Eur. Cytokine Netw. Vol. 36, n° 3, *September 2025* 24-37

REVIEW ARTICLE

Igniting the Tumor: Targeting Mitochondrial Stress to Prime Breast Cancer for Immunotherapy

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To cite this article: Lin H-Y, Wu H-J, Chu P-Y. Igniting the Tumor: Targeting Mitochondrial Stress to Prime Breast Cancer for Immunotherapy. Eur. Cytokine Netw. 2025; 36(3): 24-37. doi: 10.1684/ecn.2025.0504

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Article accepted on 4 January 2026

ABSTRACT. Immunotherapy has demonstrated limited efficacy in immunologically "cold" breast cancers characterized by absent T-cell infiltration and inadequate interferon signaling. The purpose of this work is to propose and articulate a mechanistic and therapeutic framework in which mitochondrial stress is deliberately harnessed to convert immunologically "cold" breast tumors into "hot," T cell–inflamed, immunotherapy-responsive lesions. This review synthesizes emerging evidence positioning mitochondrial stress as a strategic lever to transform these immune-excluded tumors into inflamed, therapy-responsive lesions. We examine how mitochondrial dysfunction triggers cytosolic release of mitochondrial DNA (mtDNA), a potent damage-associated molecular pattern that activates the cGAS-STING pathway, initiating type I interferon responses and secretion of T-cell-recruiting chemokines such as CCL5 and CXCL10. This axis functions as a "double-edged sword"—while acute activation converts "cold" tumors into "hot" immune-responsive states, chronic engagement drives immunosuppressive cytokine networks and therapeutic resistance, with outcomes varying across breast cancer subtypes. We explore six combination therapeutic strategies: mitochondrial poisons, radiotherapy/chemotherapy, PARP/ATR inhibitors, metabolic reprogramming agents, mitochondrial quality control modulators, and localized mitochondrial stress induction, each paired with immune checkpoint blockade. The review emphasizes "controlled ignition" as a paradigm whereby precisely dosed mitochondrial stress amplifies tumor antigenicity and favorable cytokine landscapes while avoiding chronic immunosuppression. Cytokine networks emerge as both integrators and therapeutic targets of mitochondrial-immune crosstalk. Future advances require mapping subtype-specific thresholds, developing tumor-restricted delivery systems, and implementing biomarker-guided trials to safely harness mitochondrial stress, potentially redefining these organelles as programmable immunological adjuvants in breast cancer therapy.

Key words: breast cancer; mitochondrial stress; tumor microenvironment; immunotherapy; cgas; sting; cytokines

Breast cancer remains a leading cause of mortality worldwide [1], with triple-negative breast cancer (TNBC) being particularly aggressive due to its lack of hormone receptors [2]. While immunotherapy has revolutionized treatment for some, baseline response rates in breast cancer remain low because many tumors are immunologically "cold", characterized by T-cell exclusion and mitochondrial dysfunction [3, 4]. Priming strategies are essential to overcome these resistance mechanisms and improve survival outcomes across all molecular subtypes.

Immunologically "cold" breast tumors, particularly hormone receptor–positive and many HER2-enriched and triple-negative breast cancers (TNBC), show limited benefit from current immune checkpoint inhibitors because they lack robust T-cell infiltration, interferon signaling, and effective antigen presentation [5, 6]. This therapeutic ceiling has prompted a shift toward understanding and therapeutically exploiting tumor-intrinsic and microenvironmental mechanisms that govern immune exclusion, among which mitochondrial signaling has emerged as a central and druggable node [7].

Across current trials, only a minority of breast cancer patients—most notably a subset of PD L1–positive TNBC—achieve durable responses to checkpoint blockade [8-12], with luminal and many HER2 positive tumors remaining largely non responsive [13-15]. TNBC typically displays higher mutational burden, greater chromosomal instability [2, 16, 17], and more frequent baseline activation of the cGAS–STING axis, leading to partially inflamed, 'hot leaning' immune phenotypes [18, 19], whereas hormone receptor–positive luminal tumors are often immune excluded with low TILs and

doi: 10.1684/ecn.2025.0504

cytokine milieus dominated by TGF-β and IL-10 [6, 13, 20, 21]. These subtype specific immune and cytokine landscapes imply that strategies harnessing mitochondrial stress to prime immunotherapy must be tailored—using relatively modest perturbation in TNBC to avoid chronic immunosuppression, and more intensive or repeated priming regimens, often combined with cytokine/myeloid targeted agents, in luminal and HER2 enriched disease.

Traditionally viewed as bioenergetic engines, mitochondria in breast cancer cells and infiltrating immune cells are now recognized as hubs integrating metabolism, redox state, cell death pathways, and innate immune sensing to shape the tumor immune microenvironment [22-25]. Recent work shows that mitochondrial dysfunction, altered dynamics, and metabolic rewiring in breast tumors influence antigen presentation, oxidative stress, and susceptibility to immunogenic cell death [7], while mitochondrial fitness in T cells, NK cells, and myeloid cells critically determines their effector function within the hostile breast tumor niche [26].

A key conceptual advance is that mitochondrial stress can convert organelles into platforms for innate immune activation through release of mitochondrial DNA (mtDNA) and other damage-associated molecular patterns (DAMPs) into the cytosol [27-29]. These mitochondrial signals engage pathways such as cGAS–STING to induce type I interferons and chemokines that orchestrate dendritic cell activation and T-cell recruitment, suggesting that controlled mitochondrial perturbation in breast cancer may help drive "cold-to-hot" transition required for effective immunotherapy.

Within this framework, mitochondria move from passive metabolic supporters to master regulators of breast tumor immunity whose stress responses can be pharmacologically tuned. The following sections will dissect how mtDNA–cGAS–STING signaling, its downstream cytokine and chemokine networks, and the context-dependent consequences of mitochondrial stress can be leveraged—alone and in combination with checkpoint blockade—to "ignite" non-immunogenic breast cancers and improve the depth and durability of immunotherapy responses (*figure 1*).

MITOCHONDRIA AS MASTER REGULATORS OF THE TUMOR IMMUNE MICROENVIRONMENT

Mitochondria shape the tumor immune microenvironment (TIME) through their control of cancer cell metabolism, redox balance, organelle quality, and innate immune signaling, thereby influencing how visible tumor cells are to the immune system and how effective antitumor effector cells can be [26]. In breast cancer, dysregulated mitochondrial dynamics, biogenesis, and oxidative phosphorylation (OXPHOS) not only fuel proliferation and metastasis but also remodel antigen presentation, cytokine production, and susceptibility to T-cell–mediated killing, while mitochondrial fitness in tumor-infiltrating lymphocytes and macrophages critically determines whether the TIME is "hot" or "cold" [26].

Mitochondrial dynamics and cancer cell immunogenicity

In breast cancer, metastatic and stem-like populations typically display enhanced mitochondrial fission and fragmented networks driven by factors such as DRP1 and related fission mediators, whereas more fused mitochondrial architectures are associated with lower metastatic potential and reduced aggressiveness [30]. Imbalanced dynamics have dual effects on immunogenicity: excessive fission promotes mitochondrial reactive oxygen species (mtROS), mtDNA damage, and neoantigen generation, yet also downregulates MHC-I antigen presentation and favors secretion of immunosuppressive mediators, enabling immune escape despite increased mutational load [31].

Biogenesis, mitophagy, and danger signaling

Coordinated mitochondrial biogenesis and mitophagy maintain organelle quality, whereas defective turnover permits accumulation of damaged mitochondria that leak mtROS and mtDNA, acting as DAMPs [32]. These signals can engage pathways such as cGAS–STING and NF-κB to induce type I interferons and inflammatory cytokines that, in principle, enhance dendritic cell activation and T-cell priming, but chronic, unrestrained stress skews toward immunosuppressive transcriptional programs and checkpoint upregulation, shaping a tolerant TIME [33].

OXPHOS, ROS, and antigen presentation

Breast cancer cells flexibly toggle between glycolysis and OXPHOS; high OXPHOS states provide ATP and anabolic intermediates but also generate mtROS that influence both cell death and immune visibility [34]. Moderate mitochondrial stress and ROS can promote immunogenic cell death with exposure of calreticulin, ATP release, and cGAS–STING-dependent interferon signaling, whereas excessive ROS and fragmented mitochondria impair MHC-I expression, reduce antigen presentation, and enhance secretion of factors such as IL-10 that dampen cytotoxic T-cell function [26].

Mitochondrial control of T cells in the TIME

Tumor-infiltrating $CD8^+$ T cells in solid tumors frequently exhibit mitochondrial defects, including reduced mitochondrial mass, impaired OXPHOS, and dysfunctional dynamics, which collectively drive exhaustion and limit effector cytokine production [35, 36]. Interventions that restore mitochondrial fitness—such as improving mitochondrial content and respiratory capacity through metabolic conditioning or exercise—enhance T-cell persistence, granzyme production, and tumor control, highlighting mitochondria as central regulators of T-cell functionality in "hot" versus "cold" environments [37].

Macrophages, ROS, and polarization

Tumor-associated macrophages (TAMs) integrate environmental cues via mitochondrial metabolism, with

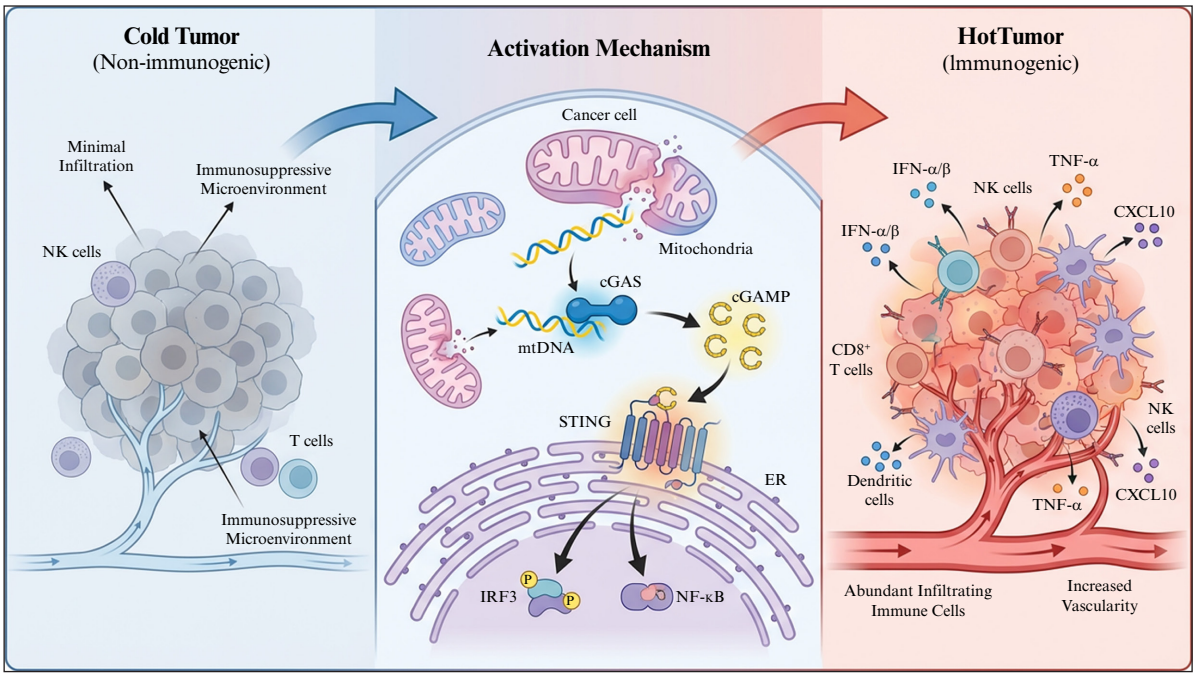

Figure 1.
The mtDNA-cGAS-STING pathway bridges cold and hot tumor phenotypes. ***Left:*** immune excluded cold tumor with poor T cell infiltration and immunosuppressive microenvironment. ***Center:*** mitochondrial damage, mtDNA release, cGAS activation and cGAMP mediated STING signaling. ***Right:*** type I interferon and chemokine induction (e.g., CXCL10, CCL5) promoting CD8 T cells, NK cells and dendritic cell recruitment and hot tumor phenotype. mtDNA: mitochondrial DNA. cGAS: cyclic GMP–AMP synthase. cGAMP: 2'3'-cyclic GMP–AMP. STING: stimulator of interferon genes. IFN: interferon (typically type I interferons, IFN-α/β, in this context). CCL5: C–C motif chemokine ligand 5. CXCL10: C–X–C motif chemokine ligand 10. CD8 T cells: CD8-positive T lymphocytes. NK cells: natural killer cells.

OXPHOS- and fatty acid oxidation–driven programs favoring M2-like, immunosuppressive phenotypes and more glycolytic, ROS-producing states supporting pro-inflammatory, M1-like functions [36]. Mitochondrial reprogramming in TAMs, influenced by tumor-derived metabolites and acidity, can thus either sustain immune evasion or, when redirected, promote antigen presentation, cytokine production, and cross-priming of CD8+ T cells within the breast TIME [36, 38].

Bidirectional mitochondrial crosstalk in the tumor microenvironment

Beyond cell-autonomous effects, tumor and immune cell mitochondria engage in bidirectional metabolic crosstalk. Tumor-derived lactate, kynurenine, and adenosine suppress T-cell OXPHOS and promote exhaustion [39, 40], while robust mitochondrial fitness in infiltrating T cells and NK cells sustains granzyme and IFN-γ production that, in turn, induces tumor mitochondrial stress, mtDNA release, and cGAS–STING activation [41, 42]—creating a reinforcing loop.

Integrating cancer and immune cell mitochondria

Collectively, mitochondrial dynamics, biogenesis, and OXPHOS in breast cancer cells dictate the balance between immunogenic stress signals and immune evasion, while mitochondrial health in T cells and macrophages governs effector capacity and polarization. This multi-compartment mitochondrial network positions mitochondria as master regulators of the TIME and provides a mechanistic basis for strategies that deliberately impose "controlled" mitochondrial stress to enhance antigen presentation, type I interferon and chemokine production, and ultimately the efficacy of breast cancer immunotherapy.

THE MTDNA–CGAS–STING AXIS: A PIVOTAL INNATE IMMUNE SENSING PATHWAY IN CANCER

The mitochondrial DNA (mtDNA)–cGAS–STING axis has emerged as a central innate immune sensing pathway that links organelle stress to inflammatory and antitumor signaling in cancer [43, 44]. In breast tumors and other solid malignancies, diverse mitochondrial insults can drive leakage of mtDNA into the cytosol, where it is recognized as a foreign-like nucleic acid, thereby triggering cGAS–STING–dependent type I interferon and chemokine responses that shape the tumor immune microenvironment [44]. *Figure 2* illustrates mechanism of cytosolic DNA sensing via cGAS-STING triggers a coordinated innate immune response.

Mitochondrial stress and mtDNA destabilization

Oncogenic signaling, hypoxia, metabolic overload, and therapy-induced damage all impose chronic stress on tumor cell mitochondria, leading to elevated ROS, impaired replication, and accumulation of oxidatively damaged mtDNA [32]. When mitophagy and mitochondrial quality control are compromised, these damaged genomes persist, increasing the likelihood that nucleoids will be mispackaged, clustered, or exposed at sites of

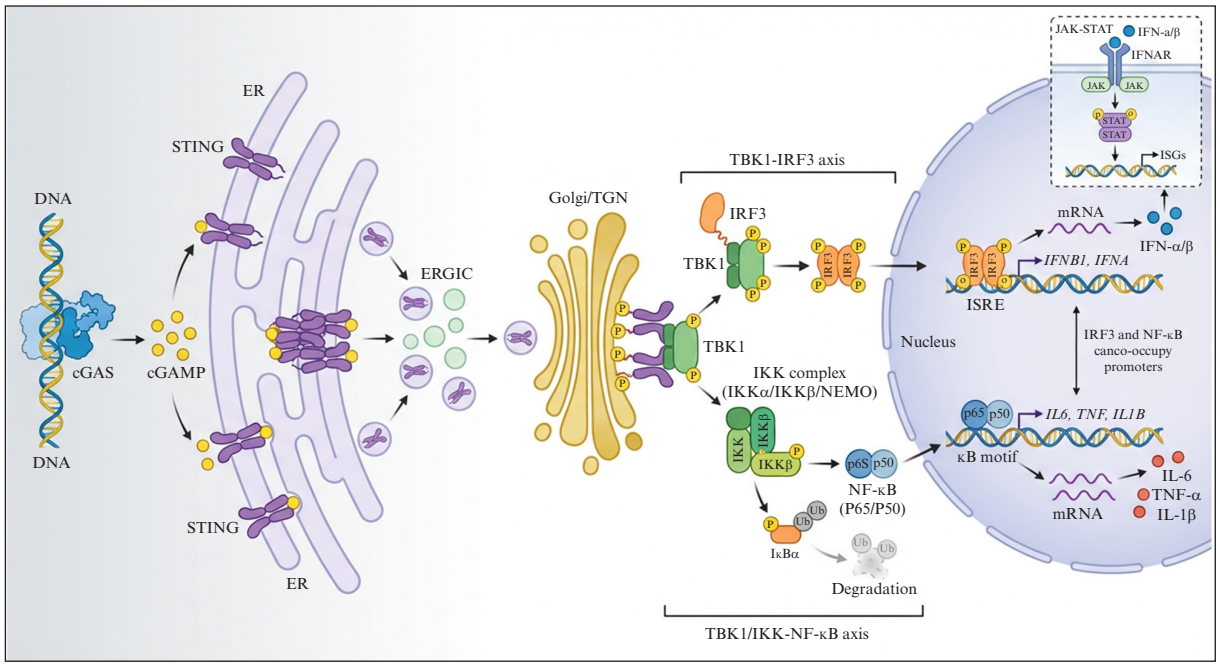

Figure 2.
Downstream signaling of cGAS–STING. Cytosolic DNA activates cGAS to produce cGAMP, which binds ER-resident STING and drives its trafficking to Golgi compartments. STING then engages TBK1–IRF3 to induce type I interferons and IKK–NF-κB to induce pro-inflammatory cytokines such as IL-6 and TNF-α. cGAS: cyclic GMP–AMP synthase. cGAMP: 2'3'-cyclic GMP–AMP. STING: stimulator of interferon genes. ER: endoplasmic reticulum. TBK1: TANK-binding kinase 1. IRF3: interferon regulatory factor 3. IKK: IκB kinase. NF-κB: nuclear factor-κB. IL-6: interleukin-6. TNF-α: tumor necrosis factor alpha. IFN: interferon (type I interferons, IFN-α/β).

membrane instability that predispose them to escape the organelle [45].

Routes of mtDNA release into the cytosol

Multiple, partially overlapping mechanisms mediate mtDNA efflux from stressed mitochondria. BAX/BAK macropores formed during mitochondrial outer membrane permeabilization can allow inner membrane "herniations" that carry nucleoids through the outer membrane, releasing mtDNA into the cytosol even under sublethal, minority mitochondrial outer membrane permeabilization (MOMP) conditions [45]. In parallel, opening of the mitochondrial permeability transition pore and voltage-dependent anion channel (VDAC)-dependent permeabilization increase inner membrane leakage, while impaired mitophagy and mitochondrial-derived vesicles can misdirect mtDNA-containing material to the cytosol rather than to lysosomal degradation, sustaining low-level DNA leakage without overt cell death [45, 46].

Cytosolic mtDNA as a DAMP sensed by cGAS

Once in the cytoplasm, mtDNA behaves as a potent damage-associated molecular pattern because of its bacterial ancestry, circular form, and relative CpG enrichment, features that distinguish it from well-packaged nuclear chromatin. The cytosolic DNA sensor cyclic GMP–AMP synthase (cGAS) binds double-stranded mtDNA in a largely sequence-independent manner, and DNA binding promotes cGAS dimerization and higher-order oligomerization, which in turn catalyzes synthesis of the cyclic dinucleotide 2′3′-cGAMP from ATP and GTP [45]. This enzymatic step converts the presence of mtDNA into a diffusible second messenger that can act cell-autonomously or spread to neighboring cells and immune populations via transport mechanisms such as gap junctions or extracellular vesicles [45, 46].

STING engagement and downstream signaling

STING, an adaptor protein residing on the endoplasmic reticulum, binds cGAMP and undergoes conformational changes that drive its oligomerization and trafficking from the ER to perinuclear compartments, including the ER–Golgi intermediate compartment and Golgi [47]. In these locations, STING recruits and activates TBK1 and IKK kinases, leading to phosphorylation and nuclear translocation of IRF3, together with NF-κB activation, thereby inducing a transcriptional program dominated by type I interferons, interferon-stimulated genes, and inflammatory chemokines such as CXCL10 and CCL5 that are critical for dendritic cell activation and effector T-cell recruitment [27, 43, 48].

In cancer biology, the mtDNA–cGAS–STING pathway functions as a molecular bridge between mitochondrial integrity, cell death pathways, and adaptive immune priming. Transient, therapy- or stress-induced mtDNA release can promote immunogenic cell death, enhance antigen presentation, and convert poorly infiltrated "cold" tumors into inflamed lesions more amenable to checkpoint blockade, whereas chronic or deregulated activation may drive tolerogenic or immunosuppressive feedback, contributing to immune evasion [43].

Understanding how distinct forms and magnitudes of mitochondrial stress control mtDNA leakage and cGAS–STING activation is therefore pivotal for rationally designing interventions that harness this axis to ignite productive antitumor immunity in breast cancer.

A DOUBLE-EDGED SWORD: CONTEXT-DEPENDENT OUTCOMES OF STING ACTIVATION

Downstream of the cGAS-STING axis (detailed in *Figure 2*), the immunological outcome is dictated by the temporal dynamics of signaling. Transient activation successfully 'ignites' the tumor by triggering an acute type I interferon wave that is crucial for dendritic cell cross-priming. In breast cancer, this context dependence is particularly evident across molecular subtypes, where STING can either ignite productive antitumor immunity or, when chronically engaged, foster immune evasion, stromal remodeling, and therapeutic resistance [49].

Igniting antitumor immunity: from "cold" to "hot"

Acute or well-timed STING activation in the tumor microenvironment triggers a robust type I interferon program that enhances dendritic cell maturation, cross-priming of CD8+ T cells, and natural killer (NK) cell activation [50-52]. Downstream of IRF3 and NF-κB, STING stimulation induces chemokines such as CXCL9, CXCL10, and CCL5, which drive recruitment and retention of effector T cells and NK cells, facilitating conversion of immune-desert or immune-excluded lesions into inflamed, T cell–infiltrated tumors [53-57]. Preclinical models show that intratumoral or systemic STING agonists can induce IFN-I–dependent tumor regression, promote trafficking of antigen-bearing myeloid cells to draining lymph nodes, and synergize with checkpoint blockade to deepen and prolong responses [58-60]. In breast cancer, transcriptomic and immunologic analyses indicate that tumors with intact cGAS–STING signaling and high STING-driven chemokine signatures are more likely to display "hot" immune phenotypes and enhanced sensitivity to immunotherapy, particularly in subsets of triple-negative disease [61-63].

Fueling resistance and immunosuppression

In contrast, chronic or dysregulated STING activation can skew cytokine output toward protumor inflammation, immunosuppression, and tissue remodeling [64]. Sustained NF-κB and inflammasome engagement downstream of STING promotes production of IL-6, TNF-α, and TGF-β, which support myeloid-derived suppressor cell and regulatory T-cell expansion, drive fibrosis and aberrant angiogenesis, and ultimately dampen effective cytotoxic T-cell function [49, 65, 66]. Breast cancer studies highlight that STING pathway status and output differ across luminal, $HER2^{+}$, and TNBC subtypes, with prolonged or maladaptive activation linked to epithelial–mesenchymal transition, resistance to HER2-targeted therapy, and upregulation of checkpoints such as PD-L1 [67, 68]. Moreover, tumor-intrinsic mechanisms (for example, MYC-driven repression or selective loss of cGAS/STING components) can either silence beneficial signaling or bias it toward tolerogenic cytokine profiles, underscoring that therapeutic strategies must carefully calibrate the intensity and duration of STING engagement to avoid tipping from immune activation into immune escape [29, 43, 69].

Despite the therapeutic potential of the STING pathway, its systemic activation poses significant safety risks, including cytokine release syndrome and T-cell apoptosis driven by excessive type I interferons. Clinical data from first-generation STING agonists revealed that unconstrained signaling can lead to dose-limiting systemic inflammation and autoimmunity [70]. To mitigate these 'dark side' effects, current strategies employ tumor-restricted delivery systems, such as mitochondria-targeted nanocarriers or pH-responsive polymers, which localize the 'ignition' signal to the tumor microenvironment. This spatial control is critical to uncouple the beneficial antitumor immunity from detrimental systemic toxicity, ensuring that mitochondrial stress serves as a precise adjuvant rather than a systemic toxin [70, 71].

Although preclinical models clearly distinguish acute, beneficial mitochondrial stress from chronic, suppressive stress, this threshold is not yet quantitatively defined in clinical settings. In practice, it will likely need to be operationalized using dynamic pharmacodynamic readouts rather than fixed dose or time cut-offs. Short-lived surges in type I IFNs and T-cell–recruiting chemokines such as CXCL9, CXCL10, and CCL5 [49, 72-76], without sustained elevation of IL6, IL8, IL10, or TGFβ [77, 78], may represent a desirable 'ignition' pattern, whereas persistent pro-tumor inflammatory and immunosuppressive cytokine signatures would signal a shift into detrimental chronic stress. Early-phase trials of mitochondrial stress–based regimens should therefore incorporate serial cytokine profiling and interferon-stimulated gene signatures, together with careful toxicity monitoring, to empirically define safe and effective activation windows.

CYTOKINE NETWORKS: FUNCTIONAL READOUTS AND INTEGRATORS OF MITOCHONDRIAL-IMMUNE CROSSTALK

Cytokine networks sit at the interface of mitochondrial stress, cGAS–STING activation, and the emergent immune phenotype of breast tumors, acting both as readouts of underlying organelle-immune crosstalk and as active sculptors of the tumor microenvironment [79]. In this context, distinct cytokine signatures—ranging from interferon- and chemokine-dominated pro-inflammatory profiles to IL-6/IL-10/TGF-β–rich immunosuppressive states—provide mechanistic insight into mitochondrial and STING pathway activity (*figure 3*), while serving as prognostic biomarkers and therapeutic targets in breast cancer.

Cytokines as readouts of mitochondrial–STING signaling

Acute mitochondrial stress with controlled mtDNA release typically engages cGAS–STING and drives a type

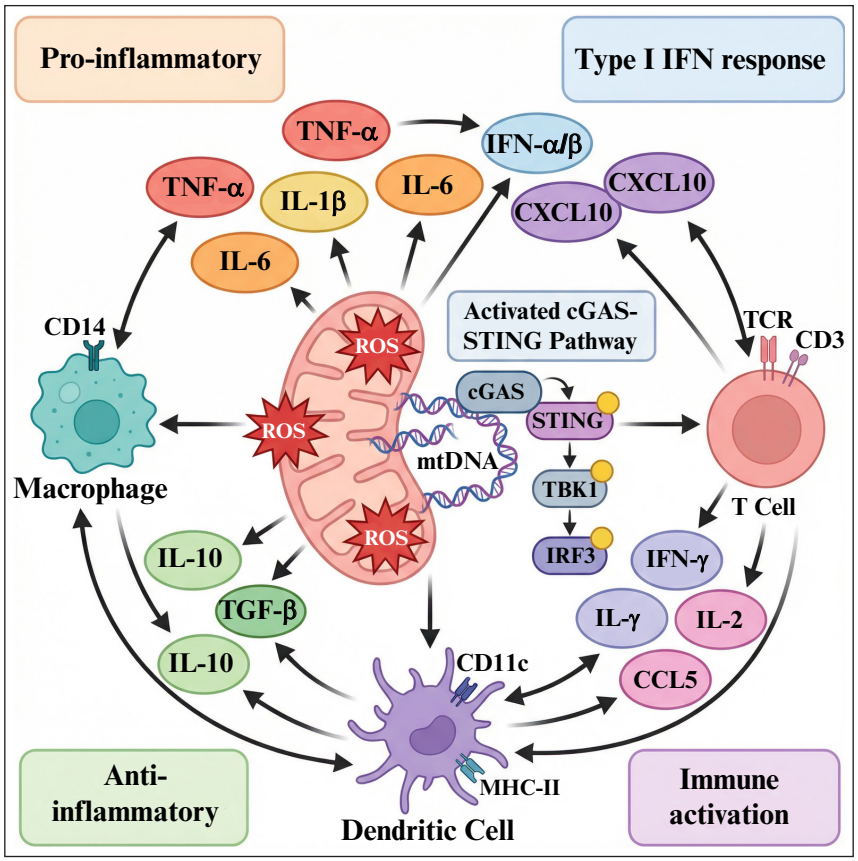

Figure 3.
Cytokine networks integrating mitochondrial stress and cGAS–STING activation. Mitochondrial ROS and mtDNA release trigger cGAS–STING signaling in tumor and immune cells, shaping production of interferons, chemokines (e.g., CXCL10) and immunosuppressive cytokines (e.g., IL 10, TGF β). The balance of these cytokines determines whether the breast tumor microenvironment is pro inflammatory or immunosuppressive. ROS: reactive oxygen species. mtDNA: mitochondrial DNA. cGAS: cyclic GMP–AMP synthase. STING: stimulator of interferon genes. IFN: interferon (mainly type I interferons, IFN α/β). CXCL10: C X C motif chemokine ligand 10. CCL5: C C motif chemokine ligand 5. IL 10: interleukin 10. TGF β: transforming growth factor beta. IL 6: interleukin 6. IL 1β: interleukin 1 beta. TNF α: tumor necrosis factor alpha. TCR: T cell receptor. TBK1: TANK binding kinase 1. TBK3: TANK binding kinase 3 (also known as IKK ε).

I interferon program characterized by IFN-α/β, interferon-stimulated genes, and T-cell–recruiting chemokines such as CXCL9, CXCL10, and CCL5 [43, 44, 80]. These cytokines correlate with enhanced dendritic cell activation, improved antigen presentation, and higher densities of cytotoxic and memory T cells in the tumor, reflecting a "hot," inflamed microenvironment that is more permissive to checkpoint blockade. In contrast, chronic or dysregulated STING and mitochondrial stress can shift the cytokine output toward IL-6, IL-1β, TNF-α, IL-8, IL-10, and TGF-β, reflecting an exhausted or rewired STING axis and establishing a milieu that supports myeloid-derived suppressor cells, regulatory T cells, and tumor-promoting inflammation [81].

Pro-inflammatory versus immunosuppressive cytokine profiles in breast cancer

Recent systematic and multiplex analyses in breast cancer show that elevated pro-tumor inflammatory and immunosuppressive cytokines—especially IL-6, TNF-α, IL-1β, IL-8, IL-10, and TGF-β—associate with higher stage, increased metastasis, and poorer survival, underscoring their value as negative prognostic biomarkers [20, 79, 82]. Conversely, signatures enriched for IL-12, IFN-γ, and interferon-induced chemokines correlate with more effective antitumor immunity, higher tumor-infiltrating lymphocyte scores, and better outcomes or improved response to immunotherapy in selected breast cancer cohorts [83]. Spatial and transcriptomic studies further reveal that many breast tumors display "mixed" cytokine niches, where immunostimulatory and suppressive factors coexist, highlighting that the net functional state of the cytokine network—rather than any single mediator—captures the integrated output of mitochondrial, STING, and cellular stress signaling [84, 85].

Cytokine signatures as biomarkers and therapeutic targets

Because cytokine patterns reflect upstream mitochondrial integrity and cGAS–STING activity, composite cytokine signatures are increasingly explored as biomarkers to stratify patients, forecast immunotherapy benefit, and monitor pharmacodynamic responses to mitochondrial- or STING-targeted agents [20, 69]. Clinical and translational studies support the development of cytokine-based indices (for example, IL-6/IFN-γ ratios or multi-cytokine panels) and systemic inflammation scores as predictors of prognosis and treatment response in breast cancer, including

inflammatory and immune-enriched subtypes [20, 86]. At the same time, cytokines themselves are being targeted or harnessed therapeutically: blockade of IL-6, IL-1β, or TGF-β aims to dismantle mitochondrial stress–driven immunosuppressive circuits, while agonistic strategies or engineered delivery of IL-12, IFN-α/β, or IFN-γ seek to amplify STING-induced pro-inflammatory signaling and consolidate cold-to-hot conversion [87-89].

While STING activation is essential for priming antitumor immunity, its consequences are highly subtype-dependent. In Triple-Negative Breast Cancer (TNBC), DNA damage-induced STING signaling predominantly drives a type I interferon response (IFN-α/β) and the secretion of CXCL10 and CCL5, which correlates with prolonged progression-free survival by recruiting CD8+ cytotoxic T lymphocytes [29]. Conversely, in hormone receptor-positive (Luminal A/B) subtypes, chronic low-level STING activation is frequently linked to an immunosuppressive cytokine milieu rich in IL-6 and TGF-β, which promotes macrophage polarization toward an M2-like phenotype and facilitates therapeutic resistance [66]. Furthermore, recent profiling of "hot" versus "cold" tumors confirms that a sustained pro-inflammatory cytokine signature (IFN-γ, IL-12, CXCL9] is the primary determinant of cytolytic activity, whereas "cold" tumors exhibit elevated TGF-β and IL-10 levels that blunt mitochondrial stress signals [71]. *Table 1* summarizes differential cytokine signatures and mitochondrial stress responses across breast cancer subtypes. Taken together, cytokine networks can be viewed as dynamic integrators that encode the balance between beneficial and detrimental consequences of mitochondrial stress and cGAS–STING signaling in breast tumors. By reading out these cytokine states—and selectively modulating them with antibodies, receptor traps, or cytokine/chemokine agonists—future therapies may both report on and recalibrate mitochondrial-immune crosstalk, enabling rational combination regimens that align controlled mitochondrial stress, STING activation, and a favorable cytokine landscape to support durable antitumor immunity.

THERAPEUTIC STRATEGIES TO EXPLOIT MITOCHONDRIAL STRESS FOR IMMUNOTHERAPY

Mitochondrial stress represents a tractable lever to convert breast tumors from immune-deserted to inflamed states, but it must be engaged in a controlled, context-sensitive manner to avoid tipping into chronic immunosuppression. *Figure 4* demonstrates mitochondria-centric strategies of combination therapy. Targeting mitochondrial function, mtDNA–cGAS–STING signaling, and associated cytokine networks has therefore become a focus of translational efforts to improve immunotherapy responses in solid tumors, including breast cancer [43, 69, 90].

Inducing controlled mitochondrial stress to trigger immunity

Several classes of agents can induce mitochondrial stress in a way that favors acute, immunogenic signaling

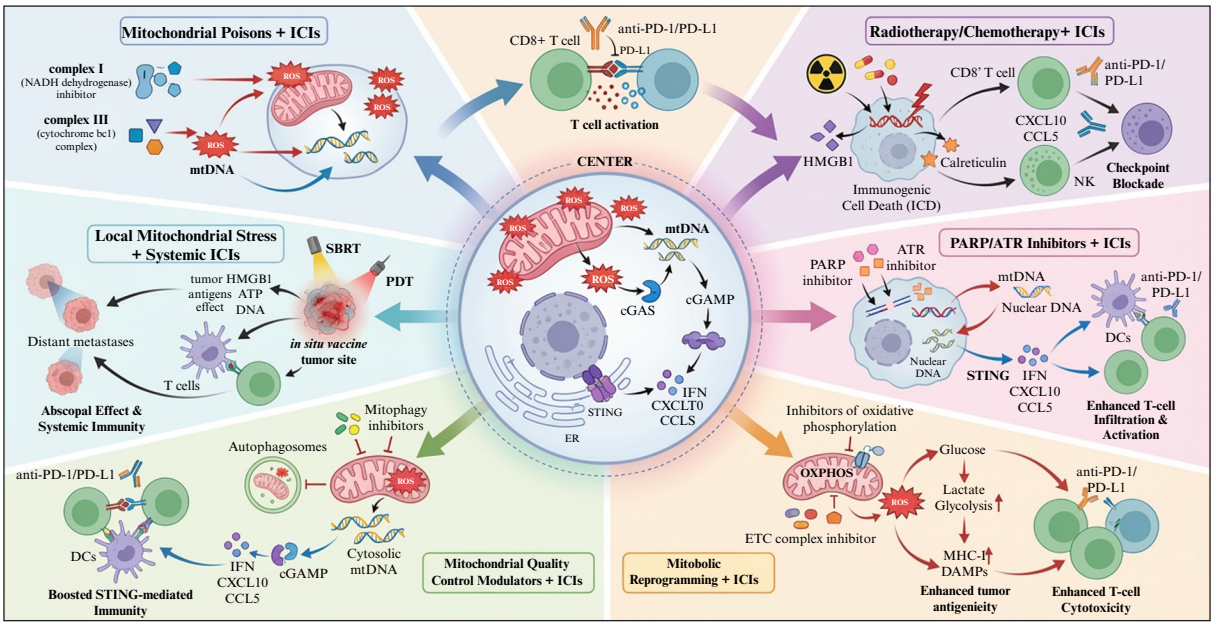

Figure 4.

Mitochondria targeting combination strategies to enhance immunotherapy. ***Center:*** mitochondrial stress in cancer cells increases ROS, mtDNA release and cGAS–STING–dependent interferon and chemokine production. ***Surrounding panels:*** examples of strategies including low dose mitochondrial poisons, radiotherapy/chemotherapy, PARP/ATR inhibitors, metabolic reprogramming agents, mitophagy modulators and local mitochondrial stress combined with systemic checkpoint blockade. mtDNA: mitochondrial DNA. ROS: reactive oxygen species. cGAS: cyclic GMP–AMP synthase. STING: stimulator of interferon genes. IFN: interferon (here primarily type I interferons, IFN-α/β). CXCL9: C-X-C motif chemokine ligand 9. CXCL10: C-X-C motif chemokine ligand 10. CCL5: C-C motif chemokine ligand 5. IL-6: interleukin-6. IL-8: interleukin-8. IL-10: interleukin-10. IL-12: interleukin-12. TNF-α: tumor necrosis factor alpha. TGF-β: transforming growth factor beta. OXPHOS: oxidative phosphorylation. FAO: fatty acid oxidation. DDR: DNA damage response. DAMPs: damage-associated molecular patterns. ISG: interferon-stimulated gene. MDSC: myeloid-derived suppressor cell. TAM: tumor-associated macrophage.

Table 1.
Differential cytokine signatures and mitochondrial stress responses across breast cancer subtypes.

Breast Cancer Subtype	Baseline Immune Phenotype	Dominant Cytokine Signature (Baseline)	Mitochondrial Stress / STING Response Potential	Pro-Inflammatory Output (Target)	Immunosuppressive Risks (Avoid)
Luminal A / B ($HR^+/HER2^-$)	"Cold" / immune-excluded with low TILs and prominent myeloid–stromal barriers that prevent effective T-cell entry [91]	Cytokine milieu dominated by TGF-β, IL-10, and CXCL12, produced by cancer-associated fibroblasts and M2-like macrophages, reinforcing T-cell exclusion and immune paralysis [91]	Intrinsic signaling (e.g., ER-driven transcriptional programs) tends to dampen cGAS–STING activation, resulting in low basal mitochondrial–STING responsiveness and weak spontaneous type I IFN signaling [66]	Therapeutic mitochondrial stress aimed at inducing type I IFNs (IFN-α/β) and CCL5 may help overcome the exclusion barrier and initiate de novo CD8+ T-cell recruitment into these tumors [66]	Chronic or uncalibrated stress risks upregulating IL-6 and IL-1β, fostering fibrosis, stromal remodeling, and endocrine-therapy resistance through an inflammatory feedback loop [71].
HER2-Enriched ($HER2^+$)	Intermediate / mixed phenotype, with some tumors exhibiting "hot" features under HER2-directed therapy but others remaining immune-desert or myeloid-dominant [92]	IL-6, TNF-α, and CCL2 are frequently elevated and contribute to HER2-targeted therapy resistance by expanding cancer stem-like populations and sustaining chronic inflammation [93]	HER2 signaling and downstream PI3K/AKT can attenuate STING, but HER2 blockade or antibody–drug conjugates can restore mtDNA–cGAS–STING activity, creating windows of enhanced innate immune sensing [66]	Properly timed mitochondrial stress combined with HER2-targeted agents can boost CXCL9, CXCL10, and IFN-γ, thus enhancing ADCC and cytotoxic T-cell retention within the tumor bed [92]	Excess or prolonged activation favors TGF-β and VEGF upregulation, promoting angiogenesis, epithelial–mesenchymal transition (EMT), and escape from HER2-directed therapy [71]
Triple-Negative (TNBC)	Often exhibits a partially "hot" phenotype with higher mutational burden and greater baseline TILs, but many cases remain functionally exhausted due to strong checkpoint and myeloid suppression [71]	Baseline inflammatory milieu enriched for IFN-γ, CXCL10, and IL-8, reflecting chronic genomic stress and ongoing innate immune sensing, yet counterbalanced by PD-L1 and immunosuppressive myeloid cells [63]	High chromosomal instability and cytosolic DNA burden confer high intrinsic cGAS–STING activation, although this signaling can be diverted toward protumor inflammation when NF-κB dominates over IRF3 [29]	Controlled mitochondrial stress or pharmacologic STING agonism can amplify IFN-α/β, IL-12, CXCL9, CXCL10, and CCL5, thereby reinvigorating exhausted T cells and strengthening T-cell trafficking into TNBC lesions [66, 94]	

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; TIME, tumor immune microenvironment; mtDNA, mitochondrial DNA; cGAS, cyclic GMP–AMP synthase; STING, stimulator of interferon genes; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; IFN, interferon; TILs, tumor-infiltrating lymphocytes.

rather than catastrophic organelle failure or chronic inflammation [95]. Low-dose mitochondrial poisons (for example, complex I or III inhibitors, mild uncouplers) and selected radiotherapy or chemotherapy regimens can enhance mtROS, promote mtDNA oxidation and release, and stimulate cGAS–STING–dependent type I interferon and chemokine production without immediately triggering irreversible cell death in all tumor cells [27, 28, 89]. However, because mitochondria are essential for neurons, cardiomyocytes, and hematopoietic cells, systemic or prolonged inhibition of respiratory complexes or mitophagy carries substantial risks of neurotoxicity, cardiotoxicity, and myelosuppression [96-104]. In a 'controlled ignition' framework, these agents are therefore best deployed as short, sublethal priming pulses, ideally using tumorrestricted delivery systems or local administration [105-110], with pharmacodynamic monitoring of both cytokine output and organ toxicity to avoid sustained offtumor mitochondrial damage. Precision dosing and scheduling are crucial to maintain "sublethal" stress that allows sufficient antigen processing and cytokine elaboration, rather than overwhelming necrosis that floods the microenvironment with tolerogenic DAMPs and suppressive cytokines [34, 88].

A second strategy exploits targeted modulation of mitochondrial quality-control pathways. Pharmacologic or genetic interference with mitophagy and nucleoid maintenance (for example, via modulation of TFAM, PINK1/Parkin signaling, or mitochondrial proteases) can increase the pool of damaged mitochondria and facilitate mtDNA leakage into the cytosol, thereby amplifying cGAS–STING activation and type I interferon responses [32, 45, 46]. When carefully titrated, such interventions enhance immunogenic signaling, but excessive or prolonged blockade risks accumulation of dysfunctional mitochondria, chronic NFκB–biased output, and a shift toward IL6/IL10/TGFβ–dominated immunosuppressive states [43, 81, 111].

Third, mitochondria-targeted delivery systems and nanomedicines are being developed to impose spatially restricted stress. Conjugating chemotherapeutics, photosensitizers, or redox-active molecules to mitochondria-targeting moieties (such as triphenylphosphonium)

or encapsulating STING-stimulating payloads in mitochondria-accumulating nanocarriers enables direct organelle engagement at lower systemic doses, enhancing immunogenic cell death, mtDNA release, and STING-driven chemokine production within the tumor while limiting off-tumor toxicity [87, 89, 90]. Photosensitizer- or radiotherapy-based mitochondria-targeted approaches are particularly attractive for localized disease or oligometastatic settings, where temporal control of light or dose can be synced with immunotherapy cycles to maximize acute immune activation [49, 112].

Finally, metabolic reprogramming agents—such as inhibitors of OXPHOS, fatty acid oxidation, or glutamine metabolism—can be used to reshape mitochondrial function in both tumor and immune compartments. In tumor cells, transient OXPHOS inhibition can augment ROS, enhance antigenicity, and increase susceptibility to T-cell killing [26, 34]. In T cells, interventions that improve mitochondrial biogenesis and spare respiratory capacity—through exercise-mimetic strategies, PGC1α activation, or cytokine support—can restore effector function and resilience in the nutrient-poor tumor microenvironment [35-37]. Here, a central challenge is separating beneficial stress in tumor cells from detrimental exhaustion in effector cells, necessitating careful attention to timing, dosing, and cell-type specificity.

Rational combination therapies: pairing mitochondrial modulators with checkpoint blockade

Because mitochondrial stress and cGAS–STING activation principally function as priming and inflaming signals, they naturally complement checkpoint blockade, which acts downstream to unleash pre-existing or nascent T-cell responses [64]. A central concept is to use mitochondrial modulators as "ignition" agents that increase tumor antigenicity, dendritic cell activation, and chemokine-driven T-cell trafficking, while PD1/PDL1 or CTLA4 blockade prevents exhaustion of the recruited effector pool [43, 69, 113]. In preclinical breast and other solid tumor models, sequencing mitochondrial stress–inducing chemotherapy, radiation, or targeted agents before or concurrent with checkpoint inhibitors enhances infiltration of $CD8^+$ T-cells and NK cells, elevates CXCL9/CXCL10/CCL5 levels, and improves response rates compared with checkpoint blockade alone [53, 58-60].

Rational combinations can be organized along several axes. Mechanistically, agents that induce mtDNA release or immunogenic cell death—such as selected DNA-damaging drugs, PARP or ATR inhibitors, and mitochondrial complex inhibitors—are combined with checkpoint inhibitors to couple antigen/IFN/chemokine induction with relief of T-cell inhibition, an approach supported by recent ATR–cGAS–STING data and PARP inhibitor–ICI combinations [28, 47]. Spatial and temporal integration is achieved by using local mitochondrial stress (for example, via mitochondria-targeted photodynamic therapy or stereotactic radiotherapy) to create an "*in situ* vaccine" effect at the primary tumor or oligometastatic sites, followed by systemic checkpoint blockade to control microscopic or distant disease [49, 88, 112]. Optimizing the interval between mitochondrial perturbation and checkpoint dosing is key to align peak antigen presentation and chemokine production with maximal T-cell reinvigoration.

Given the risk that chronic STING activation and mitochondrial stress promote IL6/TGFβ–dominated immunosuppression, combinations that add cytokine or myeloid-targeted therapies are gaining interest. Pairing mitochondrial stress–inducing regimens and checkpoint blockade with IL6 or TGFβ inhibitors, CSF1R or CXCR2 antagonists, or modulators of myeloid metabolism may tilt the balance toward a durable pro-inflammatory cytokine landscape and reduce myeloid-derived suppressor cell and M2-like TAM accumulation [20, 49, 66, 79].

Subtype specific considerations

Subtype-specific considerations are likely to be critical for mitochondrial stress based combinations. In TNBC, where where genomic instability and baseline STING activity can be relatively higher and tumor-infiltrating lymphocytes (TILs) are more abundant, milder mitochondrial perturbation or intermittent dosing may suffice to amplify type I interferons and CXCL9/10/CCL5 without provoking sustained IL 6/TGF β–dominated immunosuppression [49, 61, 62]. In hormone receptor–positive and many HER2-enriched tumors, which commonly exhibit immune exclusion and TGF-β rich cytokine milieus, more intensive or cyclic priming strategies—potentially combined with blockade of dominant suppressive cytokines or myeloid pathways—may be required to first convert the tumor into a T cell–permissive state before or during checkpoint blockade (*table 1*) [67, 68, 114]. Recent evidence further highlights that resistance to hormonal and targeted therapies in breast cancer can be driven by suppression of the NR6A1/DNMT3A axis [115], reinforcing the need to tailor metabolic and epigenetic interventions to subtype-specific vulnerabilities.

Overall, the most compelling therapeutic vision is a multi-layered regimen in which mitochondrial modulators are used not simply as cytotoxic agents but as programmable "danger signal" generators. By calibrating the intensity, duration, and cellular targets of mitochondrial stress, and embedding this within a framework of checkpoint inhibition and cytokine/myeloid control, future therapies may reliably ignite and sustain productive antitumor immunity in breast cancer while minimizing the risk that the same pathways are co-opted to drive resistance and immune escape. *Table 2* summarizes the combination strategy targeting mitochondria for Immunotherapy.

CONCLUSION AND FUTURE PERSPECTIVES

Mitochondrial stress has emerged as a unifying framework to understand and therapeutically exploit how breast tumors interact with the immune system, repositioning mitochondria from passive metabolic organelles to programmable hubs of innate immune sensing and cytokine control. By linking mtDNA leakage, cGAS–STING activation, and cytokine network remodeling to cold-to-hot tumor conversion, this paradigm offers a mechanistic basis for designing

Table 2.
Combination strategy targeting mitochondria for Immunotherapy

Combination Strategy	Biological Roles	Current Status	Reference
Low-dose mitochondrial poisons (e.g., complex I/III inhibitors) + Immunotherapy	Sublethal inhibition of mitochondrial complexes increases mtROS and mtDNA leakage, acutely activating cGAS–STING to induce type I IFNs (IFN-α/β) and T-cell–recruiting chemokines CXCL9, CXCL10, and CCL5, thereby enhancing $CD8^+$ T-cell priming and trafficking; however, chronic exposure risks skewing toward IL-6 and IL-10 upregulation, promoting myeloid-derived suppressor cell (MDSC) accumulation and immunosuppression	Predominantly preclinical (mouse models and early combination concepts with checkpoint inhibitors; no large dedicated Phase II trials yet)	[27, 28]
Selected radiotherapy or chemotherapy regimens + Checkpoint Inhibitors	DNA damage and mitochondrial injury trigger immunogenic cell death with DAMP release and transient bursts of type I IFNs and CXCL10/CCL5, supporting dendritic cell activation and effector T-cell recruitment; if fractionation or dosing drives persistent tissue damage, sustained NF-κB activation can elevate IL-6, TNF-α, and TGF-β, favoring fibrosis, T-cell exhaustion, and resistance	Preclinical + Phase I/II (multiple ongoing or completed early-phase trials combining radiotherapy or selected chemotherapies with PD1/PDL1 or CTLA4 blockade in breast and other solid tumors)	[53, 58, 60]
PARP or ATR inhibitors + Checkpoint Inhibitors	Inhibition of DNA damage response enhances cytosolic DNA and mtDNA accumulation, amplifying cGAS–STING–driven IFN-α/β and ISG expression as well as CXCL10 and CCL5, which couples enhanced antigenicity with stronger lymphocyte infiltration; prolonged DDR inhibition, however, can shift the cytokine milieu toward IL-6 and IL-8, supporting chronic inflammation and clonal selection of resistant cells	Preclinical + early Phase I/II (clinical trials testing PARP or ATR inhibitors with ICIs in TNBC and other solid tumors, often as biomarkerenriched exploratory studies)	[28, 47]
Metabolic reprogramming agents (e.g., OXPHOS inhibitors) + Immunotherapy	Transient OXPHOS or FAO inhibition in tumor cells increases mtROS and can favor a shift toward IFN-α/β and IL-12 production with higher CXCL9/CXCL10, improving antigen presentation and susceptibility to T-cell killing; in immune cells, excessive metabolic stress may drive IL-10 and TGF-β expression and T-cell exhaustion, necessitating careful dosing to preserve T-cell mitochondrial fitness	Mainly preclinical (mechanistic and efficacy studies in murine models; only limited, indirect clinical experience from metabolism-targeting drugs combined with ICIs)	[26, 34]
Modulators of mitochondrial quality control (e.g., mitophagy inhibitors) + Immunotherapy	Interference with mitophagy and nucleoid homeostasis expands the pool of damaged mitochondria and enhances mtDNA release, promoting cGAS–STING activation with acute induction of IFN-α/β and chemokines such as CXCL10 and CCL5; if blockade is prolonged, accumulation of dysfunctional mitochondria favors chronic NF-κB–biased output and increased IL-6, IL-8, and IL-10, driving protumor inflammation and T-cell dysfunction	Preclinical (proof-of-concept studies in cell lines and mouse models; no dedicated clinical trials yet combining mitophagy/nucleoid modulators with ICIs)	[45, 46]
Local mitochondrial stress (e.g., stereotactic radiotherapy, mitochondria-targeted photodynamic therapy) + Systemic Checkpoint Blockade	Spatially restricted mitochondrial damage at the tumor site generates a localized 'in situ vaccine' with high levels of IFN-α/β/γ, and CXCL9/CXCL10, driving robust local and systemic T-cell responses and abscopal effects; inadequate spatial or temporal control may provoke excessive TNF-α, IL-1β, and IL-6, increasing the risk of tissue necrosis, systemic inflammatory toxicity, and treatment-limiting adverse events	Preclinical + early Phase I (mitochondria-targeted photodynamic and ablative approaches in animal models; small early-phase studies of local ablative therapies plus ICIs in selected solid tumors)	[49, 112]

Abbreviations: TNBC, triple-negative breast cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation; IFN, interferon; ICI, immune checkpoint inhibitor; TME, tumor microenvironment; STING, stimulator of interferon genes; DAMP, damage-associated molecular pattern; ROS, reactive oxygen species.

combination strategies that move beyond empiric cytotoxicity toward deliberate immune priming in otherwise immunologically barren breast cancers [116].

Key conceptual advances

This review highlights three central advances: first, that mitochondrial architecture, quality control, and metabolic wiring in cancer and immune cells collectively determine whether mitochondrial stress yields immunogenic interferon–chemokine programs or entrenched immunosuppression. Second, mtDNA–cGAS–STING signaling operates as a dose- and context-dependent rheostat whose acute activation can ignite T cell–inflamed phenotypes, whereas chronic engagement fuels resistance, stromal remodeling, and checkpoint upregulation. Third, cytokine networks function as both readouts and effectors of this mitochondrial–immune crosstalk, integrating upstream organelle stress into prognostic signatures and actionable therapeutic targets.

Translational opportunities

Therapeutically, these insights converge on a strategy of "controlled ignition," in which mitochondrial stress is imposed in a spatially and temporally constrained

manner to amplify antigenicity, type I interferons, and T cell–recruiting chemokines while avoiding sustained NF-κB-biased, IL-6/IL-10/TGF-β–dominated states. Emerging platforms—including mitochondria-targeted small molecules and nanomedicines, rationally dosed OXPHOS and mitophagy modulators, and STING agonists or epigenetic restorers of cGAS–STING—provide a growing toolbox for such programmable danger signaling, particularly when layered onto checkpoint blockade. As multiplex cytokine profiling and immune gene signatures mature clinically, they are poised to guide patient selection, monitor pharmacodynamic responses, and adapt combination regimens in real time.

Future research directions

Several priorities must be addressed to safely and effectively bring mitochondrial stress–based immuno-oncology into the clinic. Mechanistic studies should dissect cell type–specific and subtype-specific thresholds for beneficial versus deleterious mitochondrial stress, including how luminal, HER2-enriched, and triple-negative tumors differentially tune cGAS–STING output and cytokine landscapes. Systems-level approaches integrating single-cell and spatial multi-omics with metabolic and mitochondrial profiling will be critical to map how mitochondrial reprogramming in tumor, stromal, and immune compartments co-evolves under therapy and shapes response or resistance to immunotherapy. Parallel translational work should focus on rational trial designs that sequence and dose mitochondrial modulators as priming agents around immune checkpoint inhibitors, with built-in biomarker programs capturing mtDNA–STING activity, cytokine states, and immune cell fitness. Finally, safety frameworks must anticipate off-tumor inflammation and chronic STING-driven toxicities, motivating development of tumor-restricted delivery systems, reversible agonists, and combination strategies that simultaneously ignite anti-tumor immunity and restrain maladaptive cytokine circuits. If these challenges can be met, targeting mitochondrial stress has the potential to transform immunologically cold breast cancers into consistently treatable, inflamed diseases and to redefine mitochondria as programmable adjuvants at the core of breast cancer immunotherapy.

Limitations for this study

This review is primarily conceptual and therefore has several important limitations. First, most of the discussed mitochondrial stress–cGAS–STING mechanisms and combination strategies are derived from preclinical models, with limited validation in large, prospective breast cancer trials, so their translational robustness and safety remain uncertain. Second, subtype-specific differences in mitochondrial wiring, cytokine networks, and STING pathway status are still incompletely mapped, which constrains precise patient stratification and may oversimplify the heterogeneity of luminal, HER2-enriched, and TNBC tumors. Third, the proposed "controlled ignition" paradigm does not yet incorporate quantitative thresholds for beneficial versus deleterious mitochondrial stress or fully account for systemic toxicities observed with STING agonists, highlighting the need for biomarker-guided dosing, longitudinal cytokine monitoring, and tumor-restricted delivery platforms before these concepts can be reliably applied in the clinic.

DISCLOSURE

Acknowledgement: The authors extend their sincere appreciation to the Research Assistant Center, Show Chwan Memorial Hospital, Taiwan, for providing essential technical support throughout this study. We are grateful to all personnel who assisted in this research.

Funding Statement: This research was funded by the National Science and Technology Council, Taiwan; NSTC 112-2314-B-442-003, NSTC 113-2314-B-442-002, and 114-2314-B-442-001-MY3 [recipient: Hung-Yu Lin]; NSTC 112-2314-B-442-001 and 113-2314-B-442-001-MY2 [recipient: Pei-Yi Chu]), and the National Health Research Institutes (NHRI-109BCCO-MF-202015-01 [recipient: Pei-Yi Chu]) and by the Show Chwan Memorial Hospital (SRD-112021 [recipient: Hsing-Ju Wu]).

Author Contributions: The authors confirm contribution to the paper as follows: Conceptualization, Hung-Yu Lin and Hsing-Ju Wu; methodology, Hung-Yu Lin; software, Hsing-Ju Wu; validation, Pei-Yi Chu; formal analysis, Hsing-Ju Wu; investigation, Hsing-Ju Wu; resources, Pei-Yi Chu; data curation, Hung-Yu Lin; writing—original draft preparation, Hung-Yu Lin and Hsing-Ju Wu; writing—review and editing, Pei-Yi Chu; visualization, Hung-Yu Lin; supervision, Pei-Yi Chu; project administration, Hsing-Ju Wu; funding acquisition, Hsing-Ju Wu. All authors reviewed the results and approved the final version of the manuscript.

Availability of Data and Materials: All data generated or analyzed during this study are included in this published article.

Conflicts of Interest: The authors declare no conflicts of interest to report regarding the present study.

LIST OF ABBREVIATIONS

cGAS	Cyclic GMP-AMP synthase
STING	Stimulator of interferon genes
mtDNA	Mitochondrial DNA
DAMPs	Damage-associated molecular patterns
TNBC	Triple-negative breast cancer
TIME	Tumor immune microenvironment
OXPHOS	Oxidative phosphorylation
mtROS	Mitochondrial reactive oxygen species
MHC-I	Major histocompatibility complex class I
DRP1	Dynamin-related protein 1
IFN	Interferon (IFN-α/β for type I interferons)
IRF3	Interferon regulatory factor 3
NF-κB	Nuclear factor-kappa B
cGAMP	2'3'-cyclic GMP-AMP
TNF-α	Tumor necrosis factor alpha
CCL5	C-C motif chemokine ligand 5
CXCL10	C-X-C motif chemokine ligand 10
PD-L1	Programmed death-ligand 1
NK cells	Natural killer cells
ER	Endoplasmic reticulum
HER2	Human epidermal growth factor receptor 2

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