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Tumor Hypoxia and Radioresistance

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Abstract

Tumor hypoxia is a prevalent feature of solid tumors, significantly contributing to increased tumor aggressiveness, metastatic potential, and resistance to conventional therapies such as radiotherapy. This review explores the complex relationship between tumor hypoxia and radioresistance, highlighting the molecular mechanisms involved and potential therapeutic strategies to enhance radiotherapy efficacy in hypoxic tumors. Key mechanisms include the role of hypoxia-inducible factors (HIFs), particularly HIF-1α, which regulates numerous genes involved in tumor survival, proliferation, and resistance under hypoxic conditions. The review also discusses the oxygen enhancement ratio (OER) and its impact on radiotherapy outcomes, emphasizing how hypoxia leads to reduced radiosensitivity by limiting the formation of radiation-induced DNA damage. Despite the development of various strategies to counteract hypoxia-induced radioresistance, such as HIF inhibitors, hypoxia-targeted gene therapy, and hypoxia-activated prodrugs (HAPs), clinical results have been mixed, necessitating further research. Additionally, advances in imaging techniques for detecting tumor hypoxia are explored, which may allow for more personalized radiotherapy approaches, such as dose painting. The future of overcoming tumor hypoxia in radiotherapy lies in the integration of innovative therapeutic strategies, personalized medicine, and improved imaging technologies, offering hope for enhanced treatment outcomes in cancer patients.

Keywords: Tumor hypoxia, radioresistance, hypoxia-inducible factors (HIFs), radiotherapy, oxygen enhancement ratio (OER)

Abbreviations and Acronyms:

ATP – Adenosine Triphosphate, BOLD MRI – Blood Oxygen Level-Dependent Magnetic Resonance Imaging, CAFs – Cancer-Associated Fibroblasts, CBP – CREB-Binding Protein, DCE-MRI – Dynamic Contrast-Enhanced Magnetic Resonance Imaging, DNA – Deoxyribonucleic Acid, ECM – Extracellular Matrix, ECs – Endothelial Cells, EMT – Epithelial-Mesenchymal Transition, GLUT – Glucose Transporters, HAPs – Hypoxia-Activated Prodrugs, HBOT – Hyperbaric Oxygen Treatment, HBO – Hyperbaric Oxygen, HIF – Hypoxia-Inducible Factor, HIF-1α – Hypoxia-Inducible Factor 1 alpha, HRE – Hypoxia Response Element, MAPK – Mitogen-Activated Protein Kinase, NFκB – Nuclear Factor kappa-light-chain-enhancer of activated B cells, NIRS – Near-Infrared Spectroscopy, OER – Oxygen Enhancement Ratio (ako je ipak odlučiš zadržati), PET – Positron Emission Tomography, PHD – Prolyl Hydroxylase, PI3K/AKT/mTOR – Phosphoinositide 3-kinase/Protein kinase B/Mammalian target of rapamycin pathway, RNA – Ribonucleic Acid, ROS – Reactive Oxygen Species, SBRT – Stereotactic Body Radiotherapy, VEGF – Vascular Endothelial Growth Factor

Introduction

Hypoxia is a frequent and significant characteristic of solid tumors. In tumors, hypoxia occurs when there is an imbalance between oxygen supply and demand. It is strongly linked to tumor progression, greater aggressiveness, increased metastatic potential, resistance to radiation or chemotherapy, and reduced overall survival across different tumor types. Additionally, hypoxia can promote the selection of cell clones that resist apoptosis and contribute to tumor metastasis [1]. Radiotherapy is suitable for treating roughly half of all cancers, yet local recurrence and disease relapse often happen because of clinical radioresistance. Hypoxia contributes to radioresistance via various molecular pathways, and many strategies have been devised to counteract this. However, these strategies have generally yielded disappointing outcomes, with adverse effects and limited effectiveness. Further clinical studies are necessary to gain a deeper understanding of the intricate hypoxia pathways [2]. The primary aim of this review is to explore the complex relationship between tumor hypoxia and radioresistance, with a focus on

identifying potential therapeutic targets and strategies to enhance the efficacy of radiotherapy in hypoxic tumors.

Mechanisms of tumor hypoxia

Rapid growth of tumor cells, insufficient blood supply, and hypoxia are common characteristics of the microenvironment in most solid tumors [3]. Solid tumors are composed of transformed cells encased in a framework of connective tissue or mesenchyme, creating the tumor microenvironment. This environment comprises vascular endothelial cells (ECs), cancer-associated fibroblasts (CAFs), immune cells, and the extracellular matrix (ECM). As tumor cells expand, they enlist surrounding non-tumor cells to participate in collaborative processes that create a tumor microenvironment favorable for local expansion and metastasis to distant sites. This assembly of tumor cells interacting with host cells creates an organ-like structure that is abnormal [1].

Hypoxia in the tumor microenvironment is defined by oxygen pressure levels being below 5–10 mm Hg. This condition results from heightened oxygen consumption linked to significantly increased tumor cell proliferation, and a deficient oxygen supply to cells and tissues caused by the formation of a disorganized tumor microvasculature network featuring leaky vessels that are unable to compensate for the lack of oxygen [4].

Hypoxia triggers various intricate intracellular signaling pathways, including the prominent hypoxia-inducible factor (HIF) pathway. Additional pathways influenced by hypoxia encompass PI3K/AKT/mTOR, MAPK (also recognized as ERK pathways), and NFκB. These pathways play roles in cellular functions such as proliferation, survival, apoptosis, metabolism, migration, and inflammation [5]. The Hypoxia-inducible factor (HIF) is crucial in the adaptive cellular response to hypoxia within the tumor microenvironment. HIF-1 is a type of isoform made up of one of three alpha subunits (HIF-1α, HIF-2α, or HIF-3α) and a beta subunit (HIF-1β, also referred to as aryl hydrocarbon nuclear transporter, or ARNT). HIF-1α is regarded as a key transcriptional regulator of the tumor cell response to hypoxia [3]. Under hypoxic conditions, the breakdown of HIF-1α is decreased, and it moves to the nucleus due to the inhibited function of prolyl hydroxylase (PHD). In the nucleus, HIF-1α combines with HIF-1β to form heterodimers. These HIF-1α/1β heterodimers activate the HIF target gene and enhance HIF expression by interacting with p300/CBP and the hypoxia response element (HRE) [6].

Experimental data specifically show that HIF-1α, a crucial transcription factor for adapting to hypoxia, controls the expression of more than 100 downstream genes.

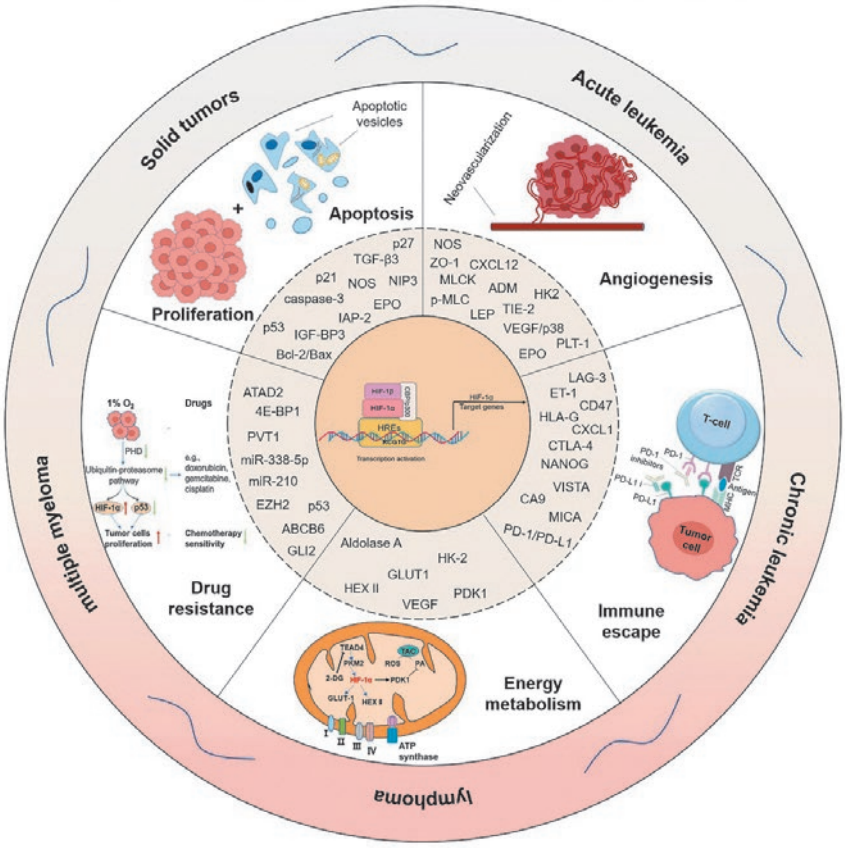

Figure 1. Malignant biological behaviors of HIF-1α in tumorigenesis under hypoxia. In the tumor microenvironment (TME), hypoxia plays a critical role in tumorigenesis due to reduced oxygen delivery and increased oxygen consumption by rapidly proliferating tumor cells. This creates a hypoxic microenvironment (HME) that fosters tumor growth. Under these conditions, HIF-1α accumulates and activates various genes that enhance tumor cell capabilities like proliferation, angiogenesis, energy metabolism, epithelial–mesenchymal transition (EMT), and immune escape, enhancing the tumor's adaptability and aggressiveness in HME.
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10425810/

These genes fall into four main categories essential for protein production and tumor processes: vascular endothelial growth factor (VEGF), glucose transport and glycolytic enzymes (GLUT), factors crucial for tumor invasion and metastasis, and proteins associated with tumor proliferation and apoptosis. During disease progression, these genes can alter the relative homeostasis of the internal environment in tissues and cells under hypoxic conditions. For instance, they regulate not only classical biological behaviors such as stem cell maintenance, cell survival, apoptosis, erythropoiesis, and angiogenesis but also affect the microenvironment and metabolic state of tumors, the energy metabolism of nucleotides, amino acids, and glucose, and participate in immune evasion. Furthermore, HIF-1α significantly adjusts genes related to drug resistance and other response alterations, positioning it as a pivotal factor in tumorigenesis [7].

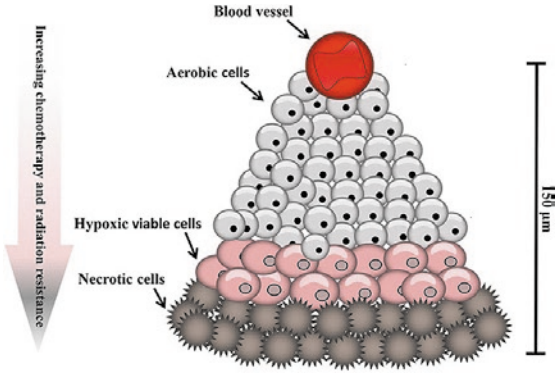

Figure 2. Hypoxic regions of solid tumors. Tumors contain regions of oxygenated cells situated near to blood vessels, becoming increasingly hypoxic with increased distance from a functional blood supply.
Source:https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2019.00004/full

Impact of hypoxia on radioresistance

While hypoxia can be fatal for many cells, a subset of tumor cells not only survives under these conditions but also develops resistance to chemotherapy and radiotherapy. The influence of hypoxia on therapy resistance has been recognized for over 60 years [5]. In 1909, in the Münchener Medizinische Wochenschrift, Gottwald Schwarz demonstrated a reduced skin response to radiation when blood flow to the irradiated area was restricted. Later, Mottram, Crabtree, Cramer, and others more thoroughly investigated the impact of oxygen on radiation effects. They found that cells were significantly more sensitive to X-rays when oxygen was present. The oxygen enhancement ratio (OER) quantifies the relationship between cellular response to ionizing radiation (IR) and available oxygen. It is defined as the ratio of radiation doses needed under hypoxic versus normoxic conditions to achieve the same biological effect. In hypoxic regions, tumor cells' survival rate against ionizing radiation is 2-3 times higher compared to normoxic areas. The concentration and timing of oxygen exposure are critical factors. For inducing apoptosis, molecular oxygen needs to be present either during radiotherapy or within the lifespan of the radiation-induced free radicals. Only a minimal amount of oxygen, about 0.5% or a pO2 of approximately 3 mmHg, is necessary for radiosensitivity [8, 9].

In oxygen-rich conditions, normoxic cells are vulnerable to radiation due to „oxygen fixation," where oxygen molecules react with DNA's free radicals caused by ionizing radiation, leading to irreversible DNA damage. Conversely, cells in hypoxic conditions resist radiation-induced death because of the reduced production of DNA radicals and decreased DNA damage, as there is a lower generation of reactive oxygen species and potential for chemical restoration of DNA [5].

Tumor radiosensitivity varies with the cell cycle. Cells are more resistant to radiotherapy during the late S (chromosome replication) and G0 phases, while being more sensitive during the G2/M phase (separation of replicated chromosomes). Radiation sensitivity shifts throughout the cell cycle, with older cells showing higher oxygen enhancement ratios (OER). In the G1 phase, cells are more radiosensitive with a lower OER compared to the S phase. Under low oxygen conditions, HIF-1α can inhibit the transition to the S phase by upregulating genes that code proteins for cell cycle regulation, such as Waf1 (p21) and Kip1 (p27), leading to cell growth arrest under hypoxic conditions [2]. Additional signaling pathways such as mTOR, NF-κB, and the unfolded protein response are influenced by hypoxia, which in turn modulates further changes in transcription and translation processes [10].

Cells require a specific oxygen concentration for aerobic respiration to produce ATP, the energy source for many biological processes. Both pathological conditions like cancer, inflammation, and diabetes, as well as non-pathological situations such as high altitude, can lead to a state of hypoxia. Cancer cells respond to hypoxia by adjusting their metabolism through changes in gene expression and proteomics, influencing various functions like energy production, vascularization, invasion, metastasis, genetic stability, cell longevity, stem cell maintenance, and resistance to chemotherapy. Hypoxia significantly affects mitochondrial functions and metabolism, including changes in ROS production and signaling. Over the past twenty years, numerous studies have explored how HIF-1 drives metabolic shifts in various pathways such as glycolysis, lipid metabolism, and mitochondrial functions like the ETC and TCA cycles. This interaction between HIF-1 and mitochondria is vital for managing the hypoxic conditions in tumor cells by maintaining oxygen balance through the suppression of mitochondrial oxidative metabolism, thus reducing oxygen use [11].

Strategies to overcome hypoxia-induced radioresistance

Radiotherapy operates on the „5 Rs" of radiobiology: repair of sublethal damage, reassortment within the cell cycle, repopulation, intrinsic radioresistance, and reoxygenation. Developing effective strategies requires consideration of these principles [8]. Ever since the discovery of the hypoxic tumor environment, research has primarily concentrated on sensitizing hypoxic tumor cells and enhancing the hypoxic conditions within tumors. The main approaches to treating hypoxic tumors involve administering drugs that specifically target hypoxic conditions and

enhancing the oxygenation of the tumor environment. Various strategies have been suggested to target hypoxic tumor cells, including specific inhibition of HIFs, gene therapy, and focusing on pathways critical to hypoxic cells like the mTOR pathway. Additionally, the lower pH of tumor tissue compared to healthy tissue provides a unique target for directing acids to induce tumor cell death [3].

Due to the critical role of the HIF system and related hypoxia in cancer cells, they are considered potential therapeutic targets. In recent years, various strategies and drugs aimed at inhibiting HIF activity and its pathways have been developed, though only a few have progressed to clinical trials because of issues like tolerance, selectivity, and specificity concerning HIF isoforms. The primary method involves blocking different stages of HIF activation, including transcription, translation, stability, nuclear transport, heterodimerization, DNA binding, transcriptional activity, and affecting HIF target genes. HIF-1α inhibitors have been studied more extensively than those for HIF-2α, with several chemical agents being tested for these purposes [11].

Hypoxia-targeted gene therapy is a promising approach for selectively treating tumors, enhancing the effectiveness of radiation therapy. This strategy involves the selective delivery of treatments to hypoxic areas of tumors, controlled by hypoxia-dependent transcription and oxygen-sensitive prodrug metabolism, allowing for targeted action against hypoxic, radioresistant tumor cells both in vitro and in vivo. It is now considered important to explore the potential of gene therapy as a supplement to radiotherapy [12]. An effective method to reduce HIF activity involves disrupting the HIF-1α/P300 complex, crucial for hypoxia-induced transcription. Inhibiting the interaction between HIF-1 and P300 curtails HIF-1 expression. The ODD domain of HIF, rich in proline residues, undergoes hydroxylation by prolyl hydroxylase (PHD 1–3), which facilitates HIF-α's binding to the VHL complex, leading to the degradation of HIF proteins. Additionally, IDH1's role in converting isocitrate to α-ketoglutaric acid (α-KG) influences HIF-1α's stability, with increased α-KG lowering HIF-1α expression [3].

Hypoxia-activated prodrugs (HAPs) are bioreductive drugs designed to be selectively activated in the low-oxygen conditions of solid tumors, effectively targeting their hypoxic regions. Currently under investigation, notable examples include tirapazamine and evofosfamide. These drugs have shown promising anti-tumor effects in a variety of pre-clinical and clinical trials, both as standalone treatments and in combination with other therapies [1].

Hyperbaric Oxygen Treatment (HBOT) is a medical procedure that involves administering 100% oxygen at pressures higher than the normal atmospheric levels [13]. Radiotherapy combined with Hyperbaric Oxygen (HBO) therapy is employed in two clinical settings: (1) as a treatment for managing late radiation injuries, and (2) as a radiosensitizer to enhance the efficacy of radiotherapy [14]. Currently, respiratory hyperoxia is frequently used as a supplementary treatment for various conditions, particularly those involving hypoxia or ischemia. In the context of triple-negative breast cancer, HBO (Hyperbaric Oxygen) therapy has been shown to reduce tumor hypoxia, which in turn can curb tumor growth and metastasis. HBO therapy is known to inhibit the hypoxia-activated STAT3, slowing tumor progression and reducing drug resistance. Historical and clinical evidence suggests that HBO improves tumor oxygenation and enhances the effectiveness of both radiotherapy and cytotoxic drugs in treating solid tumors [3].

Radiotherapy modifications: dose escalation and hypofractionation

Conventional fractionation has been a cornerstone of radiation oncology for many years, utilizing a split of the total radiation dose into daily fractions of 1.8 to 2 Gy, administered five days a week, reaching a total of 40–70 Gy. This approach leverages the biological differences between tumor and normal tissues, typically causing less damage to normal tissues while effectively controlling tumor growth. The process of reoxygenation occurs when radiosensitive normoxic cells are depleted after a low dose of ionizing radiation (IR). This leads to the gradual reoxygenation of the surviving, more hypoxic tumor cells over hours or days. With conventional fractionation, this reoxygenation repeats throughout the treatment, improving tumor control by continuously targeting these reoxygenated cells without affecting normoxic normal tissue [15].

Hypofractionation is a type of radiation therapy where fewer but larger doses of radiation, typically greater than 2 Gy per fraction, are administered, leading to a shorter overall duration of treatment compared to conventional low dose fractionated regimens. The effectiveness of hypofractionation is primarily due to the increased biologically effective dose delivered to tumor cells. Additionally, damage to tumor vasculature and the stimulation of antitumor immunity from higher doses per fraction may also contribute significantly. The impact of hypoxia on hypofractionation's effectiveness remains an open question [15]. Research has demonstrated that vascular injury-induced secondary or indirect cell death significantly contributes to the effectiveness of high-dose radiation treatments in tumors. Specifically, exposing an experimental rodent tumor to 10 Gy or more has been shown to cause severe vascular damage, which subsequently leads to indirect tumor cell death [16].

Recent studies, primarily from the Vozenin lab, have revealed that FLASH irradiation, which is administered at ultra-high dose rates exceeding 30-40 Gy/s, significantly reduces normal tissue toxicity compared to traditional clinical irradiation rates of a few Gy/min. The exact biological mechanisms behind the unique sparing effect of FLASH irradiation on normal tissues compared to tumor tissues remain unclear. However, several theories have been suggested, including the rapid depletion of oxygen leading to temporary hypoxia, interactions between radicals, and differences in immune responses when compared to traditional dose rate irradiation [17]. The once popular but now discredited oxygen depletion hypothesis suggested that normal tissues could temporarily resist radiation after exposure to ultra-high dose rates, possibly due to the preservation of stem cell niches in hypoxic regions. Another theory proposed that healthy tissues could better eliminate reactive organic hydroperoxides, preventing harmful Fenton reactions. Additionally, the differential mitochondrial metabolism between normal and malignant tissues has been considered a potential explanation for the observed FLASH effect in radiation

therapy. Before proton FLASH therapy can be routinely applied in clinical settings, several challenges remain, such as defining treatment plans and dose rates for pencil beam scanning. Currently, FLASH conditions cannot be achieved with the photon linear accelerators available on the market. Despite these hurdles, it is anticipated that these technical obstacles will eventually be resolved [25].

Clinical implications – detecting hypoxia and personalized radiotherapy approaches

Accurate detection of hypoxic regions in tumors is thought to help guide treatment choices and enhance tumor response. Although initial clinical attempts to target tumor hypoxia have been mixed, largely due to inadequate patient selection, advances in understanding hypoxia's molecular pathways and the development of new hypoxia markers are making the targeting of hypoxia increasingly feasible [18]. Methods for assessing tumor hypoxia are categorized into three main types: those directly measuring oxygen levels, those analyzing physiological processes involving oxygen, and those assessing the expression of endogenous markers in response to hypoxic conditions [19].

Direct methods for assessing oxygen levels can be implemented either through tissue-based techniques such as needle electrodes and fiberoptic probes, or through blood-based methods which involve measuring or imaging oxyhemoglobin saturation and oxygen diffusion.

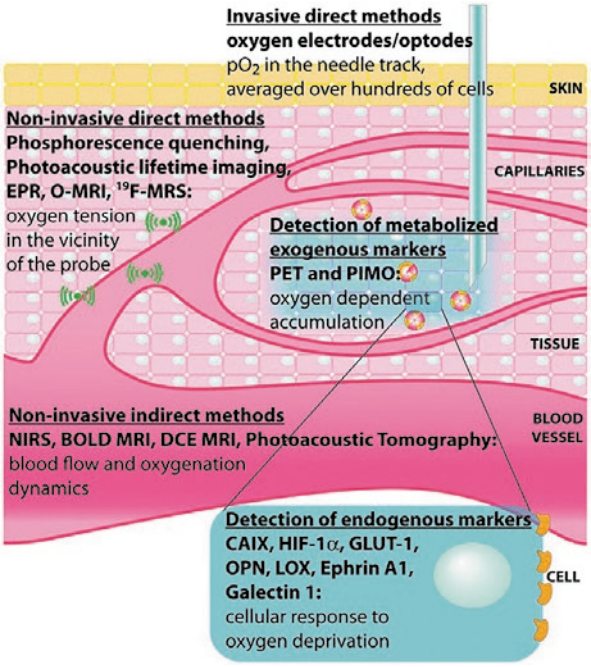

Figure 3. Hypoxia imaging methods and the type of information provided by each modality. BOLD MRI, blood oxygen level-dependent magnetic resonance imaging; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; EPR, electron paramagnetic resonance; HIF-1α, hypoxia-inducible factor 1α; NIRS, near-infrared spectroscopy; OMRI, Overhauser-enhanced MRI; PALI, photoacoustic lifetime imaging; PAT, photoacoustic tomography; PET, positron emission tomography; PIMO, pimonidazole.
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4159937/

Other methods for identifying hypoxic cells in tumors include the immunohistochemical detection of exogenously administered drugs like pimonidazole and EF5, which specifically label hypoxic cells. Additionally, non-invasive imaging techniques such as positron emission tomography (PET) with hypoxia-specific tracers (e.g., 2-nitroimidazole, ^18F-labeled tracers like MISO and FMISO), and MRI methods like blood oxygenation level dependent (BOLD) or tissue oxygenation level dependent (TOLD) MRI, are also used for this purpose. Endogenous molecular markers for tumor hypoxia include proteins and genes that are activated by exposure to low oxygen conditions. The hypoxia-inducible factor-1 (HIF-1) pathway is extensively studied in this context, as it regulates genes associated with critical cellular functions such as metabolism, angiogenesis, invasion, metastasis, and apoptosis [20].

In typical clinical settings, radiotherapy treatments generally involve a uniform dose and fractionation across all patients. Specifically, the same radiation dose is administered to every part of the tumor, without considering the unique biological characteristics and radiosensitivity of different tumor subregions. The technique known as dose painting in radiotherapy involves customizing treatment based on imaging that identifies hypoxic areas within a tumor. Essentially, this method involves selectively increasing the radiation dose to regions of the tumor that are more resistant to standard doses, thereby targeting those areas more effectively [21]. Encouraged by promising preclinical findings of bystander and systemic effects, and positive initial clinical outcomes, this approach is currently being advanced to a phase I clinical trial [15].

Future directions

Various strategies have been developed to target tumor hypoxia, including methods to directly deliver oxygen to tumors, such as the catalytic breakdown of endogenous hydrogen peroxide and light-triggered water splitting. Additionally, numerous clinical trials are exploring hypoxia-targeted therapies using different drugs. A significant focus is on HIF inhibitors, such as PX-478 and LW6, which have shown promising anti-tumor effects both as standalone treatments and in combination with other therapies [1].

Numerous past and ongoing clinical trials are examining anticancer therapies that target the HIF pathways. It's crucial to recognize that while HIF targeting is promising for future cancer treatments, it poses significant challenges, such as the need for specificity to prevent affecting normal tissue functions. Current trials are assessing the toxicities and effectiveness of various HIF-targeted strategies, and more research is needed to fully understand HIFs' complex roles in cancer [23]. Hypoxia-activated prodrugs (HAPs) are bioreductive drugs that become active specifically in the low-oxygen conditions of solid tumors, targeting these hypoxic areas effectively. Research on HAPs, including drugs like tirapazamine and evofosfamide, is ongoing. Both pre-clinical and clinical studies have shown promising anti-tumor results with these drugs, whether used alone or in combination with other treatments. One significant area of focus in targeting tumor hypoxia is the mTOR pathway, crucial for tumor metabolism, where mTOR-targeted drugs help regulate the

tumor microenvironment in hypoxic conditions. Extensive research has aimed to enhance the effectiveness of anti-vascular treatments (like anti-VEGF/VEGFR drugs such as bevacizumab and sunitinib). These strategies suggest that alleviating tumor hypoxia and improving perfusion could boost the effectiveness of radiotherapy, chemotherapy, and immunotherapy. Moreover, blocking PD-L1, which is upregulated by HIF-1α under hypoxic conditions, might offer a new approach to cancer immunotherapy [1]. Hypoxia-activated prodrugs specifically target hypoxic tumor cells and demonstrate selective toxicity and extensive antitumor effects. Drugs that target HIF and downstream genes have effectively suppressed tumors, significantly enhanced patient survival, and shown better tolerability. However, these drugs do come with some toxic side effects. Many clinical trials lack adequate data to fully assess the safety and effectiveness of the drugs being tested [24].

Our current understanding of how tumor cell destruction and normal tissue damage occur in hyperfractionated radiotherapy and stereotactic body radiotherapy (SBRT) and their clinical impact is quite limited. Developing sensitive tools to monitor tumor hypoxia before and during radiotherapy is crucial for overcoming resistance and treatment failures. Hypoxia-targeted dose painting is a promising personalized radiotherapy strategy based on detecting spatial variations in tumor hypoxia, though its impact in routine clinical practice remains minimal [25].

As we look to the future of overcoming tumor hypoxia in radiotherapy, it is clear that interdisciplinary approaches will be pivotal. Innovations in molecular biology and technology promise new therapeutic strategies that could significantly improve oxygenation within tumors, thereby enhancing the efficacy of radiotherapy. Personalized medicine, based on genetic profiling of tumors, may allow us to tailor treatments that specifically target the hypoxic zones, potentially overcoming one of the major hurdles in effective cancer treatment. Furthermore, advancements in imaging techniques could provide more precise mapping of hypoxic areas, enabling targeted radiotherapy that spares healthy tissue while intensifying treatment in resistant tumor sections. Finally, ongoing research into novel agents and modalities, including the use of nanoparticles and hyperbaric oxygen therapy, opens up additional avenues for addressing the challenge of tumor hypoxia. The integration of these new tools and approaches holds great promise for improving outcomes in patients undergoing radiotherapy for cancer.

Conclusion

In conclusion, the relationship between tumor hypoxia and radioresistance presents a significant challenge in the treatment of cancer, yet it also offers a fertile ground for innovative therapeutic strategies. As we have explored, understanding the mechanisms by which hypoxia contributes to radioresistance can lead to more effective treatments, including the use of hypoxia-targeted therapies and advanced radiotherapy techniques. The future holds promise for integrating new technologies and personalized approaches to specifically counteract the protective shield that hypoxia provides to tumors. By continuing to refine our understanding and improving our technological toolset, we can enhance the precision and efficacy of radiotherapy, ultimately leading to better patient outcomes. The journey to conquer tumor hypoxia is complex and requires a concerted effort from researchers, clinicians, and technologists alike, but the potential to significantly improve cancer treatment is clear and compelling. ■

Hipoksija tumora i radiorezistentnost

Sažetak

Tumorska hipoksija predstavlja čestu karakteristiku solidnih tumora, značajno pridonoseći povećanoj agresivnosti tumora, njegovom metastatskom potencijalu i otpornosti na konvencionalne terapije poput radioterapije. Ovaj pregled analizira složenu povezanost između tumorske hipoksije i radiorezistentnosti, ističući molekularne mehanizme koji sudjeluju u tom procesu te potencijalne terapijske strategije usmjerene na povećanje učinkovitosti radioterapije kod hipoksičnih tumora. Ključni mehanizmi uključuju ulogu faktora induciranih hipoksijom (HIF), s posebnim naglaskom na HIF-1α, koji regulira brojne gene uključene u preživljavanje, proliferaciju i otpornost tumora u uvjetima hipoksije. U pregledu se također raspravlja o omjeru povećanja kisika (OER) i njegovom utjecaju na ishode radioterapije, naglašavajući kako hipoksija smanjuje radiosenzitivnost ograničavanjem nastanka oštećenja DNA izazvanih zračenjem. Unatoč razvoju različitih strategija za suzbijanje radiootpornosti uzrokovane hipoksijom, poput inhibitora HIF-a, genske terapije ciljane na hipoksične stanice i pro-lijekova aktiviranih hipoksijom (HAPs), klinički rezultati su često neujednačeni, što ukazuje na potrebu za dodatnim istraživanjima. Osim toga, pregledava se napredak u tehnikama snimanja za detekciju tumorske hipoksije, što bi moglo omogućiti preciznije i personaliziranije pristupe radioterapiji, poput „dose painting“ metode. Budući napori u prevladavanju tumorske hipoksije u kontekstu radioterapije usmjerit će se prema integraciji inovativnih terapijskih strategija, personalizirane medicine i naprednih tehnologija snimanja, nudeći nadu za poboljšane ishode liječenja kod oboljelih od raka.

Ključne riječi: Tumorska hipoksija, radiorezistentnost, faktori inducirani hipoksijom (HIF), radioterapija, omjer povećanja kisika (OER)

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