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Research Progress of Hypoxic Tumor Microenvironment in Tumorigenesis

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ABSTRACT

This article talks about the hypoxic tumour microenvironment (HTM) in several types of tumours, such as ovarian cancer, breast cancer, pancreatic ductal adenocarcinoma, lung cancer, and liver cancer. Researchers have found that hypoxia can make hypoxia-inducible factors (HIFs) work, especially HIF-1α. It is very important for how tumour cells grow, divide, invade, and get away from the defence system. HTM also changes the growth of blood vessels in tumours, the way immune cells work, and how tumour cells get away from immune monitoring. These results show how complicated HTM's part is in the growth of tumours and point the way to possible targets for the creation of new treatment approaches. Starting from now on, it is very important to fully comprehend how HTM works and how it is controlled. This not only helps to find the deep rule of how tumours grow, but it also encourages the creation of more precise medical treatments for HTM. Some examples are drugs that stop HIF-1α from working properly, treatments that stop tumours from growing new blood vessels, and vaccines that change the immune system's surroundings. It's possible that therapy will be used to treat cancer in the future. It was also looked into how HTM affects other factors in the tumour microenvironment, like acidity and interstitial pressure. It will also give us a new way to think about how to treat tumours in a more complete way.

KEYWORDS

Tumor microenvironment; Hypoxia inducible factor; Tumor

1. OVERVIEW OF TUMOR MICROENVIRONMENT AND HYPOXIC TUMOR MICROENVIRONMENT

The special place where tumour cells live is called the tumour microenvironment (TME) [1]. This is a complicated and varied group of cells where tumours grow [2]. This structure is mostly made up of tumour cells, immune cells, fibroblasts that are linked to cancer, endothelial cells, parietal cells, other tissues, resident cells, and the fluid, vascularised extracellular matrix that these cells interact with [3]. As cancer gets worse, the oxygen intake isn't enough because tumour cells are multiplying so quickly and randomly.TME has hypoxia, which means that tissues can't get the usual amount of oxygen (normoxia) they need [4]. Having a hypoxic tumour microenvironment (HTM) can change more than just the metabolism and biological behaviour of tumour cells. It can also change how immune cells work, how tumour blood vessels form, how tumours spread and migrate, and how they respond to treatment [5].

Hypoxia-inducible factors (HIFs) are very important for tumour cells to stay alive and do their work when oxygen levels are low. They help tumours grow into cancerous cells by controlling the production of certain genes or the growth of certain miRNAs [6]. Hypoxia-inducible factor 1 (HIF-1α) is turned on when HTM is in a hypoxic state. HIF-1α controls many types of cells in the TME to

make glycolytic genes more active. And slow down the mitochondrial breathing rate of tumour cells that are in places with low oxygen.Also, the immunity escape process that HIF-1α controls makes tumour cells much more likely to survive [7]. But oxygen may control miRNA activity in new ways at the molecular level, in addition to changing how miRNAs are expressed and processed. It was found that M1 type linear ubiquitination change of the AGO2 protein controls the balance of mRNAs when oxygen levels are low. This gives us a new way to look at how tumour cells adjust to low oxygen levels [8]. Therapeutic strategies for HTM include reversing tumor hypoxia, neutralizing tumor acidity, scavenging reactive oxygen species, and reducing interstitial pressure. It is being actively explored in order to enhance the infiltration of immune cells into tumors and enhance anti-tumor immune response.

In conclusion, coming up with new ways to treat cancer requires a deep understanding of the role of HTM in tumour growth and treatment. This will not only make current treatments work better, but it may also help find new targets for therapy. This has a huge effect on how tumours are treated in the clinic. Therefore, the research of HTM is a hot spot in the field of oncology. Its scientific exploration is of immeasurable value for future cancer treatment.

2. THE POSSIBLE MECHANISM OF HYPOXIC TUMOR MICROENVIRONMENT PROMOTING TUMORIGENESIS

2.1. Liver Cancer

When there was mild hypoxia, HIF-1αbecame more stable. This makes tumor-associated macrophages, which are the main pro-inflammatory cells in the tumour, release more interleukin (IL)-1 beta. More IL-1βis found in the area around the tumour, and this helps HCC cells make more HIF-1α through cyclooxygenase-2 [9]. Hepatocellular carcinoma (HCC) cells can also go through epithelial-mesenchymal transition (EMT) when HIF-1αlevels are too high. miRNA controls this process and makes it easier for tumour cells to move and invade other cells.And help them avoid planned cell death [10]. Hypoxic conditions or HIF prolyl hydroxylase inhibitors caused transmembrane 4L6 family member 1-antisense RNA 1 levels to rise in HCC cells.Stopping HIF-1α from working can greatly lower its levels, which can have an impact on how quickly HCC cells divide, move, and invade other cells [11]. Also, HIF-1α can directly increase the expression of RAS-like CAAX1, and the amount of expression of RAS-like CAAX1 in HCC cells is linked to it in a good way. Its down-regulation can slow the movement and spread of HCC cells caused by low oxygen [12]. At the same time, the high level of HIF-1α when oxygen levels are low can make up for the fact that HIF-1α silence stops HCC cells from migrating and invading by increasing IL-8Action [13]. Also, less HIF-1α and HIF-2α expression stopped RNF146, a new HIF target gene, from becoming more active when oxygen levels dropped. Changes in its expression have big impacts on the growth, colony formation, and glycolytic activity of hepatoma cells [14].

2.2. Gastric Cancer

Hypoxia-inducible factor-1α (HIF-1α) levels are high in stomach cancer tissue, which is linked to tumour cells spreading and multiplying more quickly [15]. According to the research, the rise in HIF-1α is caused by more aerobic glycolysis, which causes target glycolytic genes to be expressed more and mitochondrial biosynthesis to slow down. This gives tumour cells more energy and biosynthetic precursors, which helps them grow [16]. Furthermore, high levels of HIF-1αwere strongly linked to the activation of macrophages that are linked to tumours and the invasion of epithelial-mesenchymal transition (EMT) cells. EMT is an important cell biology process that lets epithelial cells become mesenchymal cells. These mesenchymal cells have better movement and invasion abilities, which are important for the growth and spread of tumours [17]. In conditions with low oxygen, the production of CXCL6 (a chemokine ligand) went up a lot in stomach cancer cells. Through a transcriptional

regulation process, HIF-1αcontrols the production of CXCL6. This, in turn, changes the ability of gastric cancer cells to migrate and invade [18]. CXCL6 is a key inflammation factor that brings immune cells to the area around a tumour.But the fact that its expression goes up in tumours may also have something to do with how tumour cells invade and spread. The high amount of HIF-1α also increased the production of VEGF, which is a vascular endothelial growth factor. VEGF helps new blood vessels grow by attaching to the right receptors on vascular endothelial cells and starting signalling pathways for low oxygen [19]. Through this process, oxygen and nutrients are delivered to tumour cells, which helps them keep growing and spreading.

2.3. Lung Cancer

A protein called hypoxia-inducible factor-1α (HIF-1α) is very important in the development and spread of lung cancer [20]. Studies have shown that HIF-1α expression is greatly increased in human lung cancer cells and CAFs that are connected to tumours. These results show that a low-oxygen situation can help fibroblasts make more HIF-1α and change them into CAFs [21]. Some substances that block or turn off HIF-1α can greatly lower the activity of CAFs. It was found that type I collagen α 2 and α smooth muscle actin were expressed less. Also, HIF-1α in CAFs can turn on the nuclear factor κB signalling pathway, which makes it easier for CC chemokine ligand 5 to be released.In this way, it helps the tumour grow [22]. It was also found that the expression of neuropilin 1 was positively linked to the production of HIF-1α. A bad outlook is linked to their high expression and vasculogenic mimics.By controlling neuropilin 1, HIF-1αcan help lung cancer cells move, invade, and grow into vasculogenic mimics [23-24]. Higher amounts of HIF-1α were found in non-small cell lung cancer (NSCLC) cells. A gene called Yes related protein (YAP) helps most tumour cells grow. YAP is easier to find in the nucleus when there isn't enough oxygen, and cancer cells have lower levels of phosphorylation for it [25-26]. YAP protein increased the number of tumour cells and helped NSCLC cells move and invade other cells. So, HIF-1αcontrols apoptosis by starting the YAP signalling pathway and encouraging NSCLC cells to grow and spread [27].

2.4. Breast Cancer

Hypoxia in the tumour setting sets off a complex set of molecular processes that cause breast cancer to grow.In order for breast cancer cells to avoid being killed by the defence system. First, breast cancer cells use the CD47 protein, which is found on the outside of the cell, to avoid being eaten by tumor-associated macrophages (TAMs) and bone marrow-derived suppressor cells (MDSCs) [28]. The signal binds with SIRP alpha on the surface of immune cells. This stops immune cells from engulfing tumour cells [29]. The activity of HIF-1αis increased when there isn't enough oxygen in the blood. This not only increases the amount of the CD47 gene on the surface of breast cancer cells, but it also raises the expression of programmed death ligand 1 (PDL1). When PDL1 binds to the PD-1 receptor on the surface of CD8+ T cells, it stops these cells from fighting tumours. This is a very important "immune checkpoint" [30]. At the same time, tumor-associated macrophages (TAMs) release molecules such as transforming growth factor beta (TGF beta). TAMs help tumour cells avoid being detected by the immune system because they have M2 type traits that reduce inflammation and promote repair [31]. VEGF, a vascular endothelial growth factor, is released by M2 macrophages when oxygen levels are low. This may also help tumour development. It makes it easier for tumours to get air and food, and it may also control how immune cells move and work [32]. When there isn't enough oxygen in the tumour area, there is more FoxP3, which controls the development of regulatory T cells (Tregs). Increasing the number of Tregs stops CD8+ T cells from killing cancer cells and slows down the killing process [33-34].

To sum up, breast cancer cells change molecules in low oxygen levels to affect immunity cells in a number of different ways. Among these are directly stopping immune cells from killing, changing the makeup of immune cells, and stopping an effective immune response through an immune checkpoint route to allow immune escape in the tumour microenvironment.

2.5. Pancreatic Ductal Adenocarcinoma

A low-oxygen situation is an important part of how pancreatic ductal cancer (PDAC) grows and spreads. It can greatly increase the activity of two important cell signalling pathways, namely the PI3K/proteinAKT signalling pathway and the transforming growth factor-beta (TGF-β) signalling pathway [35]. Turning on these paths is a very important part of many biological processes, including how tumour cells grow, differentiate, stay alive, and use energy. In particular, TGF-β helps tumours grow in a number of ways because it is a multipurpose cytokine. Not only can it help tumour cells grow and spread, but it can also help control cell differentiation and dedifferentiation. The PI3K/AKT signalling system controls cell growth, metabolism, and the process of stopping cells from dying. It controls how long tumour cells live and how many of them there are [37]. During this process, it was seen that hypoxia increased the production of FBLN5 (fibrin-5). FBLN5 is a protein that works in the extracellular matrix (ECM). It does this by stopping fibronectin and integrins from interacting with each other on the surface of cells. This breaks the link between the ECM and tumour cells. This kind of damage can affect the ECM's molecular stability and change how cells interact with the matrix, making it easier for tumour cells to stay alive and grow. So, the increased level of FBLN5 in the area around the tumour, mainly in CAFs (cancer-associated fibroblasts), may help lead to the growth of PDAC [38].

2.6. Ovarian Cancer

It is thought that ovarian cancer grows and spreads in an area with low oxygen levels by interacting with many different molecules and signalling pathways. To begin, hypoxia is a key part of tumour angiogenesis, which helps new blood vessels grow by getting VEGF to be made. HIF-1α plays a big role in this process [39]. Hypoxia can also make ovarian cancer cells produce CD147, an MMP inducer that plays a part in the inflammatory reaction as well as the invasion and metastasis of tumours. It's possible that high levels of CD147 are linked to tumour growth quickly and low oxygen levels. The 3'flanking end of the CD147 gene is a target site for HIF-1α.Hypoxia was found to be a trigger for CD147 upregulation [40]. At the same time, hypoxia stops SIRT1 from coding and starts the epithelial-mesenchymal transition (EMT). This last one is very important for the development of organs in embryos and the spread of cancer. Hypoxic stress can cause the production of SUMO ligase PIASy, which lowers the expression of SIRT1 [41]. This can help EMT happen.Also, the production of LOX, which is controlled by HIF-1α, is closely linked to the spreading and invasion of epithelial ovarian cancer. Higher levels of HIF-1α and LOX are found when there is not enough oxygen in the blood [42]. Stopping LOX action can help cancer cells spread and invade more areas [42]. Hypoxia also makes ovarian cancer cells more likely to spread by increasing MT1-MMP levels through Snail.Overexpressing Snail protein may make cells more likely to invade other cells. However, transfecting Snail with siRNA can lower MT1-MMP production and cell invasion [43]. The levels of TAZ and YAP, which are part of the Hippo-YAP signalling system, changed when oxygen levels were low. The phosphorylation and overall production of YAP went down when there was hypoxia, but the phosphorylation of TAZ went up.It's possible that this will help epithelial ovarian cancer grow and spread [44]. It's also possible for hypoxia to lower the amount of methylation in the hypoxia response element of the S100A4 gene. It has been shown that HIF-1αcan attach to hypomethylated HRE and help ovarian cancer spread and invade [45]. In a low-oxygen setting, these complicated chemical processes work together to help ovarian cancer grow and spread.

3. CONCLUSION AND PROSPECT

This article talks about the hypoxic tumour microenvironment (HTM) in several types of tumours, such as ovarian cancer, breast cancer, pancreatic ductal adenocarcinoma, lung cancer, and liver cancer. Hypoxia-inducible factors (HIFs), especially HIF-1α, are activated by low oxygen levels. HIF-1α is a key factor in how tumour cells grow, divide, invade, and get away from the immune system. By

controlling the production of certain genes and miRNAs, HIF-1α helps tumours grow and become resistant to treatment.HTM also changes the growth of blood vessels in tumours, the way immune cells work, and how tumour cells get away from immune monitoring. HTM has many effects on tumour growth, such as helping tumour cells change their metabolism, making it easier for tumour cells to invade and metastasise, starting immune escape mechanisms, and changing the structure and function of the tumour microenvironment by changing the make-up of the extracellular matrix. These results show how complicated HTM's part is in the growth of tumours and point the way to possible targets for the creation of new treatment approaches.

Starting from now on, it is very important to fully comprehend how HTM works and how it is controlled. This not only helps to find the deep rule of how tumours grow, but it also encourages the creation of more precise medical treatments for HTM. Some examples are drugs that stop HIF-1α from working properly, treatments that stop tumours from growing new blood vessels, and vaccines that change the immune system's surroundings. It's possible that therapy will be used to treat cancer in the future. It was also looked into how HTM affects other factors in the tumour microenvironment, like acidity and interstitial pressure. It will also give us a new way to think about how to treat tumours in a more complete way. More and more research is being done on the role of HTM in the development of cancer. This research can not only lead to new ways to treat cancer, but it may also find new therapeutic targets that are important for future cancer treatment, both in terms of science and medicine.More study needs to be done on how HTM works at the molecular level and how it affects other things in its surroundings. And the creation of new ways to treat HTM.

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