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| RESEARCH ARTICLE

Synchronization of Tumor Oxygenation and Metabolic Windows to Enhance Immunogenic Cell Death in Photodynamic and Sonodynamic Cancer Therapy

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| ABSTRACT

Photodynamic therapy (PDT) and sonodynamic therapy (SDT) have become the most least invasive forms of cancer treatment that can achieve immunogenic cell death (ICD). Nevertheless, their therapeutic efficacy is grossly limited by tumor hypoxia and tumor metabolic reprogramming in the tumor microenvironment. More current developments in nanomedicine have allowed a very high degree of spatiotemporal control of oxygenation and metabolic activity levels, which has generated transient therapeutic windows allowing increased reactive oxygen species production and augmentation of ICD. This is a systematic review of the mechanistic interplay between the tumor oxygen dynamics, metabolic remodeling, and immune activation in PDT- and SDT-based cancer therapies. We point out oxygen-producing and regulative metabolic nanoplatforms that coordinate these windows to overcome immune suppression, stimulate dendritic cells, as well as establish long-term antitumor immunity. Lastly, we comment on the translational challenges and future opportunities to combine synchronized oxygen -metabolic modulation with multimodal and immunotherapeutic interventions and position PDT and SDT as the future systemic cancer immunotherapies.

| KEYWORDS

Immunogenic cell death, Photodynamic therapy, Sonodynamic therapy, Tumor hypoxia, Metabolic reprogramming, Nanomedicine

| ARTICLE INFORMATION

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1. Introduction

1.1 Limitations of Conventional PDT and SDT and the Role of Immunogenic Cell Death

Photodynamic therapy (PDT) and sonodynamic therapy (SDT eliminate tumor cells by way of the production of reactive oxygen species (ROS) after activation of sensitizers by light or ultrasound. Since ROS generation is an inherently oxygen-dependent process, the hypoxic character of solid tumors is an inherent limitation to both modalities. Low oxygen supply in the poorly vascularized areas of tumor is a serious constraint in the ROS yield and leads to failure to destroy the tumor completely and an increased chance of its recurrence.

In addition to hypoxia, tumor cells have a high degree of metabolic plasticity, which can reconfigure glucose, mitochondrial, and redox pathways to tumor therapeutic stress. This metabolic plasticity facilitates quick detoxification of ROS, ATP generation and redox homeostasis, thus reducing the cytotoxic effect of PDT and SDT. At the same time, these metabolic changes transform the microenvironment of the tumor to an immunosuppressive niche, which has lactate, an acidic pH, and inhibited immune cell infiltration. Consequently, immune evasion

mechanisms do not allow the emergence of effective systemic antitumor immunity even in cases of local tumor ablation success.

1.2 Rationale for Spatiotemporal Synchronization of Oxygen Availability and Tumor Metabolism

Not only does the presence of photosensitizers or sonosensitizers determine the therapeutic efficacy of photodynamic and sonodynamic cancer therapies, but also a relationship between the spatiotemporal localization of oxygen availability and tumor metabolic state during the activation of the therapeutic modality. The tumor microenvironment is highly heterogeneous and dynamically controlled, such that there are transient areas where the tumors can be susceptible to damage by reactive oxygen species. The inability to take advantage of such windows results in non-optimal ROS production, fast metabolic adaptation, and partial induction of immunogenic cell death (ICD).

The aspect of spatial synchronization is very vital as hypoxia and metabolic activity concentrations among various tumor regions vary greatly, with hypoxic cores and metabolically active invasive margins having different therapeutic vulnerabilities. Specific make-up of oxygen or in-situ generation of oxygen in hypoxic niches is used to increase the ROS production in the otherwise ineffective areas of PDT and SDT. At the same time, localized antioxidant buffering is inhibited by spatial modulation of tumor metabolism, including lactate depletion, glycolysis inhibition, or glutathione exhaustion, and therefore, oxidative stress is elevated and the induction of ICD is uniformly distributed across the tumor mass.

Time synchronisation is also critical, since the metabolism of the tumor quickly changes according to changes in oxygen and therapeutic insult. Temporary oxygenation can even counteractially enhance the survival of tumors in cases where metabolic processes are not disturbed and the cancer cells can recover the redox balance and avoid immune detection. Timing of the metabolic interference in correlation with oxygen enrichment and sensitizer activation maximizes the intensity of ROS bursts, overwhelms, and stabilizes the cell defense mechanisms, and standardizes ICD signaling. The effect of this temporal convergence is a multiplication in the release of the damage-related molecular patterns, dendritic cell activation, and an enhancement in systemic antitumor immune response.

1.3 Scope and Objectives of the Review

This review is an integrative and detailed analysis of the recent developments of photodynamic therapy (PDT) and sonodynamic therapy (SDT with particular interest in the spatiotemporal synchronization of tumor oxygenation and metabolism to improve immunogenic cell death (ICD). The study area of this review includes mechanistic understanding of the effects of tumor hypoxia, metabolic plasticity and redox homeostasis on ROS-dependent therapeutic outcomes and the formation of antitumor immune responses.

In particular, this review aims at: (i) to clarify the biological and physicochemical mechanisms involved in ICD induction during PDT-based and SDT-based cancer therapies; (ii) to critically review nanomedicine-based strategies in modulating the oxygen accessibility and tumor metabolism, including the oxygen-generating system, metabolic interference, and redox regulation; (iii) to assess how spatiotemporal control of these variables can trigger immune activation and overcome tumor immune resistance; and (iv) to discuss the current challenges, translational limitations By using this framework, the review will help to bring out the new design principles that can be used to further develop PDT and SDT beyond localized tumor ablation technologies to systemic and long-lasting cancer immunotherapies.

2. Tumor Hypoxia and Metabolic Reprogramming as Barriers to ICD

2.1 Tumor Hypoxia and Metabolic Reprogramming as Barriers to ICD

PDT and SDT have the same effects with the antitumor effect being mainly mediated by the production of reactive oxygen species (ROS) after photoactivation of photosensitizers and sonoactivation of sonosensitizers. The process itself is an oxygen-dependent process because to produce cytotoxic singlet oxygen and other ROS species, the presence of molecular oxygen is needed. As a result, the hypoxic microenvironment experienced in the majority of solid tumors is a significant resistance factor to both PDT and SDT, which results in decreased ROS generation, incomplete tumor destruction, and inadequate treatment outcomes (Hou et al., 2020; Hu et al., 2021; Datta et al., 2024).

Notably, HIF-1α, which is a product of hypoxia signaling, is also involved in suppression of immunity in the tumor microenvironment. High HIF-1 levels have been linked to enhanced immunosuppressive mediator expression, dendritic cells maturation, decreased infiltration of cytotoxic T-cells, and facilitated proliferation of an immunosuppressive metabolic environment that is rich in lactate and acid byproducts (Tang et al., 2025; Ma et al., 2024). Consequently, in the case of localized tumor cell death induced by PDT or SDT, immune evasion by hypoxia suppresses induction of immunogenic cell death and establishment of a lasting systemic antitumor immune response (Wang et al., 2023; Cheng et al., 2021).

2.2 Metabolic Constraints on Immunogenic Cell Death

One of the key obstacles to successful induction of immunogenic cell death (ICD) of photodynamic and sonodynamic cancer therapy is tumor metabolic reprogramming. The uncontrolled lactate accumulation as a result of aerobic glycolysis is one of the most striking metabolic characteristics of the tumor microenvironment. High lactate concentrations cause extracellular acidosis, which in addition to increasing stress-resistant tumor cell survival, strongly inhibits antitumor immunity. Acidic environment disrupts the development of dendritic cells, prevents the growth of cytotoxic T- cells and production of cytokines and favors T-cell exhaustion, thus undermining immunological amplification that is characteristic of ICD (Tang et al., 2025).

Besides lactate-mediated immune-suppression, tumor cells display high levels of glucose addiction that promotes high ATP production and redox homeostasis. Increased glucose uptake helps to repair the reducing equivalents and antioxidant molecules, including NADPH and glutathione, which counteract reactive oxygen species caused by therapy and dampen endoplasmic reticulum and mitochondrial stress signaling required to kick off ICD. This buffering of the metabolism restricts the exposure of damage-related molecular patterns and suppresses the immunostimulatory capability of tumor cell death induced by PDT and SDT (Wang et al., 2024).

The state of mitochondrial dysfunction also contributes to ICD resistance by modifying the oxidative compartmentation of phosphorylation, the ROS signal transduction threshold, and providing metabolic plasticity during situations of hypoxia and nutrient scarcity. Dysfunctional, but adaptable, mitochondria in cancer cells enable them to adapt to glycolysis and oxidative stress and help them to circumvent the irreversible oxidative stress and suppress ICD-related immune response. Recent nanotherapeutic approaches that address glutathione depletion and redox resetting have noted that it is important to overcome these mitochondrial and metabolic countermeasures to reestablish vigorous ICD and functional antitumor immunity (Dangi et al., 2025).

Table 1: Metabolic Constraints on Immunogenic Cell Death and Their Therapeutic Implications

Metabolic Constraint	Key Features in Tumor Microenvironment	Impact on ICD Induction	Implications for PDT/SDT and Immunity	Key References
Lactate accumulation	Excessive aerobic glycolysis; lactate export via MCTs; acidic extracellular pH	Suppresses DAMP release signaling; impairs dendritic cell maturation	Reduces antigen presentation and weakens ICD-driven immune priming	Tang et al. (2025)
Tumor acidosis	Low extracellular pH; proton accumulation	Inhibits T-cell activation and cytokine secretion	Limits immune amplification following PDT/SDT-induced tumor damage	Tang et al. (2025); Ma et al. (2024)
T-cell exhaustion	Chronic antigen exposure; metabolic competition	Reduces cytotoxic T-cell proliferation and effector function	Prevents systemic antitumor immunity despite local ICD	Tang et al. (2025)
Glucose addiction	Upregulated glucose transporters; high glycolytic flux	Enhances ROS detoxification and redox buffering	Attenuates ER stress and ICD signaling pathways	Wang et al. (2024)
Redox homeostasis (GSH)	Elevated glutathione and NADPH levels	Neutralizes therapy-induced ROS	Limits oxidative damage required for ICD	Dangi et al. (2025)
Mitochondrial dysfunction	Altered OXPHOS; metabolic flexibility	Dampens mitochondrial ROS and apoptotic signaling	Enables resistance to PDT/SDT and weak ICD induction	Wang et al. (2024); Dangi et al. (2025)

3. Mechanisms of Immunogenic Cell Death in PDT and SDT

3.1 ROS-Mediated ER Stress and Mitochondrial Damage

Reactive oxygen species (ROS) are quickly produced in photodynamic (PDT) and sonodynamic therapy (SDT) when photosensitizers or sonosensitizers are activated. Most of these ROS specifically attack intracellular organelles, the endoplasmic reticulum (ER) and mitochondria being most susceptible to it. ER oxidative damage disrupts protein folding, calcium homeostasis, and triggers the unfolded protein response that causes a stress environment and prepares the cell to signal immunogenic (Jin et al., 2021). At the same time, the accumulation of mitochondrial ROS damages the integrity of the membrane, disruption of oxidative phosphorylation, and release of pro-apoptotic factors (Cheng et al., 2021). The synergistic effect of ER and mitochondrial stress causes intracellular ROS, stabilizes ICD-associated signaling, and creates the conditions required of the cell to be exposed and release immunostimulatory signals (Luo et al., 2025).

3.2 Release of DAMPs: Calreticulin, ATP, HMGB1

Another characteristic of immunogenic cell death (ICD) caused by photodynamic therapy (PDT) and sonodynamic therapy (SDT) is active release of damage-associated molecular patterns (DAMPs) by stressed tumor cells. The endoplasmic reticulum (ER) stress triggered by ROS stimulates the pre-apoptotic presentation of calreticulin on the cell surface, a putative eat-me signal that enhances the dendritic cells to recognize and phagocytize them (Jin et al., 2021). Simultaneously, compromised mitochondrion and derailed cell membrane cause extracellular release of ATP, which is an attractive factor to antigen-presenting cells and a maturation cue (Cheng et al., 2021). At later stages of ICD, the release of high-mobility group box 1 (HMGB1) of the nucleus and mitochondria, which helps to process antigens and promote adaptive immune activation, involves the involvement of pattern recognition receptors on immune cells (Luo et al., 2025). Exposure and secretion of calreticulin, ATP, and HMGA cytokine constitute the molecular signature of ICD and are critical in the connection between local cell death in tumors and systemic antitumor immunity.

3.3 Dendritic Cell Maturation and CD8⁺ T-Cell Priming

Photodynamic therapy (PDT) and sonodynamic therapy (SDT) result in the release of damage-associated molecular patterns (DAMPs), which is an effective activator of the adaptive immune system. Calreticulin exposure, extracellular ATP, and HMGB1 stimulate the engagement and activation of dendritic cells (DCs), which induce their maturation with increased co-stimulatory molecules and improved antigen processing ability (Jin et al., 2021). Mature DCs effectively prime naïve CD8 + T cells with tumor antigens, which are then maturated into cytotoxic T lymphocytes that identify and destroy the remaining and dispersed tumor cells. Such a process builds a systemic antitumor immune response, which turns localized death of tumor cells with PDT- or SDT- into an in situ vaccination strategy (Cheng et al., 2021; Luo et al., 2025). PDT and SDT mediate a direct cytotoxicity through adaptive immune response by connecting organelle-targeted ROS damages, release of DAMP and persistent immunogenicity.

4. Synchronizing Oxygenation Windows

4.1 Oxygen-Generating and Oxygen-Carrying Nanoplatforms

A significant limitation to the effectiveness of photodynamic therapy (PDT) and sonodynamic therapy (SDT) is the fact that the ROS production process is oxygen-dependent. In an attempt to address this shortcoming, oxygen producing and oxygen-ferrying nanoplatforms have proven to be useful to tune tumor oxygenation in a targeted fashion and to increase ROS-mediated cytotoxicity.

Catalase-like nanozymes are artificial nanomaterials, which imitate the catalase enzyme, catalyzing the breakdown of endogenous hydrogen peroxide (H 2 O 2) to oxygen and water. These nanozymes overcome hypoxia and form localized oxygen stores that generate additional ROS in situ depending on PDT or SDT by converting intratumoral H 2 O 2 to oxygen. This leads to direct tumor cell killing, as well as, induction of immunogenic cell death (Tang et al., 2025; Cheng et al., 2021).

4.2 Hypoxia-Relief–Driven Immune Reprogramming

Tumor hypoxia relief is not limited to enhancing the production of reactive oxygen species (ROS) in photodynamic and sonodynamic therapy and is the crucial role in tumor microenvironment reprogramming. Hypoxia is a significant cause of immune dysfunction that facilitates the accumulation of immunosuppressive cell compartments and restrains the infiltration of effector immune cells. The immune cell behavior is reconfigured by the oxygen-modulating nanoplatforms through the restoration of oxygen supply and the amplification of antitumor immune responses.

Tumor-associated macrophage (TAM) polarization reversal is one of the largest immunological impacts of hypoxia therapy. The hypoxia condition favors the proliferation of M2-like macrophages, which promote tumor development by angiogenesis, extra-cellular matrix, and T-cell activity inhibition. Nanoplatforms generate oxygen to silence hypoxia-driven signaling and metabolic signals that maintain the M2-like phenotype to induce repolarization of the pro-inflammatory M1-like phenotype. M1 macrophages promote antigen presentation, release inflammatory cytokines and promote immune activation, which forms a tumor microenvironment that promotes immunogenic cell death and immune amplification (Tang et al., 2025; Gao et al., 2023).

Simultaneously, hypoxia rescue also increases the cytotoxic T-cell infiltration and activity to a considerable extent. Enhanced oxygenation reduces the level of metabolic competition and acidosis in the tumor microenvironment, replenishes T-cell viability, proliferation, and effector functions. Increased recruitment and retention of CD83+ T cells in oxygenated tumors are mediated by synergy between PDT- and SDT-mediated antigen release and T cells in enhancing adaptive immune response. In addition, it can be designed to mediate spatial and temporal interactions between the relief of hypoxia and immune activation using oxygen-responsive nanoplatforms, which enhances T-cell-mediated antibody against cancer and facilitates long-term antitumor immunotherapy (Yin et al., 2025; Tang et al., 2025).

5. Metabolic Window Modulation to Amplify ICD

As much as hypoxia is relieved and this improves the oxygen supply needed to generate reactive oxygen species (ROS), successful induction of immunogenic cell death (ICD) also relies on the metabolic status of tumor cells during

therapy. Cancer cell metabolism is dynamic and within a short time, cancer cells re-organize the use of glucose, redox buffering, and mitochondrial activity in response to an oxidative stress. These adaptations have the potential to reduce the stress of ER, cancel ROS, and inhibit immune signaling, which suppresses the immunogenicity of photodynamic and sonodynamic treatments. This has resulted in accurate regulation of tumor metabolic processes to generate temporary metabolic windows of susceptibility turning out to be a key approach to enhancing ICD.

The concept of metabolic window modulation is to provide transient inhibition of tumor metabolic defence mechanisms during the activation of PDT or SDT, which would guarantee that ROS damage surpasses cell repair limits. The glycolysis, lactate, glutathione, and mitochondrial sensitization interventions interfere with ATP generation and redox homeostasis and inhibit the rapid removal of ROS. The resulting effect of this metabolic destabilization is increased ER stress and mitochondrial dysfunction that result in the increased release and exposure of damage-associated molecular patterns (calreticulin, ATP, and HMGB1). Consequently, the tumor cell death is moved out of the immunologically silent apoptosis and into the strong ICD.

5.1 Lactate Depletion and Glycolysis Interference

Aberrant glycolysis and excessive lactate production are hallmark features of tumor metabolic reprogramming that significantly constrain the induction of immunogenic cell death (ICD). Tumor-derived lactate accumulates in the tumor microenvironment (TME), leading to extracellular acidosis and metabolic competition that suppress antitumor immune responses. Elevated lactate levels impair dendritic cell differentiation and antigen-presenting capacity, inhibit cytotoxic T-cell proliferation, and promote T-cell exhaustion, thereby limiting the immune-amplifying effects of photodynamic and sonodynamic therapies (Tang et al., 2025).

Importantly, glycolysis interference and lactate depletion contribute to the restoration of antigen presentation following ROS-based therapies. Improved metabolic conditions enhance dendritic cell maturation, promote efficient processing of tumor-associated antigens, and facilitate cross-presentation to $CD8^+$ T cells. This metabolic reprogramming prevents lactate-mediated suppression of immune signaling pathways and enables PDT- and SDT-induced tumor cell death to elicit robust adaptive immune responses (Tang et al., 2025). Collectively, lactate-targeted metabolic modulation amplifies ICD by simultaneously sensitizing tumor cells to oxidative damage and reactivating immune surveillance within the TME.

5.2 Glutathione Depletion and Redox Resetting

Tumor cells maintain a highly adaptive redox balance that enables rapid detoxification of reactive oxygen species (ROS), thereby limiting the effectiveness of photodynamic and sonodynamic therapies. Central to this redox defense is glutathione (GSH), a major intracellular antioxidant that neutralizes ROS and preserves mitochondrial and endoplasmic reticulum (ER) homeostasis. Elevated GSH levels in tumor cells attenuate oxidative stress, suppress ER stress signaling, and restrict the initiation of immunogenic cell death (ICD), even under conditions of enhanced ROS generation (Dangi et al., 2025).

Glutathione depletion and redox resetting strategies aim to transiently dismantle this antioxidant shield, creating a metabolic window in which tumor cells become highly susceptible to ROS-mediated damage. Nanotherapeutic systems capable of consuming GSH, inhibiting GSH synthesis, or disrupting NADPH regeneration effectively lower intracellular antioxidant capacity. This redox imbalance amplifies mitochondrial dysfunction and ER stress, promoting sustained ROS accumulation and facilitating the exposure and release of damage-associated molecular patterns essential for ICD induction (Dangi et al., 2025; Wang et al., 2024).

Beyond sensitizing tumor cells to oxidative injury, redox resetting exerts profound immunological effects within the tumor microenvironment. Reduction of tumor antioxidant defenses enhances oxidative signaling that supports dendritic cell activation and improves antigen processing and presentation. Additionally, redox modulation mitigates immunosuppressive metabolic signaling and restores effector T-cell function, allowing ICD-associated immune activation to proceed efficiently (Ma et al., 2024). When synchronized with oxygen enrichment and ROS-based therapies, glutathione depletion transforms PDT and SDT into potent immune-activating treatments capable of eliciting durable antitumor immunity.

6. Nanoplatform-Enabled Spatiotemporal Synchronization of Oxygen and Metabolic Windows

Effective amplification of immunogenic cell death (ICD) through photodynamic and sonodynamic therapies requires not only sufficient reactive oxygen species (ROS) generation but also precise coordination of oxygen availability and tumor metabolic vulnerability. Conventional approaches often fail due to temporal mismatches between oxygen delivery, ROS production, and immune activation. Nanoplatform-enabled spatiotemporal synchronization has therefore emerged as a critical strategy to overcome hypoxia, metabolic plasticity, and immune evasion in the tumor microenvironment (TME) (Tang et al., 2025).

6.1 Programmable Oxygen Modulation via Smart Nanocarriers

Advanced nanoplatforms are increasingly engineered to deliver, generate, or preserve oxygen in a controlled and tumor-specific manner. Oxygen-carrying nanoparticles, perfluorocarbon-based systems, and hemoglobin-mimetic carriers improve intratumoral oxygen tension and sustain ROS production during PDT and SDT. In parallel, oxygen-generating nanomaterials incorporating catalase-like nanozymes or Fenton/Fenton-like catalysts decompose endogenous hydrogen peroxide to produce oxygen in situ, directly counteracting hypoxia-driven therapeutic resistance (Gao et al., 2023).

Importantly, these systems allow temporal regulation of oxygen release, ensuring that oxygen availability peaks during sensitizer activation and ROS generation. Such synchronization maximizes oxidative damage to tumor cells while minimizing premature oxygen consumption, thereby enhancing ER stress, mitochondrial dysfunction, and downstream ICD signaling (Yin et al., 2025).

6.2 Coupling Oxygen Relief with Metabolic Window Activation

Beyond oxygen modulation, next-generation nanoplatforms integrate metabolic interference functions to exploit transient vulnerabilities in tumor metabolism. By co-delivering glycolysis inhibitors, lactate-depleting enzymes, or glutathione-consuming agents, these multifunctional systems create a synchronized metabolic window that sensitizes tumor cells to ROS-mediated injury. This dual modulation strategy ensures that oxidative stress coincides with weakened antioxidant defenses and impaired metabolic compensation (Tang et al., 2025; Wang et al., 2024).

Such coupling is particularly effective in preventing hypoxia-induced metabolic rewiring, including HIF-1α–driven glycolysis and antioxidant upregulation. Temporally aligned oxygen enrichment and redox resetting amplify ICD hallmarks, including calreticulin exposure, ATP release, and HMGB1 secretion, transforming localized tumor ablation into a systemic immune-stimulating event (Luo et al., 2025).

6.3 Immune-Oriented Spatiotemporal Reprogramming of the TME

Spatiotemporally synchronized nanoplatforms also exert profound effects on immune cell dynamics within the TME. Hypoxia relief and metabolic normalization reverse immunosuppressive signaling pathways, including M2 macrophage polarization and T-cell exhaustion. Enhanced oxygenation improves cytotoxic T-cell infiltration and persistence, while metabolic reprogramming restores dendritic cell maturation and antigen presentation efficiency (Tang et al., 2025; Gao et al., 2023).

By aligning oxygen delivery, metabolic disruption, and immune activation in space and time, nanoplatform-enabled strategies convert PDT and SDT into immunologically "hot" therapies. This coordinated reprogramming of the TME enables robust $CD8^+$ T-cell priming and long-term antitumor immunity, addressing key limitations of ROS-based treatments and positioning synchronized nanotherapeutics as a cornerstone for next-generation cancer immunotherapy (Yin et al., 2025).

Table 2: Comparison of Conventional PDT/SDT and Spatiotemporally Synchronized Nanoplatforms

Feature	Conventional PDT/SDT	Spatiotemporally Synchronized Nanoplatforms
Oxygen availability	Strongly limited by tumor hypoxia; rapid oxygen depletion during ROS generation	Active oxygen generation or delivery via catalase-like nanozymes, perfluorocarbon carriers, or Fenton/Fenton-like reactions enables sustained oxygen supply (Gao et al., 2023; Yin et al., 2025)
ROS generation efficiency	Inconsistent and transient due to oxygen dependence	Temporally aligned oxygen release maximizes ROS production during sensitizer activation (Tang et al., 2025)
Tumor metabolic adaptability	High metabolic plasticity enables resistance through glycolysis and antioxidant upregulation	Coordinated metabolic window modulation (lactate depletion, glycolysis inhibition, GSH consumption) limits adaptive resistance (Tang et al., 2025; Wang et al., 2024)
Redox balance	Elevated glutathione and NADPH buffering reduce oxidative damage	Redox resetting via glutathione depletion amplifies ER stress and mitochondrial dysfunction (Dangi et al., 2025)
ICD induction	Often incomplete or non-immunogenic cell death	Robust ICD with enhanced calreticulin exposure, ATP release, and HMGB1 secretion (Jin et al., 2021; Luo et al., 2025)
Dendritic cell activation	Impaired by hypoxia, lactate accumulation, and oxidative suppression	Restored DC maturation and antigen presentation under optimized oxygen–metabolic conditions (Tang et al., 2025)
$CD8^+$ T-cell response	Limited infiltration and functional exhaustion	Enhanced cytotoxic T-cell infiltration, persistence, and priming (Gao et al., 2023; Yin et al., 2025)
Tumor microenvironment (TME)	Immunosuppressive ("cold" tumor phenotype)	Immune-reprogrammed ("hot" tumor phenotype) through synchronized oxygenation and metabolism control (Tang et al., 2025)
Therapeutic outcome	Predominantly local tumor control with high recurrence risk	Local tumor ablation coupled with systemic antitumor immunity and memory responses (Luo et al., 2025)
Clinical potential	Limited by resistance, hypoxia, and weak immune activation	High translational promise for combination immunotherapy and durable cancer control (Yin et al., 2025)

7. Challenges, Clinical Translation, and Future Perspectives

Despite compelling preclinical evidence supporting spatiotemporally synchronized oxygen–metabolic nanoplatforms for enhancing immunogenic cell death (ICD) in photodynamic and sonodynamic therapy (PDT/SDT), several scientific, translational, and clinical challenges remain.

7.1 Biological and Tumor Heterogeneity Challenges

Tumor hypoxia and metabolic reprogramming are highly heterogeneous across cancer types, disease stages, and even within different regions of the same tumor. This spatial and temporal variability complicates the precise synchronization of oxygen availability and metabolic intervention required for optimal ROS generation and ICD induction (Tang et al., 2025; Datta et al., 2024). Moreover, tumors can activate compensatory pathways, including alternative metabolic fuel utilization and antioxidant upregulation, which may attenuate long-term therapeutic efficacy (Dangi et al., 2025).

7.2 Nanoplatform Design, Safety, and Scalability

The complexity of multifunctional nanoplatforms—integrating oxygen generation, metabolic modulation, and PDT/SDT sensitization—raises concerns regarding reproducibility, batch-to-batch consistency, and large-scale manufacturing. Potential issues such as long-term biodistribution, off-target ROS toxicity, and immune-related adverse effects must be rigorously evaluated to ensure clinical safety (Gao et al., 2023; Mariano et al., 2024). Simplifying nanostructure design while retaining spatiotemporal control remains a key engineering challenge.

7.3 Treatment Parameter Optimization and Clinical Implementation

Precise control over treatment parameters, including light or ultrasound dosage, timing, and penetration depth, is critical for achieving synchronized oxygen–metabolic windows in vivo. Variability in tissue optical and acoustic properties may limit uniform activation of PDT/SDT across tumor sites, particularly in deep-seated malignancies (Hou et al., 2020; Datta et al., 2024). Advanced imaging-guided and feedback-controlled treatment systems may be required to improve clinical reliability.

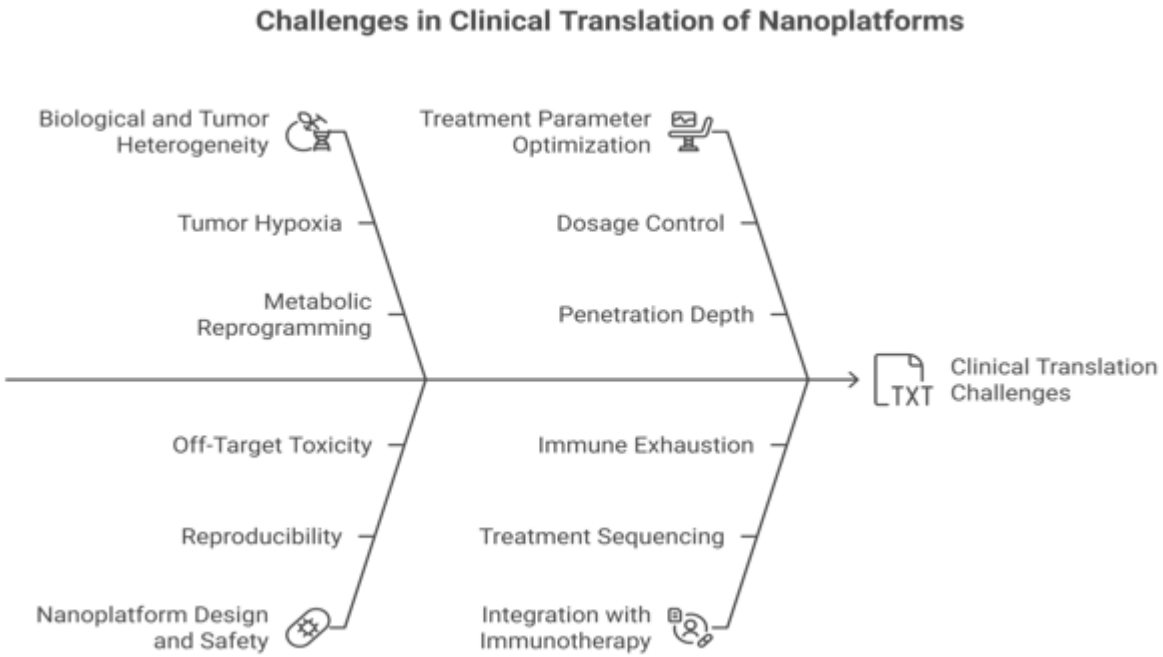
7.4 Integration with Immunotherapy and Combination Regimens

While synchronized nanoplatforms effectively convert "cold" tumors into "hot" immune-responsive phenotypes, their optimal integration with immune checkpoint inhibitors, adoptive cell therapies, or cancer vaccines remains to be fully defined. Treatment sequencing, dosing strategies, and patient stratification will be crucial to avoid immune exhaustion or antagonistic interactions (Chen et al., 2025; Ma et al., 2024).

7.5 Future Directions and Translational Outlook

Future research should prioritize the development of stimuli-responsive nanoplatforms capable of adaptive oxygen and metabolic regulation in response to dynamic tumor cues. Greater emphasis on clinically relevant tumor models, standardized ICD biomarkers, and longitudinal immune monitoring will accelerate translation (Luo et al., 2025; Fan et al., 2025). Ultimately, the convergence of nanotechnology, metabolic intervention, and immune modulation offers a promising pathway toward durable, systemic cancer control beyond localized PDT/SDT.

Figure: The diagram below shows the Challenges in Clinical Translation of Nanoplatforrms



8. Future Directions

The convergence of nanotechnology, tumor metabolism, and immunotherapy opens new opportunities to further enhance immunogenic cell death (ICD)–based photodynamic and sonodynamic cancer therapies. Future advances will likely focus on intelligent treatment timing, patient-specific therapeutic design, and rational integration with established immunotherapies.

8.1 AI-Guided Optimization of Oxygen and Metabolic Windows

Artificial intelligence (AI) and machine learning approaches offer powerful tools to dynamically optimize the timing and sequencing of oxygen delivery, metabolic intervention, and PDT/SDT activation. By integrating multimodal imaging, metabolic profiling, and real-time physiological data, AI-driven systems could predict transient oxygenation and metabolic states within tumors, enabling precise spatiotemporal synchronization of ROS generation and ICD induction (Datta et al., 2024; Chen et al., 2025). Such adaptive platforms may overcome tumor heterogeneity and improve treatment reproducibility across patients.

8.2 Personalized Design of Immunogenic Nanotherapies

Interpatient variability in tumor metabolism, immune competence, and hypoxia severity necessitates a shift toward personalized ICD-based therapeutic strategies. Future nanoplatforms may be tailored according to tumor-specific metabolic dependencies (e.g., glycolysis addiction, glutamine utilization) and redox profiles to maximize immunogenic outcomes (Wang et al., 2024; Dangi et al., 2025). Personalized nanomedicine design could enhance dendritic cell activation, sustain $CD8^+$ T-cell responses, and reduce off-target toxicity.

8.3 Integration with Immune Checkpoint Blockade

Combining synchronized PDT/SDT nanoplatforms with immune checkpoint inhibitors (ICIs) represents a promising strategy to translate local tumor destruction into durable systemic immunity. By enhancing antigen release and overcoming immunosuppressive barriers, ICD-inducing therapies may sensitize tumors to PD-1/PD-L1 or CTLA-4 blockade, improving response rates in otherwise resistant cancers (Ma et al., 2024; Luo et al., 2025). Future studies should focus on optimal treatment sequencing, dosing intervals, and biomarker-guided patient selection to maximize synergy while minimizing immune-related adverse events.

9. Conclusion

Photodynamic therapy (PDT) and sonodynamic therapy (SDT) offer powerful approaches for localized tumor ablation, yet their full potential has historically been limited by tumor hypoxia, metabolic plasticity, and immune evasion. Recent advances in oxygen-generating and oxygen-carrying nanoplatforms have enabled precise modulation of intratumoral oxygen, overcoming ROS-dependent therapy resistance and enhancing immunogenic cell death (ICD) (Tang et al., 2025; Gao et al., 2023).

Integration of these strategies into spatiotemporally synchronized nanoplatforms has demonstrated the ability to convert immunologically "cold" tumors into "hot" immune-responsive environments, facilitating dendritic cell maturation, $CD8^+$ T-cell priming, and systemic antitumor immunity (Jin et al., 2021; Luo et al., 2025; Yin et al., 2025). Looking forward, the incorporation of AI-guided therapy optimization, personalized metabolic and immune targeting, and combination with immune checkpoint blockade promises to further enhance treatment precision and clinical outcomes (Datta et al., 2024; Ma et al., 2024; Chen et al., 2025).

Overall, the convergence of nanotechnology, tumor metabolism, and immunotherapy represents a transformative paradigm for ROS-based cancer treatments, enabling robust local tumor control while simultaneously eliciting durable systemic antitumor immunity. These advances provide a roadmap for next-generation PDT and SDT strategies with improved efficacy, reduced resistance, and heightened clinical translatability.

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