Review

Sheng Hao*

NADPH promotes the rapid growth of the tumor

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Abstract: NADPH oxidase is the main source of intracellular reactive oxygen species (ROS). ROS plays an important role in a variety of tumor types. The ROS mediated by NADPH oxidase increases the expression of hypoxia-inducible factor alpha (HIF- α) through multiple signaling pathways in tumor, and HIF- α could be regulated and controlled by downstream multiple targeted genes such as vascular endothelial growth factor, glucose transporter to promote tumor angiogenesis, cell energy metabolism reprogram and tumor metastasis. Meanwhile, HIF- α can also regulate the expression of NADPH oxidase by ROS, thus further promoting development of tumor. In this review, we summarized the functions of NADPH in tumorigenesis and discussed their potential implications in cancer therapy.

Keywords: Pentose phosphate pathway, Metabolic flow, Biosynthesis, ROS, HIF-1 α , HIF-2 α

1 Introduction

In 2000, six main characteristics of tumor cells were present; after that in 2011, Hanahan and Weinberg added three new characteristics: metabolic disorders, immune escape and inflammatory reaction [1]. More and more attention has been paid to the metabolism of tumor cells in the development of tumor. The pentose phosphate pathway (PPP) is one of the important pathways for glucose catabolism. The PPP provides not only cellular ribose 5-phosphate (R5P) but also NADPH, which plays a key role in the biosynthesis of lipids and elimination of reduction in intracellular reactive oxygen species (ROS). For this reason, the change in PPP is directly related to the growth of cells. As solid tumors have unique low oxygen conditions that make cells that only adapt to the environment to survive, this forces tumor cells to metabolic reprogram for growth advantage. Warburg [2] discovered that differentiation of the normal cells takes place mainly using mitochondrial oxidative phosphorylation capacity. Hence, a vast majority of cancer cells rely on aerobic glycolysis and generate a lot of lactic acid, a phenomenon known as “Warburg effect”. Tumor cells enhancing aerobic glycolysis compete with normal cells to uptake nutrients needed to quickly produce energy and accumulate biosynthesized intermediate metabolites to obtain proliferation. However, the Warburg effect is just an aspect of the tumor metabolic features. Warburg effect reflects typical characteristics of metabolic disorders including mitochondrial function of cancer cells and can produce abnormally high levels of ROS [3]. ROS is a series of different types of oxygen-free radical; collectively, it is a by-product of normal cell metabolism process and has different effects on cells according to its concentration. Low levels of ROS can promote cell proliferation and survival, while high levels of ROS can damage biological macromolecules, induce cell senescence and apoptosis [4] and cause harmful oxidative stress, leading to cell death. Cells producing antioxidant molecules, such as NADPH, can reduce the level of ROS to offset the negative impact of it [5]. The antioxidant systems rely on the reduction of NADPH to urge regeneration of antioxidant activity. NADPH not only can act as antioxidants in tumor cells during the rapid proliferation but also is involved in the synthesis

The First Affiliated Hospital, Biomedical Translational Research Institute, Jinan University, Guangzhou, Guangdong 510632, China

*Correspondence: Sheng Hao, E-mail: 1669613650@qq.com

of many biological macromolecules. Therefore, NADPH is a key molecule in the process of tumor adaptive metabolic changes [6,7]. Further study revealed that cancer cells can reduce glycolysis flow and increase the use of glucose in PPP to produce more NADPH in the oxidative stress state [8-10].

2 NADPH regulates tumor cells' colonization, invasion, metastasis and apoptosis

Studies have shown that tumor cells increase production of intracellular ROS under hypoxia and radiation stimulation and that high levels of ROS can regulate the expression of HIF- α through a series of signaling pathways [11]. Simultaneously, stable expression of HIF- α can promote cells' ROS levels to rise and raise the expression of NADPH oxidase, thus promoting the development, invasion and metastasis of tumor [12]. Under normal circumstances, the NADPH oxidase produces ROS as signaling molecules and gene expression switch involved in cell differentiation, proliferation, apoptosis (cell endogenous ROS) and intercellular signaling pathways [13]. Under stimulation of vascular pathology stimulating factors, growth factors, inflammatory mediators, ultrasmall particles, calcium ions and drugs, organisms produce highly expressed and highly active protein NOX and excessive ROS formation of oxidative stress [14]. High levels of ROS can lead to a number of pathological changes, such as protein and DNA damage, cell senescence and apoptosis, and induce cardiovascular disease, inflammation, diabetes, kidney disease and activation of oncogene [15]. ROS produced by NOX1 can also promote the growth and metastasis of tumor cells and promote the epithelial-mesenchymal transition that further promotes the development and invasion of tumor [16,17]. ROS produced by NOX4 activates STAT3/5 and promotes the HIF-1 α /HIF-2 α expression and then the development of tumor [18,19]. In summary, NADPH and NADPH oxidase are closely related to colonization, invasion, metastasis and apoptosis of tumor cells.

3 NADPH promotes tumor cell proliferation and migration

ROS regulates HIF-1 α by signal transducer and activator of transcription 3 (STAT3) signal pathway, a member of the STAT family, high expressed in many tumors and having a close relationship among tumor cells' colonization, angiogenesis, invasion and metastasis. Previous studies found that the NOX4 mediates increase in ROS by raising the c-Src activity to promote STAT3 phosphorylation in melanoma A375 cells and promotes the proliferation of melanoma cells [18]. Hypoxia stimulates the activation of STAT3 that results in combination of STAT3 and HIF-1 α promoter and then recruits the original binding protein p300/CBP to form active compounds that promote the expression of HIF-1 α protein, activate the transcription of downstream target genes and promote tumor cell proliferation, invasion and metastasis in human breast cancer cells and renal cell cancer cells [20]. Zhang et al. found that when xenografted nude mice was treated with NSC74859 (inhibitor of STAT3), the expression of HIF-1 α and vascular endothelial growth factor (VEGF) is restrained, cell proliferation and metastasis are suppressed, which result in increased apoptosis and susceptibility to radiation [21]. Low oxygen treatment of esophageal squamous cell carcinoma (ESCC) cells can also stimulate the phosphorylation of STAT3, further increasing the expression of HIF-1 α and VEGF. In gastric cancer cells, the activation of STAT3 through STAT3/p-STAT3→HIF-1 α pathway promotes proliferation, invasion and metastasis of cancer. HIF-1 α indirectly regulates NADPH oxidase by downstream genes in human leukemia B1647 cells, such as the HIF-1 α target gene VEGF can activate the NADPH oxidase subunits NOX2 and NOX4 and then increases ROS produced in the cell, which promotes the proliferation of tumor cells [22,23]. In non-small cell lung cancer cells, overexpression of NOX4 can increase the production of IL-6 that results in activating the IL-6/STAT3 signaling pathway. On the other hand, the exogenous expression of IL-6 can also increase the expression of NOX4, leading to active

NOX4/ROS/Akt signal pathway. Therefore, the combination function of NOX4 and IL-6 promotes tumor cell proliferation and survival. Because IL-6 is the target gene of HIF-1 α , HIF-1 α can activate the transcription of IL-6. Furthermore, moderate hypoxia can increase expression of HIF-1 α that limits the toll-like receptor expression, leading to reduction in the production of IL-6 and ROS and ultimately promotion of cell proliferation. Collectively, speculating that HIF-1 α may regulate the expression of NOX4 through IL-6, but the mechanisms need further researching [24]. To sum up, the increased level of ROS mediated by NADPH oxidase in tumor, resulting from activating ERK1/2, PI3K/Akt and STAT3 signaling pathways, promotes stable expression of HIF- α . Simultaneously, the increase in HIF-1 α can promote production of ROS and further promote the expression of NADPH oxidase and increase its activity, resulting in tumor cell proliferation, invasion and migration.

In summary, targeting the pentose phosphate pathway to reduce the generation of NADPH is expected to obtain antitumor breakthrough in cancer cells.

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