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Review

The mechanism between epithelial mesenchymal transition in breast cancer and hypoxia microenvironment

Tong Gao, Jia-zhi Li, Ying Lu, Chun-ying Zhang, Qing Li, Jun Mao, Lian-hong Li*

Pathology Department of Dalian Medical University, Liaoning 116044, China

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ABSTRACT

Hypoxia microenvironment widely exists in solid tumor tissues, which is mainly due to the rapid growth of cells within the tumor more than the speed of capillary in neoplasm, resulting in tumor tissue hypoxia. In hypoxia, hypoxia inducible factor 1 (HIF-1) is activated and regulate the expression of a series of hypoxia inducible genes, resulting in a series of hypoxia adaptation reaction. Researchs proved that, HIF-1 is closely related to the invasion, metastasis, prognosis of the tumor, and the expression of HIF-1 is higher in metastatic tissues compared with primary cancer tissues. In the evolution process of breast cancer, epithelial mesenchymal transition (EMT) define the characteristics of migration and invasion of breast cancer cells, which can also allow cancer cells to acquire the ability of self-renewing and stemness, so as to promote the generation of breast cancer stem cells. The incidence of EMT cancer stem cells are higher within the resistant to conventional treatment. This review focuses on breast cancer (stem cells), targeting the mechanism between hypoxia and EMT in tumor (stem cells), with the purpose of finding the new therapy to breast cancer.

Contents

* Corresponding author.
E-mail address: lilianhong@dlmedu.edu.cn (L.-h. Li).

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1. Introduction

Breast cancer is the most frequently diagnosed cancer and a major cause of death in women worldwide. Evidence indicates that the hypoxic microenvironment plays an significant role in progression and metastasis of breast cancer. About 25–40% of invasive breast cancers exhibit in hypoxic regions [1]. Studies have shown that intra-tumoral hypoxia has negative implications for survival of breast cancer patients, independent of prognostic parameters. Hypoxic tumors are associated with a more aggressive phenotype, increasing risk of metastasis, resistance to radiotherapy and chemotherapy, and induced cancer immune suppression [2].

Breast cancer stem cells are considered to be the reaction of the development and metastasis of breast cancer cells in the process of hypoxia, showed significantly resistant to chemotherapy.

2. Hypoxia microenvironment

In normal tissues, sufficient supply of oxygen survive the cells. However, in tumor tissue, with the reason of tumor cells have unlimited proliferative capacity, it consume a large amount of energy and oxygen in the growth process. In addition, the inner tissue can not establish effective network or neovascular dueing to tumor angiogenesis function and morphological abnormalities to meet the demanding of tumor blood supply, tumor cells in the condition of low perfusion state, causing microenvironmental hypoxia [3]. Meanwhile, the metabolism rate of tumor tissue is higher than those in normal tissues, its internal fluid leakage to the tissue gap, which increasing the blood viscosity resistance, as well as the dissemination of metabolic products, further aggravating hypoxic microenvironment. In recent years, people found that, hypoxia can influence the biological behavior of tumor cells through a variety of ways. Therefore, hypoxia in tumor microenvironment has caused widespread attention.

2.1. Hypoxia inducible factor 1 (HIF-1)

HIF- family consist of HIF-1α, HIF-2α and HIF-3α, they have similar mechanism induced by hypoxia. HIF-1 acts as a master regulator of oxygen-regulated gene expression in response to hypoxia. In most solid tumors, this hypoxic response is chiefly regulated by hypoxia-inducible factor-1 (HIF-1), which can regulate the expression of millions of genes involved in many biological processes, including angiogenesis, cell survival of hypoxia and apoptosis escape. In response to the hypoxia, the expression of oxygen tolerance relevant gene have changed with the increasing stability of HIF [4], which may lead to further increase tumor cell of invasion, adhesion, migration, metastasis and survival.

HIF-1 is a basic helix-loop-helix transcription factor composed of two subunits, HIF-1αand HIF-1β. The HIF-1αsubunit is constitutively expressed, whereas the expression of HIF-1α is regulated by oxygen tension. Under normal oxygen tension, HIF-1α is rapidly degraded by posttranslational ubiquitination triggered proteolysis. However, under low oxygen tensions, HIF-1αis stabilized and heterodimerizes with HIF-1α mediating nuclear translocation and binding to hypoxic responsive elements within the promotor regions of target genes. High level of HIF-1α at diagnosis act as a predicter of early relapse and metastasis, and correlates with poor clinical outcomes in human breast cancer. It has been reported that expression of HIF-1 target genes is increasing in the triple-negative breast cancer subgroup. HIF-1 plays key roles in many crucial aspects of breast cancer biology behavior, including angiogenesis, stem cell maintenance, metabolic reprogramming, EMT, invasion, metastasis, and resistance to radiation therapy and chemotherapy. Inhibition of HIF-1 activity in mice after orthotopic transplantation of triple-negative breast cancer cells, which has a dramatic effect on primary tumor growth as well as metastasis to lymph nodes and lungs (Fig. 1) [1].

Knocking out HIF-1α in mammary epithelial cells, we did not find the transfer target genes, however, the metastasis of breast cancer in situ to the lung which had been inhibited [5]. Hypoxia induced and HIF-1 dependent lysyl oxidase can promote in situ transplantation tumor model of lung metastasis microenvironment formation in mouse mammary carcinoma [6]. Evidences have indicated that inhibit the activity of HIF in breast cancer by RNA interference or digoxin intervention,which can inhibit the growth of tumor in situ, inhibiting the metastasis of breast cancer via the inhibition of angiopoietin like protein 4 (ANGPTL4) and L1 cell adhesion [7].

Moreover, HIF-1 was first shown to regulate angiogenesis through identifying VEGF which act as a direct HIF-1 target genewhich encodes vascular endothelial growth factor. VEGF plays

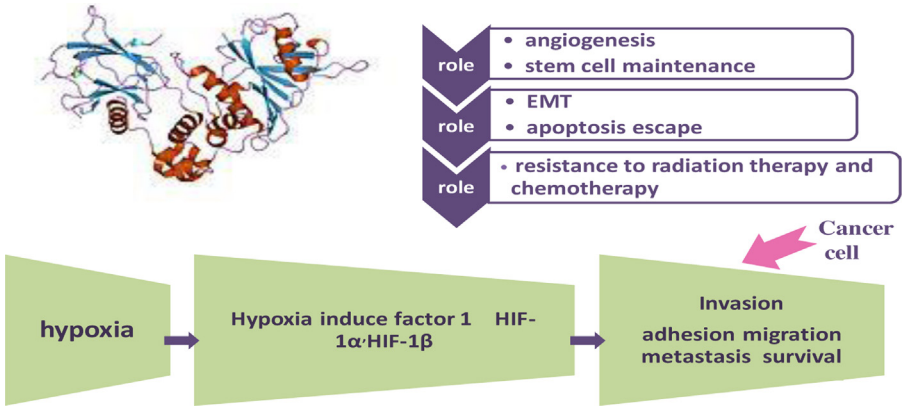

Fig.1. Hypoxia induce factor 1 (HIF-1).