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Natural product target on HIF inhibition

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Abstract. Lack of oxygen limits the growth of healthy cells. Surprisingly, however, 90% of solid tumors exhibit hypoxia, and this property of hypoxia is directly linked to tumor proliferation, differentiation, angiogenesis, energy consumption, the emergence of treatment resistance in cancer, and a worse prognosis for patients. However, as a tumor grows and oxygen levels drop, a gene called hypoxia-inducible factor (HIF1) is activated. Through its function as a transcriptional regulator, HIF1 reduces or even completely shuts down oxygen consumption processes in mitochondria, particularly oxidative phosphorylation, making glycolysis the primary source of energy for cancer cells. Given the link between cancer cells and HIF1, HIF1 is expected to be an effective pharmacological target for cancer therapy. This paper tends to introduce several inhibitors according to the characteristics of HIF1, which will provide a new idea for cancer treatment.

Keywords: HIF inhibition, natural product, HIF signaling pathway.

1. Introduction

Genetic mutations lead to unchecked growth and reproduction in human cells, which results in cancer. Human regular cells and malignant cells both require nutrition and oxygen to multiply. Once a cancer cell has been formed in the body, it divides and multiplies day and night while competing with healthy cells for nourishment. When the number of cancer cells grows large enough, tumor tissue can be seen. Tumor tissue must have an extremely high cell density to form, but because the body can only hold so much oxygen, the tumor tissue's microenvironment is anoxic. A key transcription factor that regulates cellular oxygen fluctuations and body homeostasis is HIF-1. It is composed of HIF-1a and HIF-1b subunits. Previous research has shown that the activity of HIF is controlled by the proteasome's response to the presence of oxygen in its component. The VHL E3 ubiquitin ligase interacts with HIFS at physiological oxygen levels, and the presence of ubiquitin causes HIF1a to become unstable and express less [1, 2].

By increasing the transcription of multiple oncogenic genes, HIF1 are essential for the adaptability of tumor cells to hypoxia and nutritional restriction [3]. Hypoxia is induced by tumor cells using a variety of ways. Through a variety of blood vessel-related effects, they disrupt oxygen transport or disrupt endothelial function, creating a chronic hypoxic environment, activating the hypoxia-inducing factor HIF signaling pathway, and increasing tumor development, invasiveness, and metastasis. As a result, HIF1 inhibition can be a useful target for cancer therapy. In order to achieve this, the various HIF1 synthesis and degradation processes will be examined below, and a summary of HIF-1 inhibitors in some natural products of the HIF1 signaling pathway will be given.

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2. Inhibitors of HIF-1α synthesis

The transcription, translation, and degradation processes for HIF-1 protein are the same as those for regular proteins. As a result, this section will discuss the HIF-1 protein's inhibitors in the transcription, translation, and modification processes.

The mechanism of HIF-1 protein synthesis that has drawn the most interest from researchers is the PI3K/AKT/mTOR signaling pathway, which regulates the translation of HIF-1A. Insulin, PC-3, DU145, EGF, and HIF-1 were all raised. These complexes increase the expression of erythropoietin, VEGF, and GLUT1, after they associate with the HRE and p300/CBP.

By inhibiting PI3K, the antibiotic wortmannin, which is produced by Penicillium wortmanni, prevents HIF1 nuclear accumulation. By inhibiting PI3K, rapamycin prevents insulin- and hypoxia-induced HIF-1 accumulation in human ARPE-19 cells and PC-3 cells. Everolimus (RAD001), an oral medicinal substitute for rapamycin, improved HIF-1 inhibitory effect in vivo and prevented the RMG-1 tumor from developing in ovarian clear cell adenocarcinoma.

Studies showed that PI3K/AKT/mTOR inhibition decreased HIF-1 activity, which in turn inhibits tumor angiogenesis. These compounds demonstrated hypoxia-selective growth inhibition and downregulation of the HIF-1. Further investigation indicated that the protein RPAP3, which results in mTOR dysfunction, is the precise target of dictyoceratins. It was discovered that verucopeptin, a cyclic isolated peptide from Actinomadura verrucosospora, inhibits the HIF-1 signaling pathway.

Verucopeptin suppresses HIF-1's transcriptional activity by inhibiting the accumulation. Six chiral centers were built to create the side chain unit of the verucopeptin, and the Fmoc-SPPS unit underwent macroscopic endocannabinoidization to produce the dipeptide core. The first comprehensive synthesis was finished in its last step by linking [4]. Verucopeptin, which has the ability to inhibit mTOR/p70S6K, has been demonstrated to have a considerable effect on the vesicular H+-ATPase subunit V1G in recent studies. V erucopeptin is resistant to human melanoma in vivo A375 and in vitro multidrug-resistant cancer cells. The plant-derived flavonoid apigenin and the plant antitoxin glyceollin I work together to inhibit the PI3K/AKT pathway and reduce the production of the HIF-1. Apigenin inhibits the angiogenesis of human ovarian cancer OVCAR-3, PC-3, and HUVEC tube-forming tumors in vivo. Both the mTORCI (mTOR/Raptor) and mTORC2 (mTOR/Rictor) complexes may include the mTOR kinase. The synthesis of the insulin receptor substrate-1 rises in response to the mTORCI inhibitor rapamycin, which prevents the feedback inhibition of this route and activates AKT. Rapamycin may, however, inhibit mTORC2 in particular cell types as the incubation time increases. Rapamycin inhibits VEGF synthesis during in vivo angiogenesis. mTOR is suppressed by the tsc2-TSC1 protein complex. VEGF and HIF-1 are highly produced by tsc2-deficient cells. Rapamycin treatment reduced VEGF levels but did not completely reduce HIF-1a levels. The mTOR signaling motif located at the N-terminal end of HIF-1 was showed to mediate the interaction between the mTOR regulatory-related protein (Raptor) and HIF-1. The production of VEGF is suppressed by rapamycin during in vivo angiogenesis. Simolimus, sometimes referred to as rapamycin, is a macrolide immunosuppressant that prolongs the lives of model species like mice by inhibiting the mTOR protein kinase [5]. The protein combination tsc2-TSC1 has a detrimental effect on mTOR. TSC2-deficient cells have large amounts of HIF-1 and VEGF. Rapamycin treatment reduced HIF-1a levels while also reducing VEGF levels in these cells. Raptor, a protein that controls mTOR, interacts with the mTOR signaling motif that may be present at the N-terminal end of HIF-1. In order for HIF-la to bind the coactivator CBP/p300 and work correctly in hypoxic conditions, this motif is required. The dual mTORC1/mTORC2 inhibitors OSI-027 and OXA-01 significantly reduce angiogenesis and regeneration, according to study [6].

3. Inhibitor of promoting HIF protein decomposition

Since HIF-1A is a protein, it is inevitably impacted by the processes of degradation. With increasing levels of degradation, HIFA expression declines. One of the most crucial elements in the stability of HIF-1 is the HSP90, a part of the cellular chaperone process. In addition to a number of other client proteins, HIF-1 has been discovered as an HSP90 client protein. The microbiological byproducts

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geldanamycin and rhizomycin act as HSP90 inhibitors by tightly adhering to the ATP/ADP binding site. The HSP60 inhibitor epolactaene tert-butyl ester (ETB), which is made from the fungus metabolite epo-lactaene, supports the idea that HIF-1 protein downregulation mediated by HSP60 inhibitors. Though it was demonstrated that ETB inhibited chaperone proteins by binding to HSP60 Cys442, it's unknown how HSP60 and HIF-1 operate together [1].

TSA, a popular and typical histone deacetylase inhibitor, is a product of the fungus Streptomyces hygroscopicus. TSA was first found to increase the expression of VHL and decrease the levels of HIF-1 and VEGF in HepG2 cells. In a Lewis lung cancer mouse model, TSA also stopped the angiogenesis induced by hypoxia.

It has been discovered that ichthyone, antimycin A, and oligomycin are all naturally occurring inhibitors of mitochondrial complexes I, III, and V in Lonchocarpus utilis and other species. These mitochondrial electron transport chain inhibitors were found to impair the HIF-1 in a variety of cell lines. Saururus cernuus dineolignans manassantin B and its derivatives were shown to be strong inhibitors of HIF-1 that reduce mitochondrial oxygen consumption by bioassay-guided screening. By decreasing oxygen consumption or boosting reactive oxygen species, mitochondrial failure raises intracellular oxygen levels and destabilizes the HIF-1 protein.

4. Block downstream HIF-1 inhibitor

HIF-1 and HIF-1/ARNT form dimeric complexes with p300/CBP and engage in interaction before binding to HRE. Numerous organic substances have been identified as HIF-1 downstream inhibitors without affecting HIF-1 expression. Echinomycin is a naturally occurring, DNA-binding substance that was first discovered in Streptomyces echinococcosis. Echinomycin prevents DNA carrying the HRE consensus sequence from binding to HIF-1 in human glioma U251 cells, preventing HIF-1 from inducing the production of VEGF. It has been demonstrated that the fungus Trichoderma reesei's (chetomium sp.) metabolite chetomin interferes with the interaction between p300 and HIF-1. Additionally, Chetomin reduced HIF-1-mediated expression in both in vitro and in vivo tests, which prevented the development of HCT116 and PC-3 tumors from human colon cancer in vivo. By searching for HIF-1/HIF-1 dimerization inhibitors, the antibiotic/anticancer pigment acridine flavonoid was found. In addition to inhibiting spheroid formation (stem cell-like properties) in non-cancer stem cell (NCSC) and non-small cell lung cancer (NSCLC), chetomin, an active component of hair follicles, also reduces proliferation and chemoresistance in NCSC cultures of NSCLC [7].

Phosphoflavones directly bind to the HIF-1 PAS structural domain in vivo, limiting the downstream HIF-1 signaling cascade and preventing the development of the PC-3 tumor and the mobilization of angiogenic cells. The primary component of turmeric, curcumin, has several biological properties that have been well shown, including HIF-1 inhibitory action. In vivo, curcumin prevents the development of Hep3B tumors and HUVEC tubes brought on by hypoxia. The down-regulation of ARNT expression is one of the potential effects of curcumin [1]. The foundation of curcumin analogs is, however, somewhat shaky, and isolated curcumin (nearly invariably a combination of curcumin) has limitations as a workable therapeutic strategy [8].

5. Current application of HIF inhibitor in the field of cancer

In Hepatoma cells (HCC cells), the induction of HIF-1 and HIF-2 protein degradation inhibits the transcriptional activity of HIF. Inhibition of HIF-1 and HIF-2 activity in HCC tumors affects not only tumor growth and angiogenesis but also the immunological milieu of the tumor, enhancing antitumor immunity and enhancing response to anti-PD1 treatment. When CD47, CD73, and PDL1 are expressed in an HIF-dependent way, the capacity of the innate and adaptive immune systems of human breast cancer cells to eliminate cancer cells is diminished. This study demonstrates that BIRC2 expression in melanoma and breast cancer decreases CXCL9 expression and prevents the migration of NK cells and CD8+ T cells into tumors. In contrast, hypoxia did not cause the induction of BIRC2, CD47, or CD73 in cultured Hepa1-6 cells. However, 32-134D reduced the expression of the checkpoint ligands B7H4 and PDL1 as well as the checkpoint receptor TIM3 in Hepa1-6 tumors, both

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of which were linked to HCC mortality. After 32-134D therapy, there was decreased production of the Th2 cytokines IL-4 and IL-13, which cooperate with CXCL1 to support or draw immunosuppressive MDSCs and TAMs. Treatment with 32-134D also resulted in a reduction in CD70 expression, which in glioblastoma and RCC contributes to immune evasion of cancer cells by triggering T cell failure or death. Cancer cells decrease immune function by competing with immune cells for the absorption of glucose (through SLC2A1/GLUT1), producing lactate (by LDHA), and creating an acidic extracellular environment (via CA9). The enhanced CD8+ T cell and NK cell recruitment caused by the increased CXCL9 and CXCL10 production in the tumors of 134D-treated mice accelerated the response to anti-PD1 therapy. Together, these studies have shown various immunosuppressive processes that are brought on by hypoxia in HCC and prevented by 32-134D therapy. Therefore, systemic HIF inhibition in HCC has the overall effect of reducing immunosuppression by promoting the tumor's recruitment of CD8+T and NK cells [9]. Numerous researches have looked at the function of HIF-1 in diverse metabolic reprogramming pathways during the past 20 years. HIF-1 restricts oxidative mitochondrial metabolism, promotes oxygen homeostasis under hypoxia, and inhibits oxidative mitochondrial metabolism by lowering oxygen consumption. This interaction between HIF-1 and mitochondria is critical for tumor cells facing hypoxia.

Significant advancements have been achieved in understanding of HIF-1, a crucial regulator of cancer development and a potential target for cancer treatment, in cancer cells. But there are some things about HIF membership that require clarification. For instance, the precise functions played by each family member and the interactions between HIF-1 and other family members (HIF-2 and HIF-3) during hypoxia adaptation. It's crucial to comprehend regulatory mechanisms in order to pinpoint precise treatment targets. Targeting hypoxia, which is closely related to HIF, is a potential therapeutic strategy to stop the spread of different malignancies and increase patient survival over the long term [10].

6. Conclusion

The intricate metabolic reprogramming that takes place in cancer cells that are repeatedly exposed to hypoxia has been emphasized in numerous studies. Through the oxygen-sensing PHD enzyme, the transcriptional complex hif serves as a key oxygen level sensor. Through mediation, HIF controls a variety of biological processes, such as cell division and metabolism. In this review, the focus was on the HIF-1 system's function in the metabolic adaptation of cancer cells to hypoxia, a process that is essential for promoting cancer cell survival, proliferation, and metastasis. Critical functions in the creation and suppression of cancer cells are played by hIF1 signaling pathways and downstream expression. Inhibiting PI3K/AKT/mTOR slows down HIF-1 activity, which in turn slows angiogenesis and tumor progression in terms of protein synthesis. Systemic HIF inhibition in HCC has the overall impact of reducing immunosuppression by promoting the tumor's recruitment of CD8+ T lymphocytes and NK cells. Fisetinone, antimycin A, TSA, and oligomycin each have a facilitative effect on HIF1 degradation and related organismal activity, respectively. Further testing of HIF signaling inhibitors may result in the discovery of novel potent HIF-targeted anticancer medicines with improved selectivity and reduced toxicity because natural compounds like microbial metabolites and plant metabolites have distinctive structures and intriguing modes of action.

References

[1] Feng, S., Bowden, N., Fragiadaki, M., Souilhol, C., Hsiao, S., et al, “Mechanical Activation of Hypoxia-Inducible Factor 1α Drives Endothelial Dysfunction at Atheroprone Sites,” Arteriosclerosis, Thrombosis, and Vascular Biology 37(11), 2087–2101 (2017).

[2] Mekhail, K., Gunaratnam, L., Bonicalzi, M.-E. and Lee, S., “HIF activation by pH-dependent nucleolar sequestration of VHL,” Nature Cell Biology 6(7), 642–647 (2004).

[3] Albadari, N., Deng, S. and Li, W., “The transcriptional factors HIF-1 and HIF-2 and their novel inhibitors in cancer therapy,” Expert Opinion on Drug Discovery 14(7), 667–682 (2019).

DOI: 10.54254/2753-8818/21/20230867

[4] Takahashi, N., Hayashi, H., Viktors Poznaks and Hideaki Kakeya., "Total synthesis of verucopeptin, an inhibitor of hypoxia-inducible factor 1 (HIF-1)," Chemical Communications 55(79), 11956–11959 (2019).
[5] Arriola Apelo, S. I. and Lamming, D. W., "Rapamycin: An InhibiTOR of Aging Emerges From the Soil of Easter Island," The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 71(7), 841–849 (2016).
[6] Karar, J. and Maity, A., "PI3K/AKT/mTOR Pathway in Angiogenesis," Frontiers in Molecular Neuroscience 4, 00051 (2011).
[7] Min, S., Wang, X., Du, Q.-Y., Gong, H., Yang, Y., et al, "Chetomin, a Hsp90/HIF1α pathway inhibitor, effectively targets lung cancer stem cells and non-stem cells," Cancer Biology & Therapy 21(8), 698–708 (2020).
[8] Nelson, K. M., Dahlin, J. L., Bisson, J., Graham, J., Pauli, G. F., et al, "The Essential Medicinal Chemistry of Curcumin," Journal of medicinal chemistry 60(5), 1620–1637 (2017).
[9] Salman, S., Meyers, D. J., Wicks, E., Yat, S., Datan, E., et al, "HIF inhibitor 32-134D eradicates murine hepatocellular carcinoma in combination with anti-PD1 therapy," Journal of Clinical Investigation 132(9) (2022).
[10] Infantino, V., Santarsiero, A., Convertini, P., Todisco, S. and Iacobazzi, V., "Cancer Cell Metabolism in Hypoxia: Role of HIF-1 as Key Regulator and Therapeutic Target," International Journal of Molecular Sciences 22(11), 5703 (2021).