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Review Article

Current research progress on hypoxia and tumor

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ABSTRACT

Hypoxia is the decrease of normal oxygen tension in tissues. It often occurs in the tissues of acute and chronic vascular diseases or lung diseases and cancerous lesions. Severe or persistent hypoxia can lead to the death of cell. The lack of oxygen in the tumor is mainly due to the absence or deficiency of normal tumor blood vessel function, which results in a decrease of the oxygen diffusion function within the tumor, eventually leading to a series of biochemical reactions. Although hypoxia is toxic on tumor cells, tumor cells still have a strong adaptability. In the hypoxic microenvironment of tumors, tumor cells can produce adaptive changes or genetic changes so that the tumor could survive in an oxygen-deficient environment, even proliferate. Finally, tumor progression will happen. This process visualizes malignant phenotype of the tumor and makes them more aggressive. The epithelial mesenchymal transition in the tumor microenvironment plays an important role in tumor cell migration, invasion, malignant progression and metastasis. Hypoxia leads to epithelial-mesenchymal transition in tumor tissue, reconstitution of extracellular matrix in tumors, and induction of resistance to antitumor drugs. There are many researches related to hypoxia and tumors. The research contents are complex. Targeted therapy for hypoxia is receiving more and more attention, but the overlapping of signal molecules due to the related mechanism between hypoxia and tumors. An effective hypoxia-targeted therapeutic drug that can be used clinically which requires hard work and arduous exploration from researchers.

Keywords: HIF-1α, HIF-2α, Hypoxia, Tumor

INTRODUCTION

Hypoxia is the decrease of normal oxygen tension in tissues. It often occurs in the tissues of acute and chronic vascular diseases or lung diseases and cancerous lesions. Severe or persistent hypoxia can lead to the death of cell. The lack of oxygen in the tumor is mainly due to the absence or deficiency of normal tumor blood vessel function, which results in a decrease of the oxygen diffusion function within the tumor, eventually leading to a series of biochemical reactions. Although hypoxia is toxic on tumor cells, tumor cells still have a strong adaptability. In the hypoxic microenvironment of tumors, tumor cells can produce adaptive changes or genetic changes so that the tumor could survive in an oxygen-deficient environment, even Proliferate. Finally, tumor progression will happen. This process visualizes malignant phenotype of the tumor and makes them more aggressive.

Tumor microenvironment and hypoxia

The tumor microenvironment is one of the most important factor for proliferation, apoptosis, migration and invasion of tumor cell, including the blood vessels around the tumor cells, pH, internal and external environment of the tumor tissue itself, the structure and

function of tumor tissue, metabolic state.[1-5] These factors can act as independent factors or interact together on tumor cells. In this way, changing the survival state of tumor cells, biological behaviors, and metabolism of tumor cells, providing nutrients or oxygen for the proliferation, apoptosis, migration, and invasion of tumor cells and Providing proteins that inhibit tumor progression, activate signaling pathways that inhibit tumor progression, and provide sites for antitumor drugs.

Before the 1950s and 1950s, humans knew little about the hypoxia of tumor tissues. After Gray and other researchers found that the effect of radiotherapy on tumors was closely related to the oxygen concentration in tumors, people began to pay attention to the internal the state of oxidation, which led to decades of research.[6] Finally, they confirmed that oxygen in the tumor microenvironment played a very important role in the proliferation, apoptosis, and malignant progression of tumor tissues.[7-9] The epithelial mesenchymal transition in the tumor microenvironment plays an important role in tumor cell migration, invasion, malignant progression and metastasis. Hypoxia leads to epithelial-mesenchymal transition in tumor tissue, reconstitution of extracellular matrix in tumors, and induction of resistance to antitumor drugs. However, these biochemical changes will not appear alone and are often the intricate interlinkages between multiple factors.[10] The lack of oxygen in the tumor promotes glycolysis, which leads to acidic metabolites accumulate rapidly in the tumor microenvironment and alterations in metabolic pathways in the microenvironment, etc. All those above contribute to the stress response of tumor cells in the presence of hypoxia.[11]

Immunologic cells in the tumor microenvironment also participate in hypoxia stress reactions. Through the hypoxia-inducible factor transcription system or other signaling molecular pathways, lymphocytes and myeloid-derived cells can sense hypoxia and respond accordingly.[12] In many target genes of HIFs, glucose transporter (GLUT-1), glycolytic rate-limiting enzyme, and pyruvate dehydrogenase kinase play a key role in the metabolism of T-lymphocytes and regulate the metabolism of T-lymphocytes activity. The carbon atoms of the pyruvate dehydrogenase kinase enter the trioxygenase cycle and control the activity of mitochondria, active oxygen metabolites, and oxygen consumption in the respiratory transport chain, thereby controlling the activation of T-lymphocytes.[13] Also, the relationship between tumor-associated mast cells and hypoxia in myeloid-derived cells has been studied extensively.[14]

Tumor hypoxia and angiogenesis

The blood vessels inside the tumor

Oncology can provide blood flow through a variety of mechanisms and approaches, including the generation of new blood vessels by sprouting, mimicry of blood vessels, and the conversion of cancer cells to endothelial cells.[15] More than 40 biomolecules are involved in blood vessel formation in these processes. However, among these biomolecules, the most thoroughly studied one is vascular endothelial growth factors and their receptors. The imbalance between the growth of tumors within the tumors and the signal pathways that inhibit tumors growth leads to dysfunction of tumors blood vessels and is affected by tumor blood supply. The blood supply provided by these dysfunctional blood vessels does not satisfy the need for tumor growth, thus making the difference in blood vessels between tumors at different stages and at different sites.[16] This step-by-step heterogeneity of blood supply is a problem to be faced in cancer therapy. If the tumor needs blood supply for growth and metastasis, how does the tumor control angiogenesis and meet its own requirements for nutrients and oxygen? This problem can be understood from this perspective: the overgrowth of tumor cells, the decrease of blood supply, the production of acidic metabolites during cell metabolism, and the resulting local hypoxic environment can in turn promote angiogenesis in tumors and try to satisfy tumor cells'own needs.[17]

Abnormal blood supply eventually leads to changes in the tumor's microenvironment, resulting in tumor cells having the ability to escape in the face of anti-tumor drugs and the body's own immune system, thus being able to survive for a long period of time and continue to proliferate and undergo malignancy changes. Under normal physiological conditions, the body's immune system monitors the body's internal environment, continuously kills pathogens, engulfs foreign antigens, and abnormal cells. However, this immune surveillance functions lost in the tumor microenvironment where blood supply is disordered, anoxic, and acidic substances accumulate. Consequently, macrophages no longer have the role of recognition, phagocytosis, and removal of pathogens.[18-20] In the tumor microenvironment, the accumulation of hypoxia and acidic substances can reduce the killing ability of immune cells and allow tumor cells to survive. However, hypoxia can also screen tumor cells to make tumor cells that survive in a hypoxic environment more malignancy. Because hypoxia can promote the development of tumor-associated proteins that promote tumor cell invasion.[21] This indicates that correcting the hypoxic environment inside the tumor tissue may inhibit the growth and invasion of tumor cells inhibited.

Compared with the blood vessels of normal tissues, the blood vessels of the tumor tissue are more tortuous, cystic and intertwined inside the tissue.[22] The structure of the vascular wall of the tumor tissue is also an abnormal vascular wall structure. It has large gaps between endothelial cells, loses adhesion to pericytes, and its stroma membrane becomes abnormal thick or thin. In addition, leakage of certain parts of tumor blood vessels happens, and these blood vessels changes with the growth

of tumors and anti-cancer treatment constantly. Those are the characteristics of the tumor blood vessel wall.

These features of tumor vasculature lead to uneven perfusion of the tumor in time and space.[23] The reasons for these changes come from two aspects:

- The unlimited growth of solid tumors increases the volume. Thus, it will inevitably generate more pressure, which will compress the blood vessels inside the tissue. Eventually, the blood flow in the blood vessels of the tumor decrease or no blood flow go through.
- Excessive leakage leads to hemoconcentration and extravasation of blood in the blood vessels, and the blood vessels constrict themselves to regulate blood flow inside the tumor.[24]

This abnormal blood supply has many negative effects: the drug cannot form effective therapeutic concentrations in the tumor, the immune cells cannot reach the tumor interior, the tumor is hypoxic, and the extracellular matrix pH is low.[25] Because of these changes, the tumor cells become more aggressive and more prone to distant metastases.

Hypoxia and vascular endothelial growth factor and its receptors

Vascular endothelial growth factor (VEGF) is an important transcriptional targeting factor for hypoxia-inducible factors. Under hypoxic conditions, three important VEGF receptors are upregulated, including: VEGFR, Angiopoietins-Tie-1/Tie-2 and Delta-Notch. Activation of these pathways helps cells self-repair during hypoxia. Regulating the output of these signaling pathways determines angiogenesis, blood supply, tissue perfusion, and tissue remodeling and repair. The VEGF gene family of mammals includes VEGF, VEGF-E, svVEGF and V EGF-A. Under hypoxic conditions, mammalian cells can induce the expression of the placenta-derived growth factor VEGF family.[26]

There are three major classes of VEGF receptors expressed in vascular endothelium and extravascular tissue. VEGFR is a receptor tyrosine kinase that contains a transmembrane domain, an intracellular ligand binding domain, and an extracellular structure. In many human tumors, VEGF expression is elevated.[27] The expression of VEGF in the tumor tissue is related to hypoxia. The more VEGF secreted by the tumor cells, the more favorable the mobilization of myeloid stem cells, and thus play a role in the tumor microenvironment.

Another role of VEGF is to promote tumor angiogenesis, while VEGF inhibitors inhibit tumor growth and metastasis. In the treatment of tumours, blocking the expression of VEGF and its receptors is better than simply blocking one of them. Gerber et al. demonstrated chimeric VEGFR-1 in animal experiments that were capable of tumor growth.[28] However, VEGF inhibitors combined with chemotherapy and radiotherapy can inhibit tumor growth more effectively than monotherapy.[29] Currently, multiple VEGF inhibitors are used for the treatment of various stages of clinical tumors, and targeted therapies targeting VEGF-VEGFR signaling pathways, such as bevacizumab, can significantly reduce the neovascularization area of tumors and are gradually accepted by clinicians and patients. However, the abnormal tumor microenvironment helps tumor cells immune escape through multiple mechanisms, so correcting the abnormal blood vessels in the tumor microenvironment may bring new hope for tumor treatment.

Studies of VEGFR signaling pathways have been shown to influence the expression of hypoxia-inducible factors and their phosphorylation. Recent studies on neuroblasts have shown that VEGF-induced VEGFR-1 activation can lead to increased expression of HIF-1α and HIF-2α proteins.[30] Studies on neuroblastoma tissue have found that HIF-2α protein expression levels are positively correlated with VEGF and affect patient outcomes.[31] In addition, the level of HIF-1α phosphorylation decreases with the inhibition of VEGF/VEGFR-1, and in this process, ERK1/2 participates in the two-way changes in the regulation of HIF and VEGF/VEGFR-1 expression. At the same time, neuroblastomas positive for VEGFR-1 expression showed increased tolerance to antitumor drugs such as etoposide, cyclophosphamide, and Adriamycin.[32] Activation of VEGFR-1 is affected by the anti-apoptotic protein bcl-2 and the angiogenic factor FGF (fibroblast growth factor). Therefore, activation or inhibition of the VEGF/VEGFR-1-HIF loop affects the tolerance of cells to drugs during hypoxia.[32]

Similarly, studies have reported that there is an interrelationship between hypoxia-induced HIF-1α and VEGF/VEGFR-2 loops within endothelial cells.[33] VEGFR-2 is an important signaling pathway molecule in endothelial cells. VEGFR-1, though less active than EVGFR-2, binds VEGF more than 10 times higher than VEGFR-2.[34] This situation may be that VEGFR-1 may act as an inducer, preventing the binding of VEGFR-1 to VEGF. However, there are reports in the literature that VEGF/VEGFR-1 is also secreted in many tumors.[35]

Hypoxia and tumor immunity

The process of tumor antigen-specific recognition in tumor microenvironment is regulated by T lymphocytes, and natural killer cells participate in the immune response process of tumor cells by recognizing antibodies on the surface of tumor cells.

Under hypoxic conditions, the physiological function of lymphocytes has undergone clear changes. The relevant mechanisms include the activation of VEGF signaling pathways, the recruitment of Treg cells, the activation of myeloid-derived suppressor cells and monocytes.[12]

Tumor infiltrating lymphocytes are widely present in different parts of the tumor tissue. At the site of tumor hypoxia, more regulatory T cells (Tregs) were seen, whereas effector T cells appeared more around the blood vessels. Because of the invasion, studying the mechanism of hypoxia-regulating T cell function, activation state, and differentiation process is the basis for understanding the role of T cells in tumor tissues.

Whether hypoxia or normoxia, T cell antigen receptor (TCR) activation is dependent on rapamycin target protein, and TCR activation results in increased expression of HIF-1α Previous studies have suggested that HIF-1α is a negative regulator of effector T cell responses, and in fact, T cell proliferation in the absence of HIF-1α shows a significant upregulation. [36,37] Hypoxia and hypoxia-inducible factors play an indirect immunosuppressive role in the tumor microenvironment, in addition to direct effects on T cells. For example, hypoxia induces TGF-beta and the chemokine CCL28, which promotes the function of Tregs into the tumor microenvironment. These regulatory T lymphocytes, in turn, can promote tumor angiogenesis and increase tumor cell tolerance to the surrounding environment.[38-40] The elevated expression of CD73 and CD39 extracellular enzymes in a hypoxic environment can metabolize extracellular ATP to adenosine, which binds to receptors on the T cell membrane and promotes the elevation of cyclic adenosine phosphate in the cell. Adenosine phosphate is a negative regulator of T cell function.[41] Summarizing these findings, we can easily find that HIF in the tumor microenvironment plays an inhibitory role in tumor immunity.

In the adaptation of tumor cells, such as the enhancement of proliferative capacity and the uninhibited growth of tumor cells, the metabolic levels and related signaling pathways in the tumor microenvironment have also changed, and this change provide nutrition for tumor cells. The energy needed for material and tumor activity. Inside the tumor tissue, tumor-infiltrating immune cells and tumor cells are in the tumor microenvironment. It is easy to understand that tumor cells and tumor-infiltrating immune cells have a similar ability to adapt to the tumor microenvironment. This is particularly evident in T lymphocytes, which rapidly proliferate and have a large energy requirement. Under hypoxic conditions, the energy of these cells depend more on anaerobic glycolysis. HIF-1α controls the metabolism of key enzymes of glycolysis and controls the entry of pyruvate into the tricarboxylic acid cycle to provide sufficient metabolic energy for immune cells.[42]

For the relationship between tumor cell hypoxia and immunosuppression and immunotherapy, there are still many mechanisms that have not yet been clearly recognized. The mechanism of hypoxia on the function of immune cells and the relationship between the immune system and hypoxia cannot be clarified. Therefore, regulating the function of immune cells in the tumor cell microenvironment, exploring the molecular mechanisms, and better applying immunotherapy to the treatment of tumors is a subject worthy of further study.

Hypoxia and hypoxia-inducible factors

Hypoxia and hypoxia-inducible factor 1α

In 1991, Semenza et al found a transcription factor in related studies of erythropoietin.[43] Further studies showed that many transcriptional regulatory genes that bind to this gene can enhance their transcriptional activity. It can often be induced by hypoxia. The gene was eventually named hypoxia-inducible factor 1α.[44] Cells are in different life cycles and their internal HIF-1α expression levels are different. In addition to the regulation of O2, transcription and synthesis of HIF-1α is also regulated by a variety of growth factor signaling pathways and signaling molecules. In normoxic conditions, HIF-1α degrades rapidly and its half-life is very short.[45] On the contrary, the structure of HIF-1α under hypoxic conditions is very stable, which is related to its receiving phosphorylation, acetylation and regulation of ubiquitination and phosphorylation in anoxic environment.

In view of the many important roles of HIF-1α in tumor progression and metastasis, inhibitors targeting HIF-1α signaling pathway are attracting more and more attention. The signaling pathways involved in HIF-1α are extremely complex, including multiple signaling pathways, and the roles of these signaling pathways overlap and cross each other. Each pathway has a target that can be used to design treatment protocols. It is also because of this that HIF-1α inhibitors are mainly targeted to endogenous molecules and have little clinical benefit. Therefore, finding new HIF-1α inhibitors is extremely difficult.[46]

Hypoxia and hypoxia-inducible factor 2α

There are three differences between hypoxia-inducible factor 2α and HIF-1α. First, the expression of HIF-2α is different from that of HIF-1α in different tissues. Secondly, the expression of HIF-2α is less demanding on hypoxia. HIF- 1α expression requires a lower oxygen concentration. Thirdly, these two express at different time. HIF-1α expression may be short-term expression, while HIF-2α expression is longer and lasts longer.[47-49] Based on the above differences, the role of HIF-2α in many aspects is different from that of HIF-1α. The two have differences in the regulation of target genes and signaling pathways. HIF-1α is more involved in endothelial cell proliferation, migration and blood vessel sprouting, while HIF-2α is involved in maintaining vascular morphology and integrity.[50]

Hypoxia and tumor metastasis

In the tumor microenvironment, hypoxia-induced pathological changes are important factors that lead to

cell development, growth, invasion and metastasis, as well as resistance to treatment.[51] In the early stage of tumorigenesis, as the tumor size increases, the demand for nutrients in tumor cell metabolism increases, gradually leading to hypoxia in tumor cells. The tumor cells away from the blood vessels, due to lack of oxygen sufficient nutrient supply and oxygen, make the tumor cells internal hypoxic signal activation. These cells produce VEGF and angiogenesis-related molecules that induce angiogenesis in tumors, which play an important role in the progression of tumor cells.[52] As the tumor size increases, hypoxia affects cells within the tumor stroma, such as: endothelial cells, tumor-associated macrophages, tumor-associated fibroblasts, and pericytes and smooth muscle cells.[53] When stimulated by hypoxia, these cells produce growth and survival-related factors that make the tumor cells more invasive and more resistant to drugs, but also tumor cells are more likely to leave distant metastases from tumor tissue.

For example, recently reported tumor-associated macrophages can help tumor cells invade blood vessels.[54]

Hypoxia not only affects the growth and vascular permeability of tumor cells, but also changes the tumor cells themselves, making them more suitable for tumor survival and growth in tumor microenvironment. At the same time, metastatic tumor cells can escape immune surveillance in the circulation, and cloning, which makes it continue to grow away from the primary site of the tumor. Hypoxia opens the process of using glycolysis to generate energy inside tumor cells. This process occurs earlier than the formation of new blood vessels within the tumor. The oxygen concentration inside the tumor temporarily returns to normal levels.[55] As previously mentioned, the disordered nature of tumor blood vessels often occurs instantaneously with no attention and conversion between concerns. This conversion results in a high concentration of reactive oxygen species in the cells. This high concentration of reactive oxygen species leads to dedifferentiation and transfer of the cells.[56]

Hypoxia and tumor resistance

After hypoxia, tumor cells induce the expression of HIF-1α and HIF-2α, which activates relevant signaling pathways. Activation of these signaling pathways not only affects the cell's proliferative capacity and invasion and metastasis capacity, but also has an impact on antitumor therapy.

HIF-1α inhibits DNA damage by inhibiting P53, thereby inhibiting apoptosis induced by DNA damage.[57] Studies have found that HIF-1α is involved in the resistance of tumor cells in a variety of tumor cells.[58] It has been demonstrated in animal experiments that the expression of HIF is inhibited and can effectively increase the anti-tumor effect of platinum-based drugs that inhibit tumor proliferation.[59] Different tumor cells, HIF induced drug resistance increases the mechanism is also different. HIF-1α can reduce the concentration of intracellular drugs by activating the expression of multi-drug resistance gene (MDR-1), thereby affecting the anti-tumor effect, and at the same time, it can increase the expression level of multi-drug tolerance-related proteins and thus cause tumor cells are resistant to drugs under hypoxic conditions.[60] HIF-2α and drug resistance in tumors may also be related to P53 genes. It has been reported in the literature that HIF-2α is involved in Fas-induced apoptosis and increases drug resistance.[61]

CONCLUSION

In short, there are many researches related to hypoxia and tumors. The research contents are complex. Targeted therapy for hypoxia is receiving more and more attention, but the overlapping of signal molecules due to the related mechanism between hypoxia and tumors. An effective hypoxia-targeted therapeutic drug that can be used clinically which requires hard work and arduous exploration from researchers.

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