sink” effect caused by blood flow, resulting in a more uniform necrotic zone.⁸² Endothelial cells are highly heat-sensitive; exposure above 44 °C causes their rapid detachment and death, leading to vessel rupture and localized hemorrhage.^{26,83,84} These vascular alterations contribute to secondary ischemic necrosis and nutrient deprivation within the tumor, extending ablation efficacy beyond direct cytotoxic effects. Subsequently, the hypoxic microenvironment activates hypoxia-inducible factor 1- α (HIF-1 α), which upregulates vascular endothelial growth factor (VEGF) and other angiogenesis-related genes.^{85–88} The HIF-1 α /VEGF pathway promotes endothelial proliferation, new vessel formation, and metabolic adaptation.^{89–91} In thyroid cancer, elevated HIF-1 α expression correlates with tumor aggressiveness and increased neovascularization.^{92–94} Excessive VEGF signaling can further stimulate vascular endothelial growth factor receptor (VEGFR)-1-mediated neovascularization in periablational zones.^{95,96} Although direct experimental validation in thyroid tumors remains limited, this signaling cascade likely plays a key role in tissue

recovery and remodeling after MWA.⁹⁷ During the repair phase, infiltrating macrophages and lymphocytes release transforming growth factor beta (TGF- β), which induces fibroblast proliferation and transdifferentiation into myofibroblasts.¹⁹ These cells synthesize collagen and extracellular matrix proteins, gradually replacing necrotic areas with fibrotic scar tissue.^{98–100} This process restores local perfusion and tissue integrity but may also facilitate tumor adaptation if excessive fibrosis occurs.

In summary, vascular injury and the subsequent hypoxia-fibrosis sequence constitute a double-edged response. On one hand, these changes support wound healing and tissue stability; on the other, they may promote residual tumor survival or recurrence through aberrant angiogenesis. Future studies should explore whether targeting HIF-1 α /VEGF or modulating fibrosis can enhance local control and minimize pro-tumor remodeling after ablation.¹⁰¹ The overall biological mechanisms of microwave ablation are summarized in Figure 2. Collectively, these local biological and cellular events not only determine the extent of thermal injury and tissue remodeling but also initiate a cascade of immune activation, which will be further discussed in Systemic Immunomodulation and Translational Implications.

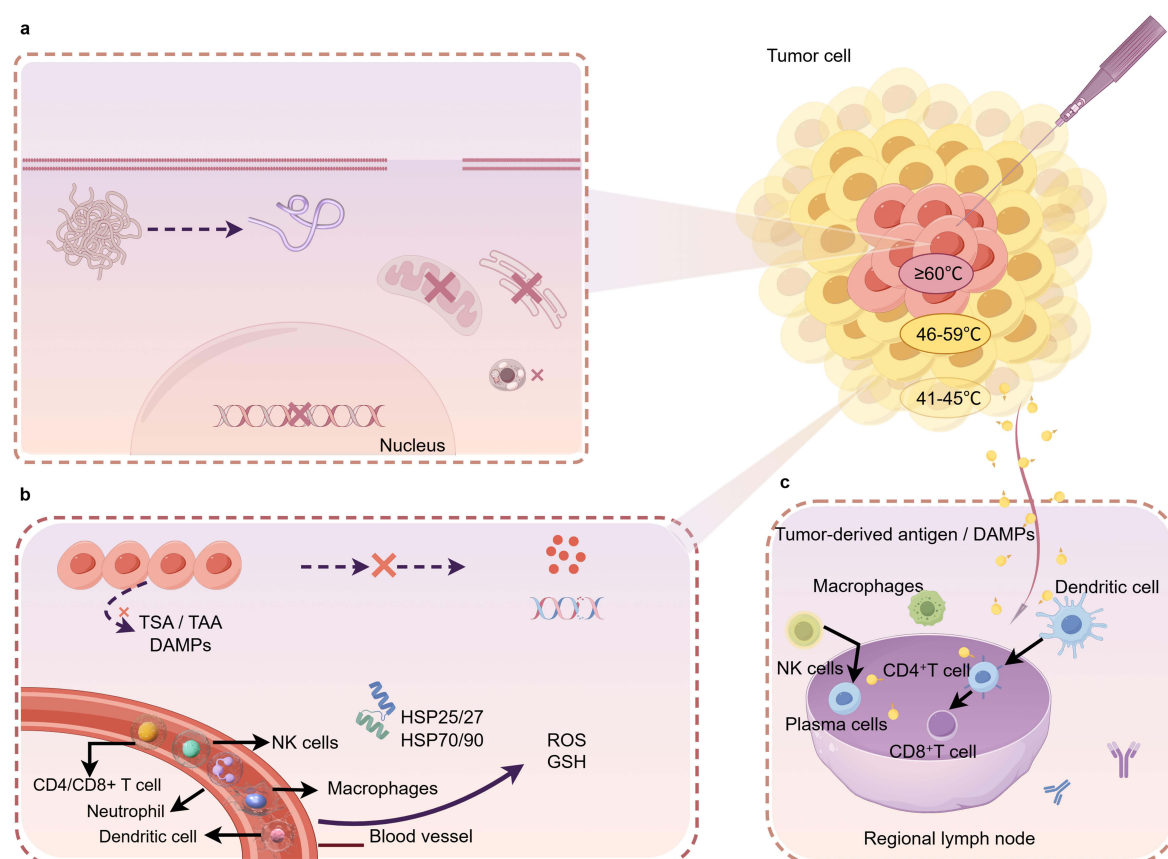


Figure 2 Schematic illustration of the biological and immunological mechanisms within thyroid tumor ablation zones. (a) Central zone: Localized microwave energy rapidly elevates tissue temperature ($\geq 60^{\circ}\text{C}$), leading to irreversible coagulative necrosis characterized by protein denaturation, membrane rupture, mitochondrial and endoplasmic reticulum damage, and DNA double-strand breaks. (b) Peripheral or transitional zone: Sublethal hyperthermia (approximately $41\text{--}59^{\circ}\text{C}$, depending on exposure duration, perfusion, and tissue properties) induces partial thermal injury with the generation of necrotic tissue fragments and promotes the release of TSA, TAA, and DAMPs, including HSPs (HSP25, HSP27, HSP70, HSP90). These molecules activate macrophages, DCs, NK cells, and $\text{CD4}^{+}/\text{CD8}^{+}$ T cells. In addition, oxidative stress, characterized by excessive ROS production and depletion of intracellular glutathione (GSH), and microvascular collapse upregulate angiogenesis-related genes and compromise DNA repair capacity. (c) Normal thyroid tissue and regional immune response: Tumor-derived antigens and DAMPs drain via lymphatic channels to adjacent lymph nodes, where dendritic cells present antigens to T cells, initiating adaptive immune activation. Activated NK cells, macrophages, and plasma cells promote CTL responses and antibody production, thereby enhancing systemic antitumor immunity after MWA.

Notes: Temperature values are approximate and may vary depending on tissue perfusion, exposure time, and water content. Outside the central coagulative zone, temperatures decrease sharply due to perfusion-mediated heat dissipation; thus, the sublethal range ($41\text{--}59^{\circ}\text{C}$) represents an expanded interpretation of this steep thermal gradient based on updated modeling and thyroid-specific data. This schematic illustration was adapted from Chu KF and Dupuy DE (*Thermal ablation of tumors: biological mechanisms and advances in therapy*, *Nature Reviews Cancer*, 2014; 14(3):199–208, doi: 10.1038/nrc3672) with modifications and additional immune-related mechanisms specific to thyroid tumor ablation.

Systemic Immunomodulation and Translational Implications

MWA not only destroys tumor tissue locally but also initiates a cascade of immune responses. The release of tumor-associated antigens and DAMPs activates antigen-presenting cells and stimulates both innate and adaptive immunity. This process converts an immunologically “cold” tumor into a “hot” one, enhancing systemic immune surveillance.^{52,58}

Systemic Immune Cell Dynamics After MWA

The dynamic variations in peripheral immune cells provide important insight into the systemic immunomodulatory effects of MWA. This treatment exerts both local and systemic actions—directly eliminating tumor cells through heat-induced cytotoxicity and indirectly activating immune responses in distant tissues.²⁶ Clinical studies in patients with papillary thyroid microcarcinoma (PTMC) have reported transient elevations in T-cell subsets following MWA. Specifically, CD3⁺ and CD4⁺ T cells, along with the CD4/CD8 ratio, significantly increase within the first two weeks post-procedure, accompanied by higher levels of interleukin-2 (IL-2) and interferon-gamma (IFN- γ). These changes typically return to baseline within one month, suggesting a temporary activation of cellular immunity.¹⁰² Comparable trends have been documented in other solid tumor ablation models, showing increased CD8⁺ T-cell activity and reduced regulatory T-cell populations.^{103,104} These alterations likely result from antigen release and DAMP-mediated activation rather than long-term lymphocyte proliferation.¹⁰⁵ Treatment parameters such as thermal dose and ablation volume also influence immune responses, providing a rationale for optimizing combination timing with immunotherapy.¹⁰⁶

Autoimmune Responses and Thyroid Function Changes

Most studies show that microwave ablation causes only mild, transient effects on thyroid function and autoantibody levels. In both benign and malignant nodules, thyroid hormones such as triiodothyronine (T3), free triiodothyronine (fT3), and free thyroxine (fT4) remain stable, while transient changes in thyroid-stimulating hormone (TSH) may occur shortly after treatment.¹⁰⁷ However, patients with pre-existing autoimmune thyroiditis or elevated thyroglobulin antibody (TGAb) and thyroid peroxidase antibody (TPOAb) levels may experience temporary antibody increases post-ablation.¹⁰⁸ In these cases, tissue injury and inflammatory activation can provoke short-lived autoimmune responses. Therefore, thyroid function and antibody levels should be closely monitored, particularly during the first week, first month, and subsequent three to twelve months after MWA. Continuous follow-up allows for early identification of persistent dysfunction and immune-related abnormalities.

Immune-Related Transcriptomic Reprogramming

Transcriptomic studies have demonstrated that MWA reshapes immune-related gene expression within both peripheral blood mononuclear cells (PBMCs) and the ablation microenvironment. Post-ablation analysis in low-risk thyroid cancer revealed suppression of nuclear factor kappa B (NF- κ B) signaling and downregulation of pro-tumor chemokines such as CXCL1, CXCL2, and CXCL8, while anti-tumor chemokine pathways including CXC receptor 3 (CXCR3) were upregulated.^{109,110} These transcriptional changes favor a Th1-dominant immune response consistent with DAMP-induced antigen presentation and T-cell priming.^{110,111} Microwave ablation also enhances innate immune signaling via pattern recognition receptor pathways, particularly Toll-like receptor (TLR) activation.¹¹² These transcriptomic alterations are time-dependent and influenced by heat intensity, tumor immune status, and host background. Multi-omics and longitudinal analyses integrating single-cell sequencing and immune profiling could further clarify the kinetics of immune activation and identify optimal therapeutic windows for combination immunotherapy.

Combination Strategies with Immunotherapy and Future Perspectives

Immune checkpoint inhibitors (ICIs) restore antitumor T-cell activity by blocking inhibitory pathways such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1/programmed death-ligand 1 (PD-1/PD-L1).¹¹³ Monoclonal antibodies targeting these checkpoints, including ipilimumab, nivolumab, and pembrolizumab, have shown durable responses across various solid tumors.^{114–116} Microwave ablation enhances the effects of ICIs by increasing antigen exposure and inducing immunogenic cell death. In preclinical models, combining MWA with PD-L1 blockade elevated CD8⁺ T-cell infiltration, improved immune memory formation, and enhanced tumor regression compared with

either therapy alone.^{116,117} This synergy likely arises from the release of tumor antigens and the reduction of immunosuppressive elements such as regulatory T cells and myeloid-derived suppressor cells.¹¹⁸

Although targeted agents such as tyrosine kinase inhibitors (TKIs) including vandetanib and cabozantinib are approved for advanced medullary thyroid carcinoma,¹¹⁹ clinical studies on MWA–ICI combination therapy in thyroid cancer remain limited. Key questions persist regarding the optimal timing of combination, the balance between thermal dosage and immune activation, and biomarkers predicting efficacy or immune-related toxicity.¹²⁰ Future studies should address these aspects to establish standardized regimens and confirm the translational potential of MWA–ICI therapy.

From a clinical perspective, the rationale for combining microwave ablation (MWA) with immunotherapy is likely to depend on both tumor histology and disease stage. In low-risk, well-differentiated papillary thyroid carcinoma (PTC), MWA may be considered as a local cytoreductive intervention that also functions as an *in situ* source of tumor antigens, potentially supporting post-ablation immune priming in carefully selected cT1–T2N0M0 patients. However, the current clinical evidence supporting thermal ablation in thyroid malignancies remains limited and is largely restricted to early-stage, well-differentiated disease.^{121–123} By contrast, clinical experience with immunotherapy in thyroid cancer has primarily accumulated in aggressive subtypes—particularly anaplastic thyroid carcinoma (ATC)—where immune checkpoint blockade and combination strategies have been more frequently explored.^{120,124,125}

Special time-sensitive clinical scenarios may also inform future translational considerations for thyroid ablation. In organ-donor settings, incidentally detected thyroid nodules require rapid and reliable risk stratification to avoid delays in organ procurement, and streamlined diagnostic approaches have been proposed to efficiently exclude clinically significant malignancy.^{126,127} These reports underscore real-world contexts in which prompt thyroid nodule assessment is essential, while prognostic associations of immunotherapy-related biomarkers, such as PD-L1, in follicular epithelial-derived thyroid carcinomas provide a broader biological rationale for continued interest in immune-informed ablation strategies.¹²⁸

In addition, MWA should not be considered interchangeable with other thermal ablation modalities, such as radio-frequency ablation (RFA) or laser ablation (LA). Differences in energy deposition and susceptibility to perfusion-mediated heat-sink effects may influence ablation geometry and thermal gradients. These biophysical distinctions could lead to divergent patterns of local inflammation and immune microenvironment remodeling, an important consideration when designing future ablation–immunotherapy combination trials.^{19,129}

Conclusion

Microwave ablation (MWA) offers a precise, minimally invasive treatment for thyroid tumors that integrates direct cytotoxicity with systemic immune activation. Through rapid tissue heating, MWA induces irreversible coagulative necrosis, protein denaturation, and cellular membrane disruption. These thermal injuries trigger multiple forms of programmed cell death—including apoptosis, pyroptosis, and ferroptosis—and promote the release of damage-associated molecular patterns (DAMPs) and heat shock proteins (HSPs). Together, these molecular events enhance dendritic cell activation, T-cell priming, and systemic antitumor immunity.

Within the ablation zone, vascular occlusion and transient hypoxia stimulate hypoxia-inducible factor 1- α (HIF-1 α) and vascular endothelial growth factor (VEGF) pathways, facilitating angiogenesis and tissue repair. Immune activation is strongest within the peripheral transitional zone, where sublethal heat stress promotes antigen release and dendritic cell priming. However, excessive remodeling may also foster fibrotic adaptation and tumor tolerance, highlighting the need to balance reparative and pro-tumor processes. Systemically, transient fluctuations in T-cell subsets, cytokine release, and autoimmune antibody levels reflect the dynamic immunoregulatory effects of MWA.

Collectively, these findings suggest that, beyond achieving local tumor destruction, MWA may influence the tumor immune microenvironment with potential implications for systemic immune regulation. Understanding these biological and immunological mechanisms will support the refinement of ablation parameters and inform future strategies combining MWA with immunotherapy. Ultimately, MWA may function as an *in situ* tumor vaccine, bridging local ablation and systemic antitumor response, and offering new insights into the integrative management of thyroid malignancies.

Overall, the integration of microwave ablation into immunologically informed treatment strategies for thyroid cancer will require further clinical validation, with particular attention to patient selection, disease stage, and procedural context.

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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