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Original article

Hypoxia Induced Cisplatin Resistance in Cancer Pathophysiology, Molecular Mechanisms and Future Therapeutic Insights

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Abstract:
Cisplatin remains a cornerstone chemotherapeutic agent for the treatment of various solid malignancies; however, its clinical efficacy is significantly compromised by the development of drug resistance. Tumour hypoxia has emerged as a critical factor contributing to cisplatin resistance, leading to poor therapeutic response, increased tumour aggressiveness, and unfavorable clinical outcomes. Hypoxia, resulting from abnormal tumour vasculature and inadequate oxygen supply, activates hypoxia-inducible factors (HIF-1α and HIF-2α), which regulate multiple cellular pathways involved in survival, angiogenesis, metabolic reprogramming, and epithelial–mesenchymal transition. These adaptations enhance DNA repair mechanisms, promote drug efflux via ATP-binding cassette transporters, suppress apoptosis, and induce autophagy, collectively reducing cisplatin cytotoxicity. Additionally, hypoxia-driven epigenetic modifications and non-coding RNA regulation further strengthen chemoresistance. The hypoxic tumour microenvironment also contributes to immune suppression, stromal remodeling, and impaired drug delivery, creating a protective niche for cancer cells. Recent therapeutic strategies targeting hypoxia-related pathways, including HIF inhibitors, hypoxia-activated prodrugs, autophagy inhibitors, and nanotechnology-based drug delivery systems, show promise in overcoming resistance. A comprehensive understanding of hypoxia-mediated mechanisms is essential for developing targeted therapies and improving treatment outcomes in cancer patients.
Keywords: *Tumour hypoxia; Cisplatin resistance; HIF signaling*

Introduction

Cisplatin is one of the most widely used and effective chemotherapeutic agents for treating various solid malignancies, including lung, ovarian, bladder, oesophageal, and head and neck cancers. Since its introduction in the late 1970s, cisplatin has significantly improved survival rates, particularly in testicular and several epithelial cancers, and remains a cornerstone of many first-line and combination chemotherapy regimens. Its anticancer activity primarily results from the formation of intra- and inter-strand DNA crosslinks that disrupt DNA replication and transcription, activate DNA damage responses, and ultimately induce apoptosis in cancer cells.[1]

Despite its clinical success, the long-term effectiveness of cisplatin is often limited by the development of intrinsic or acquired resistance, which contributes to treatment failure, tumour progression, and disease recurrence. Cisplatin resistance is a major clinical challenge associated with poor prognosis and reduced overall survival across multiple cancer types. Tumour cells develop resistance through several mechanisms, including reduced intracellular drug accumulation, increased drug efflux mediated by ATP-binding cassette transporters,

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enhanced detoxification by glutathione and metallothionein's, improved DNA repair capacity, and suppression of apoptosis signalling pathways.[2]

Among the various factors contributing to resistance, tumour hypoxia has emerged as a critical determinant of therapeutic response in solid tumour. Hypoxia, defined as reduced oxygen levels (below 1–2% O_2), occurs due to rapid tumour growth, abnormal vascularization, and inadequate blood perfusion, resulting in oxygen heterogeneity within tumour tissues. Hypoxic tumour often exhibits greater aggressiveness, metastatic potential, and resistance to chemotherapy and radiotherapy, including cisplatin-based treatments.[3]

At the molecular level, hypoxia promotes the stabilization of hypoxia-inducible factors (HIF-1α and HIF-2α), which regulate genes involved in angiogenesis, metabolic adaptation, cell survival, epithelial–mesenchymal transition, autophagy, and stemness.[4] Additionally, hypoxia alters epigenetic and post-transcriptional regulation through non-coding RNAs such as microRNAs and long non-coding RNAs, which influence DNA repair, drug transport, apoptosis, and cancer stem cell signaling.[5] Understanding these hypoxia-driven mechanisms may help identify novel biomarkers and therapeutic targets to overcome cisplatin resistance and improve cancer treatment outcomes.

Historical Perspective and Mechanism of Action of Cisplatin

Cisplatin (cis-diammine dichloro platinum II) is one of the earliest and most successful metal-based chemotherapeutic agents. Discovered serendipitously by Barnett Rosenberg in the 1960s, it was approved by the U.S. FDA in 1978 for treating testicular and ovarian cancers and is now widely used against many solid tumors. Cisplatin exerts cytotoxic effects by forming DNA crosslinks after cellular uptake and aquation, mainly creating intrastrand guanine adducts that disrupt DNA structure. These lesions block DNA replication and transcription, activating DNA damage response pathways such as ATR and p53.[6] Excessive damage triggers apoptosis via mitochondrial pathways. Drug effectiveness depends on DNA repair capacity, apoptosis signaling, and intracellular drug accumulation.

Tumor Oxygenation Normoxia versus Hypoxia

Tumour oxygenation significantly influences cancer progression and treatment response. Under normoxic conditions (2–5% O_2), cancer cells maintain normal metabolism, effective DNA damage signalling, and functional apoptosis, which enhances the efficacy of chemotherapeutic drugs such as cisplatin. In contrast, hypoxia (<1% O_2) commonly occurs in rapidly growing tumours due to abnormal vasculature and poor perfusion. Hypoxia stabilizes hypoxia-inducible factor-1α (HIF-1α), which activates genes involved in angiogenesis, glycolysis, cell survival, and pH regulation.[7] These adaptations promote metabolic reprogramming, reduced drug penetration, and suppression of apoptosis. Consequently, hypoxic tumour cells develop therapy resistance, increased metastatic potential, and contribute to tumour recurrence and poor clinical outcomes.

Hypoxia Induced Cisplatin Resistance

tumour hypoxia is a major contributor to cisplatin resistance through multiple molecular mechanisms. Hypoxic conditions enhance DNA repair pathways, including nucleotide excision repair and homologous recombination, increasing the removal of cisplatin-induced DNA damage. Hypoxia also upregulates ATP-binding cassette transporters such as ABCB1, ABCC1, and ABCG2, reducing intracellular cisplatin levels.[8] Additionally, hypoxia suppresses apoptosis by inhibiting p53 activity and increasing anti-apoptotic proteins while activating protective autophagy. It also promotes epithelial–mesenchymal transition and cancer stem cell phenotypes, which are inherently chemoresistant. Clinically, hypoxic tumors correlate with poor response to platinum-based therapy, increased recurrence, and reduced survival in several cancers.

Clinical Implications and Therapeutic Opportunities

tumour hypoxia is a key driver of cisplatin resistance and is associated with aggressive tumour behaviour, poor therapeutic response, and unfavourable clinical outcomes. Targeting hypoxia-related pathways has therefore emerged as an important strategy to restore cisplatin sensitivity. One major approach involves inhibiting hypoxia-inducible factor-1α (HIF-1α), a central regulator of hypoxic adaptation. Drugs such as PX-478, digoxin, and acriflavine suppress HIF signalling, reduce angiogenesis, and enhance chemosensitivity. Another strategy uses hypoxia-activated prodrugs, including tirapazamine and evofosfamide, which become cytotoxic specifically in hypoxic tumour regions and show synergistic effects with cisplatin.[9] argeting hypoxia-driven metabolic changes, such as glycolysis and lactate transport, also improves drug response. Additionally,

combination therapies integrating cisplatin with PARP inhibitors or autophagy inhibitors can enhance treatment efficacy. The use of hypoxia-related biomarkers like HIF-1α and CAIX may further support personalized therapeutic approaches.

Tumor Hypoxia and Its Biological Basis

Tumor hypoxia occurs when the oxygen demand of rapidly proliferating cancer cells exceeds the supply provided by abnormal tumor vasculature. Tumor blood vessels are often irregular, dilated, and poorly organized, leading to inefficient oxygen delivery and uneven perfusion. As a result, cells located 70–100 μm away from blood vessels experience oxygen deprivation, creating hypoxic microenvironments. Tumor hypoxia exists in two forms: **chronic hypoxia**, caused by limited oxygen diffusion, and **acute hypoxia**, resulting from transient fluctuations in blood flow. Chronic hypoxia promotes metabolic reprogramming toward glycolysis and contributes to therapy resistance. Acute hypoxia generates reactive oxygen species during reoxygenation, increasing genomic instability and tumor aggressiveness. Cellular adaptation to hypoxia is mainly regulated by hypoxia-inducible factors (HIF-1α and HIF-2α), which activate genes involved in angiogenesis, metabolism, and survival.[10] These responses enhance tumor growth, metabolic flexibility, and resistance to conventional cancer therapies.

HIF Dependent Mechanisms of Hypoxia Induced Cisplatin Resistance

Hypoxia-induced cisplatin resistance is mainly regulated by hypoxia-inducible factors (HIF-1α and HIF-2α), which activate transcriptional programs that enhance tumor cell survival under low oxygen conditions. HIF signaling suppresses cisplatin-induced apoptosis by increasing anti-apoptotic proteins such as BCL-2, BCL-XL, and survivin while inhibiting pro-apoptotic factors like BAX and BAK. Hypoxia also interferes with p53-mediated apoptosis, reducing the expression of key pro-apoptotic genes.[11] Additionally, HIF signaling enhances DNA repair mechanisms, particularly nucleotide excision repair, by upregulating proteins such as ERCC1 and XPF that remove cisplatin-induced DNA adducts.[12] Hypoxia further reduces drug effectiveness by inducing ATP-binding cassette transporters that actively export cisplatin from tumor cells. Moreover, HIF-mediated activation of autophagy promotes cellular survival by removing damaged components and maintaining metabolic balance. Together, these mechanisms reduce cisplatin sensitivity and promote chemoresistance, highlighting HIF signaling as a potential therapeutic target.

Hypoxia Induced Autophagy in Cisplatin Resistance

Autophagy is a cellular degradation process that maintains homeostasis by removing damaged organelles and proteins through lysosomal pathways. Under hypoxic conditions, autophagy becomes a key survival mechanism that enables cancer cells to resist chemotherapeutic agents such as cisplatin. Hypoxia stabilizes hypoxia-inducible factor-1α (HIF-1α), which upregulates autophagy-related genes including Beclin-1, BNIP3, and BNIP3L, promoting autophagosome formation and mitochondrial quality control.[13] Enhanced autophagic flux removes cisplatin-damaged mitochondria and reduces reactive oxygen species, thereby limiting apoptosis. Studies in lung cancer cells show that hypoxia greatly increases autophagy, suppressing mitochondrial apoptotic signaling. Inhibition of autophagy using genetic or pharmacological approaches restores cisplatin sensitivity, suggesting that targeting autophagy could improve chemotherapy effectiveness.

Hypoxia Induced Exosomal PKM2 and Cisplatin Resistance

tumour hypoxia alters communication within the tumour microenvironment by increasing the release of extracellular vesicles, particularly exosomes. These vesicles transfer proteins, metabolites, and nucleic acids that promote drug resistance. In non-small cell lung cancer, hypoxia enhances the packaging of pyruvate kinase M2 (PKM2) into tumour-derived exosomes through HIF-1α–mediated mechanisms.[14] When transferred to cisplatin-sensitive cells, exosomal PKM2 promotes aerobic glycolysis (Warburg effect), increasing glucose uptake, lactate production, and NADPH generation. This metabolic reprogramming strengthens antioxidant defences, reduces reactive oxygen species, and suppresses apoptosis, thereby decreasing cisplatin cytotoxicity. Exosomal PKM2 also acidifies the tumour microenvironment and impairs immune responses. Clinically, circulating exosomal PKM2 may serve as a biomarker and therapeutic target.

Hypoxia Induced Mitochondrial Adaptations in Cisplatin Resistance

tumour hypoxia induces mitochondrial adaptations that help cancer cells resist cisplatin-induced cytotoxicity. Although cisplatin damages nuclear DNA, it also accumulates in mitochondria and disrupts the electron transport chain, generating reactive oxygen species (ROS) that trigger apoptosis. Under hypoxic conditions,

tumour cells shift metabolism toward glycolysis, reducing mitochondrial respiration and ROS production. Hypoxia also causes mitochondrial membrane hyperpolarization, preserving mitochondrial membrane potential, structural integrity, and mitochondrial DNA. These changes prevent Bax activation, cytochrome c release, and caspase-mediated apoptosis. Consequently, hypoxic tumour cells survive despite cisplatin exposure. Targeting mitochondrial metabolism, redox balance, or membrane potential may therefore help overcome hypoxia-related cisplatin resistance.

Explanation of Key Mechanisms for ncRNA Mediated Epigenetic Reprogramming under Hypoxia

Hypoxia imposes strong selective pressure on tumor cells triggering extensive epigenetic and post transcriptional reprogramming that enables survival in oxygen deprived and drug exposed environments. Among the most critical regulatory layers involved in this adaptation are non coding RNAs (ncRNAs) particularly microRNAs (miRNAs) and long non coding RNAs (lncRNAs) which operate as dynamic regulators of gene expression in response to hypoxic stress.

Hypoxia Mediated Downregulation of miR-758-3p and WTAP Derepression

Under normoxic conditions, miR-758-3p acts as a tumour-suppressive microRNA by inhibiting translation of WTAP mRNA, thereby regulating RNA methylation activity. Hypoxia suppresses miR-758-3p through HIF-dependent and epigenetic mechanisms, leading to WTAP overexpression. WTAP, a component of the m6A RNA methyltransferase complex, increases RNA methylation and stabilizes transcripts involved in cell survival, metabolic reprogramming, and epithelial–mesenchymal transition. Hypoxia-induced long non-coding RNAs further reinforce resistance by recruiting epigenetic modifiers such as EZH2, DNMTs, and HDACs to regulate gene expression. Together, interactions among miRNAs, lncRNAs, and epigenetic regulators form regulatory networks that promote tumour survival, metabolic adaptation, and persistent resistance to cisplatin chemotherapy.[15]

Research Implications: Therapeutic and Diagnostic Opportunities

Understanding hypoxia-driven ncRNA epitranscriptomic networks offers important opportunities for improving cancer therapy and precision oncology. The miR-758-3p–WTAP–m6A axis and hypoxia-regulated lncRNAs represent key targets for overcoming chemoresistance. Restoring tumour-suppressive miR-758-3p using synthetic miRNA mimics can suppress WTAP expression, reduce abnormal m6A RNA methylation, and resensitize tumours to cisplatin.[16] Nanoparticle-based delivery systems may enhance targeted miRNA therapy in hypoxic tumours. Another strategy involves inhibiting WTAP or the m6A methylation machinery, which can reduce oncogenic transcript stability and restore apoptosis. Additionally, targeting hypoxia-induced lncRNAs using antisense oligonucleotides, siRNAs, or CRISPR technologies can disrupt epigenetic networks that maintain epithelial mesenchymal transition, metabolic reprogramming, and persistent chemotherapy resistance.[17]

Diagnostic and Prognostic Applications

Dysregulated expression of **miR-758-3p, WTAP, and hypoxia-induced lncRNAs** has strong potential as diagnostic and prognostic biomarkers in cancer. Reduced miR-758-3p and elevated WTAP levels indicate increased m6A RNA methylation and hypoxia-adapted tumor states, which are associated with poor chemotherapy response and unfavorable outcomes. These ncRNAs can be detected in tumour tissues or liquid biopsies, such as circulating miRNAs and exosomal RNAs, enabling early identification of treatment-resistant hypoxic tumours.[18] Integrating ncRNA biomarkers with imaging and molecular profiling may support personalized therapy selection. Future strategies combining ncRNA-targeted therapies with platinum-based chemotherapy could help overcome hypoxia-induced resistance and improve precision oncology.

Role of Additional Molecular Pathways in Hypoxia Induced Cisplatin Resistance

Tumor hypoxia promotes cisplatin resistance not only through classical HIF signalling but also via additional molecular pathways that enhance tumor cell survival. One important mechanism involves **ER stress–mediated activation of EIF2AK3 (PERK)**, which triggers the unfolded protein response and activates the **PI3K/AKT pathway**.[19] This signalling promotes cell survival by inhibiting apoptosis, enhancing DNA repair, improving metabolic flexibility, and reducing oxidative stress caused by cisplatin.

Hypoxia also activates **HIF-independent mechanisms** such as autophagy and metabolic reprogramming. Autophagy removes damaged organelles and mitochondria, reduces oxidative stress, and suppresses apoptosis, thereby promoting resistance. Metabolic adaptations, including increased glycolysis, altered mitochondrial

function, and enhanced pentose phosphate pathway activity, help maintain ATP production and reduce ROS-mediated DNA damage. Additionally, hypoxic tumor cells release **exosomes** containing proteins and non-coding RNAs that transfer resistance traits to neighboring cells. These pathways interact with ncRNA and epigenetic mechanisms, forming an integrated network that strengthens and sustains hypoxia-driven cisplatin resistance.

Summary

Hypoxia induced cisplatin resistance is thus multifactorial, involving PERK mediated ER stress and PI3K/AKT survival signaling, HIF independent autophagy and metabolic adaptation, Exosome mediated horizontal transfer of resistance traits, Integration with ncRNA and epigenetic networks. Therapeutically targeting one or more of these pathways e.g combining PI3K/AKT inhibitors, autophagy blockers, metabolic modulators or exosome secretion inhibitors offers a promising strategy to overcome hypoxia driven chemoresistance.

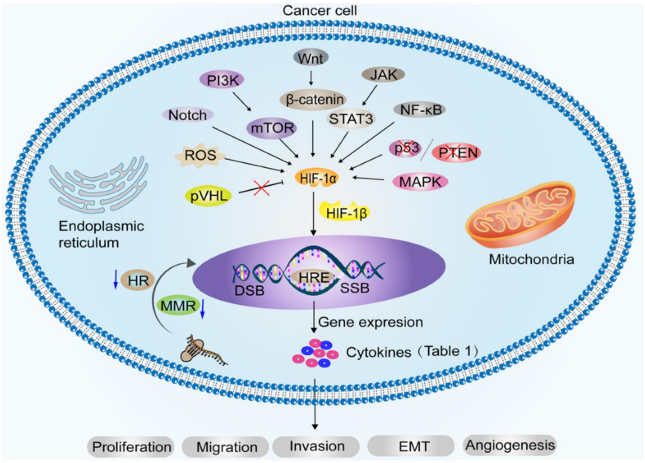

Figure 1 – Tumor Hypoxia and Cisplatin Resistance Overview

2. Vascular Abnormalities and Impaired Drug Delivery

Hypoxia promotes the formation of abnormal tumor vasculature which is structurally and functionally defective characterized by dilated, leaky and poorly organized blood vessels. (**Figure 2**) shows these vascular abnormalities result in heterogeneous perfusion, limiting cisplatin delivery to hypoxic tumor regions. Consequently poorly perfused areas act as sanctuaries for resistant tumor cells allowing them to survive chemotherapy while normoxic regions may respond to treatment[65]. This spatial heterogeneity contributes significantly to intratumoral drug resistance and therapy failure in solid tumors.

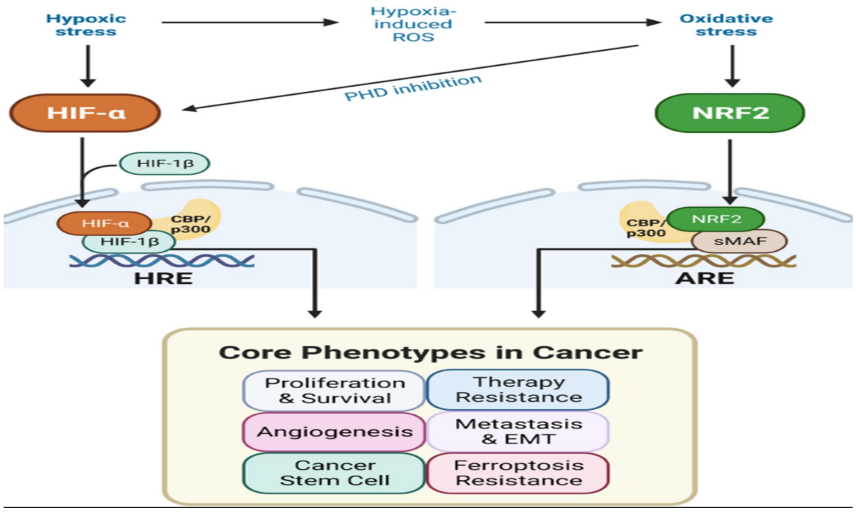

Figure 2 – HIF-Mediated Molecular Mechanisms

3. Immune Cell Modulation in the Hypoxic TME

Hypoxia reshapes the immune landscape of the TME favoring an immunosuppressive microenvironment.(**Figure 3**) shows Low oxygen tension stimulates the recruitment and expansion of Regulatory T cells, Myeloid derived suppressor cells (MDSCs), M2 polarized tumor associated macrophages (TAMs).These immunosuppressive populations secrete cytokines (e.g., IL-10, TGF-β) and growth factors that inhibit cytotoxic $CD8^+$ T-cell activity and natural killer (NK) cell function, reducing immune mediated tumor clearance. Hypoxia induced immune suppression indirectly contributes to chemoresistance by allowing tumor cells to survive despite ongoing chemotherapy[66].

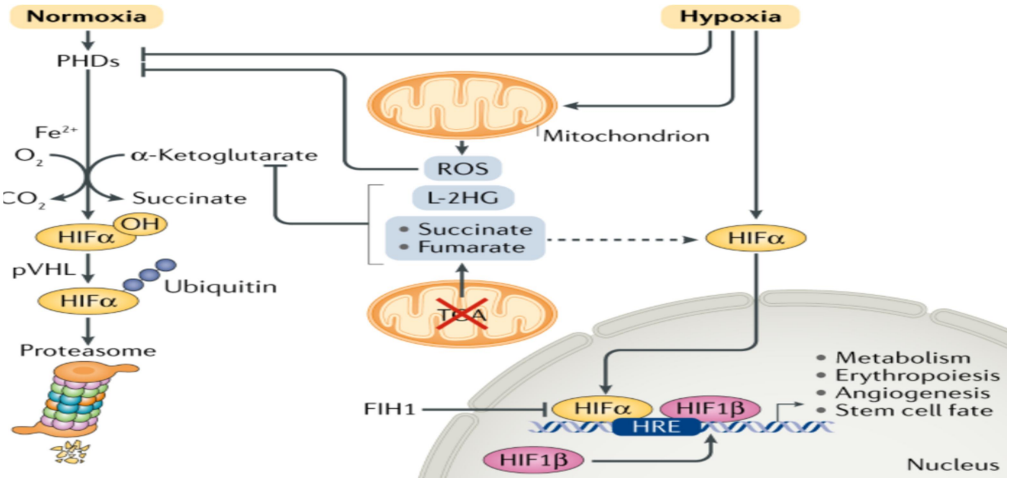

Figure 3 – Cellular Adaptations under Hypoxia

4. Stromal Remodeling and Fibroblast Activation

Hypoxia also affects the stromal compartment particularly cancer associated fibroblasts (CAFs). (**Figure 4**) shows hypoxia stimulates CAF activation via HIF-1α and TGF-β signaling promoting the deposition of extracellular matrix (ECM) components such as collagen, fibronectin and hyaluronan resulting in stromal fibrosis. This dense ECM acts as a physical barrier, impairing drug penetration and creating a sanctuary for hypoxic, chemoresistant tumor cells[67]. CAFs additionally secrete paracrine factors, including growth factors (VEGF, HGF) cytokines, and exosomes carrying miRNAs and lncRNAs which promote EMT, stemness, and cisplatin resistance in neighboring cancer cells.

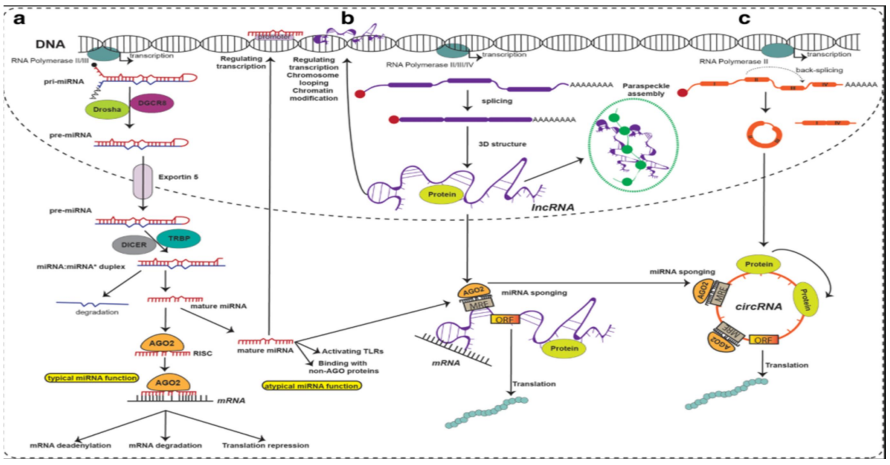

Figure 4 – Non coding RNA and Epigenetic Regulation

5. Integrated Impact on Chemoresistance

Collectively hypoxia driven changes(**Figure 5**) shows in the TME including acidosis, immune suppression, vascular dysfunction and stromal remodeling establish a multifaceted protective niche that Limits cisplatin delivery and accumulation, Enhances survival signaling in tumor cells, Promotes EMT, stemness and metabolic flexibility, Facilitates intercellular communication via exosomes, amplifying resistance[68]. These adaptive features of the hypoxic TME are major contributors to chemotherapy failure in solid tumors highlighting the importance of targeting both cancer cells and their microenvironment in therapeutic strategies.

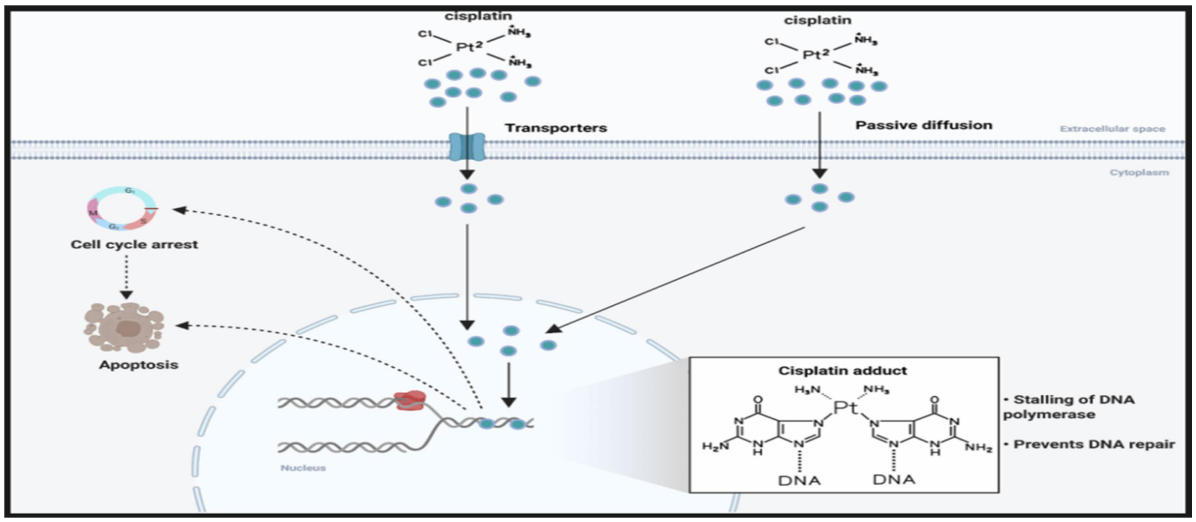

Figure 5 – Integrated Mechanism of Hypoxia Induced Cisplatin Resistance

6. Strategies to Overcome Hypoxia Induced Cisplatin Resistance

Hypoxia is a major contributor to cisplatin resistance in solid tumors (**Figure 6**) shows creating adaptive responses that protect cancer cells from DNA damage, apoptosis and oxidative stress. Therapeutic strategies aimed at modifying the hypoxic tumor microenvironment or exploiting hypoxia specific vulnerabilities have therefore gained increasing attention. Among these hypoxia modifiers and sensitizers are designed to either increase oxygen availability in tumor tissues or selectively target hypoxic cells.

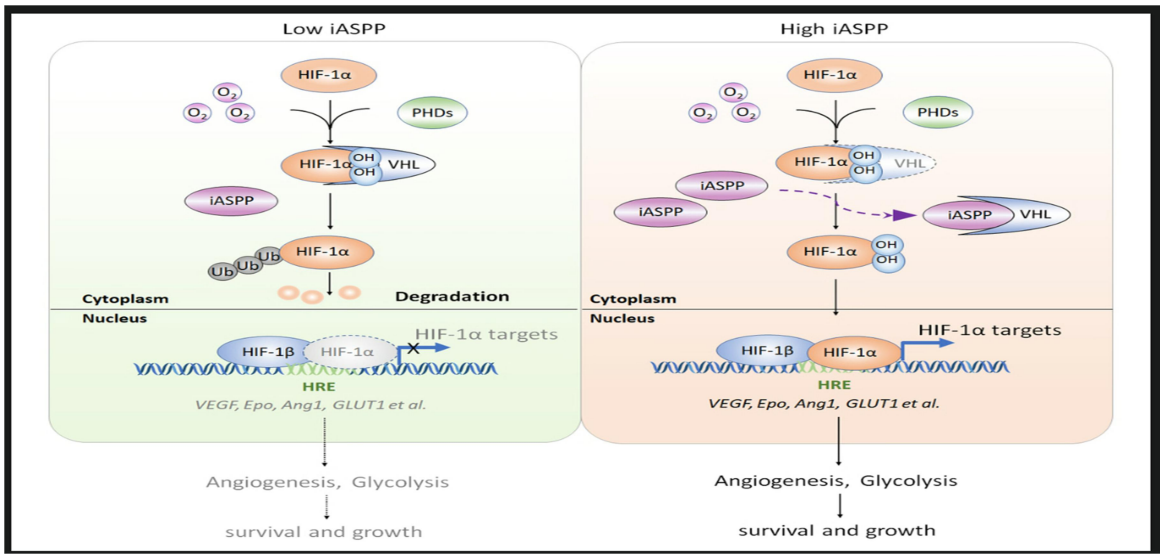

Figure 6 – Future Therapeutic Strategies

6.1 Hypoxia Modifiers and Sensitizers

Hypoxia contributes to cisplatin resistance, and several strategies aim to overcome this by improving tumour oxygenation. **Hyperoxia-based approaches**, such as supplemental oxygen or hyperbaric oxygen therapy, increase oxygen levels in tumours, normalize vasculature, enhance drug delivery, and restore ROS-mediated apoptosis. However, their effects may be temporary and limited in deeply hypoxic regions. **Oxygen carriers and nanoparticles**, including hemoglobin-based carriers, perfluorocarbon emulsions, and oxygen-loaded nanocarriers, provide targeted oxygen delivery to hypoxic tumours, reducing hypoxia-driven survival pathways. Another strategy uses **hypoxia-activated prodrugs** like tirapazamine and evofosfamide, which become cytotoxic only in low-oxygen environments. Combining these hypoxia-targeting strategies with cisplatin can enhance chemotherapy effectiveness and reduce tumour resistance.

6.2 Targeted Therapeutics

Targeting the molecular mechanisms that underpin hypoxia driven cisplatin resistance has emerged as a promising strategy to enhance chemotherapy efficacy in solid tumors. Hypoxia inducible factors (HIFs) particularly HIF-1α and HIF-2α are central mediators of the hypoxic response orchestrating transcriptional programs that regulate angiogenesis, glycolysis, epithelial mesenchymal transition (EMT), DNA repair and Autophagy and drug efflux. Pharmacological inhibition of these pathways as well as modulation of associated epigenetic regulators offers an opportunity to sensitize tumor cells to cisplatin and other cytotoxic agents.

Targeting hypoxia-driven pathways can help overcome cisplatin resistance in tumours. **HIF inhibitors**, such as belzutifan, block HIF-2α activity, preventing transcription of hypoxia-responsive genes.[20] This suppresses angiogenesis, metabolic reprogramming, epithelial–mesenchymal transition, and drug efflux transporter expression, thereby enhancing cisplatin cytotoxicity. Another strategy involves **histone deacetylase (HDAC) inhibitors** like panobinostat and vorinostat, which reverse hypoxia-induced epigenetic changes.[21] These agents promote degradation of HIF-1α, restore tumour suppressor gene expression, inhibit EMT and stemness, and reduce DNA repair capacity, increasing cisplatin-induced apoptosis. Combining HIF or HDAC inhibitors with cisplatin disrupts hypoxia-mediated survival mechanisms and improves chemotherapy sensitivity in hypoxic tumours.

6.3 Autophagy Inhibitors

Autophagy is a highly conserved cellular process that maintains homeostasis by degrading and recycling damaged organelles, misfolded proteins and cytoplasmic components via the lysosomal pathway. Under hypoxic conditions tumor cells exploit autophagy as a cytoprotective mechanism, enabling survival under metabolic stress, nutrient deprivation and chemotherapeutic pressure, including exposure to cisplatin. In hypoxic tumors autophagy facilitates the removal of cisplatin damaged mitochondria and proteins limits reactive oxygen species (ROS) accumulation, and suppresses apoptosis, thereby contributing to chemoresistance.

Autophagy inhibition is a promising strategy to overcome hypoxia-induced cisplatin resistance in cancer. Lysosomal inhibitors such as chloroquine and hydroxychloroquine block autophagosome–lysosome fusion, causing mitochondrial damage, increased ROS, enhanced DNA damage, and activation of apoptosis, though toxicity and tumor penetration remain concerns.[22] Early-stage inhibitors like 3-methyladenine prevent autophagosome formation by inhibiting class III PI3K, increasing cellular stress and sensitizing tumor cells to cisplatin, but have limited clinical use due to off-target effects.[23] Autophagy-related gene inhibitors targeting ATG5, ATG7, or Beclin-1 disrupt autophagic processes and promote apoptosis. Overall, combining autophagy inhibitors with cisplatin may restore drug sensitivity and improve treatment outcomes in hypoxic tumors.[24]

6.4 Exosome Targeting

Exosomes are small extracellular vesicles (30–150 nm) that serve as critical mediators of intercellular communication in the tumor microenvironment (TME). They carry bioactive molecules, including proteins, microRNAs (miRNAs), long non coding RNAs (lncRNAs) and metabolic enzymes which influence tumor progression, metastasis and drug resistance.

Under hypoxia, tumour cells increase exosome secretion, enabling horizontal transfer of cisplatin resistance. Exosomes from resistant cells carry PKM2, HIF-1α–regulated ncRNAs, and anti-apoptotic proteins that reprogram nearby sensitive cells, promoting glycolysis, epithelial–mesenchymal transition, enhanced DNA repair, and autophagy. They also modify the tumour microenvironment by activating cancer-associated

fibroblasts and suppressing immune responses, creating a protective niche. Therapeutic strategies include inhibiting exosome biogenesis (e.g., GW4869 or Rab27a/b inhibitors) and blocking exosome uptake by recipient cells.[25] Combining exosome-targeting agents with cisplatin can prevent resistance transfer, enhance apoptosis, and improve chemotherapy effectiveness in hypoxic tumours.

6.5 Nanotechnology and Drug Delivery Systems

Nanotechnology based drug delivery systems have emerged as a powerful strategy to enhance the therapeutic efficacy of cisplatin in solid tumors particularly under hypoxic conditions which often limit drug penetration and promote chemoresistance. Conventional cisplatin therapy faces challenges such as poor tumor selectivity, systemic toxicity, rapid clearance and inadequate drug delivery to hypoxic tumor regions due to aberrant vasculature and high interstitial pressure. Nanocarriers provide solutions to these limitations by improving drug stability, targeted delivery, controlled release and tumor accumulation.

Nanocarrier systems improve cisplatin delivery and help overcome hypoxia-induced chemoresistance. Liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles enhance drug circulation, tumour accumulation through the EPR effect, and reduce systemic toxicity.[26] Some formulations, such as liposomal cisplatin, also decrease nephrotoxicity. Hypoxia-responsive nanocarriers use pH-sensitive, redox-sensitive, or hypoxia-cleavable linkers to release cisplatin selectively within hypoxic tumour regions, increasing local drug concentration while limiting off-target effects.[27] Additionally, nanocarriers enable co-delivery strategies, combining cisplatin with HIF inhibitors, autophagy inhibitors, or oxygen-generating agents to enhance therapeutic efficacy. Preclinical studies show improved tumor uptake, restored drug sensitivity, and better treatment outcomes in hypoxic and resistant cancers.

7. Clinical Relevance and Translational Challenges

Although hypoxia-targeted therapies show promise, several translational challenges limit their clinical application. Toxicity and off-target effects arise because pathways such as HIF signaling, angiogenesis, autophagy, and metabolism are also essential for normal tissues, leading to potential systemic side effects. **Tumor and patient heterogeneity** further complicate treatment, as hypoxia varies within and between tumors, influencing therapy response and drug delivery.[28] Additionally, **monitoring tumor oxygenation** remains difficult due to limitations in current imaging techniques. To overcome these barriers, strategies include developing reliable hypoxia biomarkers, improving imaging technologies, adopting personalized treatment approaches, and using targeted drug delivery systems such as nanocarriers and hypoxia-activated prodrugs to enhance therapeutic precision and safety.

8. Future Directions

The persistent challenge of hypoxia induced cisplatin resistance in solid tumors underscores the need for innovative, integrative and personalized therapeutic strategies. Future approaches are likely to focus on simultaneously targeting hypoxic adaptation, immune evasion, and chemoresistance mechanisms to improve treatment efficacy.

Hypoxia promotes both cisplatin resistance and immune suppression in tumors by increasing PD-L1 expression, recruiting immunosuppressive cells, and impairing T-cell activity. Modulating hypoxia through oxygenation therapies, HIF inhibitors, and hypoxia-responsive nanocarriers can restore immune function and enhance chemotherapy. Combining these approaches with immune checkpoint inhibitors may produce stronger antitumor responses. Identifying predictive biomarkers—such as HIF-1α, CAIX, GLUT1, and hypoxia-regulated ncRNAs—and using advanced imaging or liquid biopsy can improve patient stratification and treatment monitoring. Future strategies emphasize multimodal therapies integrating cisplatin with hypoxia-targeted agents, immunotherapy, and nanocarriers. These approaches support precision oncology by enabling personalized treatment, optimized dosing, reduced toxicity, and improved clinical outcomes.

9. Conclusion

tumour hypoxia is a major driver of cisplatin resistance in solid cancers. Low oxygen activates HIF-dependent and independent pathways that enable tumour survival through transcriptional reprogramming, metabolic adaptation, autophagy, and exosome-mediated transfer of resistance. Hypoxia also promotes epigenetic changes and dysregulation of non-coding RNAs, including reduced tumour-suppressive microRNAs and increased lncRNAs, supporting epithelial–mesenchymal transition and chemoresistance. Additionally, the hypoxic tumour

microenvironment causes immune suppression, stromal barriers, vascular dysfunction, and poor drug delivery. Overcoming resistance requires multimodal strategies combining hypoxia modulation, targeted therapies, immunotherapy, and nanotechnology-based drug delivery. Integration of hypoxia-specific biomarkers and imaging will enable patient stratification, treatment optimization, and improved clinical outcomes.

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