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Review

The hypoxia-related signaling pathways of vasculogenic mimicry in tumor treatment

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ABSTRACT

Tumors require a blood supply for survival, growth, and metastasis. It is widely accepted that the development of the tumor microcirculation compartment need the production of new blood vessels (angiogenesis). Vasculogenic mimicry (VM) is an alternative type of blood supplement independent of endothelial vessels which refers to the formation of tumor cell-lined vessels and is associated with tumor invasion, metastasis and poor cancer patient prognosis. Although a variety of proteins and microenvironmental factors are known to contribute to VM, the mechanisms underlying its formation remain unclear. The induction of VM seems to be related to hypoxia, which may promote the plastic, transendothelial phenotype of tumor cells capable of VM. Here, with regard to the above aspects, we review the advanced research on VM including molecular mechanisms and its clinical significance; and explore the development of VM-related strategies which are being utilized for anticancer treatment.

Contents

1. Introduction

The growth and metastasis of tumors has been thought to be an angiogenesis-dependent process. However, a non-angiogenesis-dependent pathway in which tumors can feed themselves has also been reported [1]. In 1999 Maniotis et al. first described a new blood supply system in malignant melanoma [2]. Formation of vascular channels by aggressive tumor cells was named vasculogenic mimicry (VM), which emphasizes formation of these channels de novo, without implication of endothelial cells, independently of angiogenesis [3]. The formation of these channels is vasculogenic and mimicry because the channels are not formed from preexisting vessels and are not true blood vessels but merely mimic the function of vessels [4]. Since VM was introduced as a novel paradigm for melanoma tumor perfusion, many studies have contributed new findings illuminating the

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underlying molecular pathways supporting VM in a variety of tumors, including carcinomas, sarcomas, glioblastomas, astrocytomas, and melanomas [5–7]. The wall of the VM channel was positive for PAS staining, while tumor cells lining the external wall were negative for CD31 or CD34 staining. VM constructs like a lacunar architecture which is formed by tumor cells, while without endothelial cells lining cover. Red blood cells can be seen in those channels [8]. The presence of free blood cells in the central spaces formed in VM has been observed by electron microscopy in experimental human breast cancer and ocular melanoma [4]. VM represents the formation of perfusion pathways by tumor cells. The physical connection between VM and blood vessels may also facilitate haematogeneous dissemination of tumor cells. As a unique perfusion way, VM is associated with tumor invasion, metastasis and poor cancer patient prognosis [1].

VM is completely different from angiogenesis and vasculogenesis, in another word, the blood supply to tumors is proposed to involve three types: tumor-cell-lined vessels, mosaic vessels, and endothelium-dependent vessels. Several observations reported that tumor cells are located in the walls of tumor blood vessels and form a part of the vessel surface while the remaining part is covered by endothelium. This is known as 'mosaic vessels' where tumor cells undergo intravasation into the lumen and stay temporally in the vessel wall [9]. VM channels could be the main source of blood supply in the early stage of tumor growth. Endothelium-dependent vessels could then replace VM channels via a transitional step as mosaic vessels to become the dominant blood supply pattern at the late stage of tumor growth [10]. It has been demonstrated that VM provides convenience of tumor perfusion and dissemination functioning either independently of or simultaneously with angiogenesis [8]. Many factors are necessary in VM formation, including the microenvironment, the interaction between tumor cells and their surroundings, changing to endothelial genotype of the tumor cells, and extracellular matrix (ECM) remodeling [11]. The underlying induction of VM seems to be related to hypoxia, which may also promote the plastic, transendothelial phenotype of tumor cells capable of VM. Understanding the biology of VM, the linkage between blood vessels and relapse may provide crucial new therapeutic strategies. In this review, we will discuss molecular mechanisms of VM, factors affecting VM formation, and its clinical significance; and explore the development of novel tumor-targeted treatments that are based on the biochemical and molecular events that regulate VM [12].

2. Hypoxia and VM

The tumor microenvironment, which provides a supportive framework to the cancer cells, is composed of numerous cell types including cancer associated fibroblasts, vascular components such as endothelial cells and pericytes, immune cells such as tumor associated macrophages and ECM [12]. Under the microenvironment of the tumor, hypoxia is the most common phenomena because of the vast energy and oxygen consuming [13]. As tumors grow, their microenvironment becomes increasingly hypoxic. Tumours as small as 1–2 mm in diameter may show signs of hypoxia and may depend on angiogenesis for further growth. Although hypoxia is toxic to normal cells, the tumor cells undergo adaptive changes that allow them to survive and even proliferate in a hypoxic environment [14]. Under hypoxic conditions, a signaling pathway involving a crucial oxygen response regulator, hypoxia-inducible factor (HIF), is switched on. The α subunit of HIF-1 (HIF-1α) is a nuclear factor and a well-established mediator in cancer response to hypoxia [13]. HIF-1α protein can be translocated

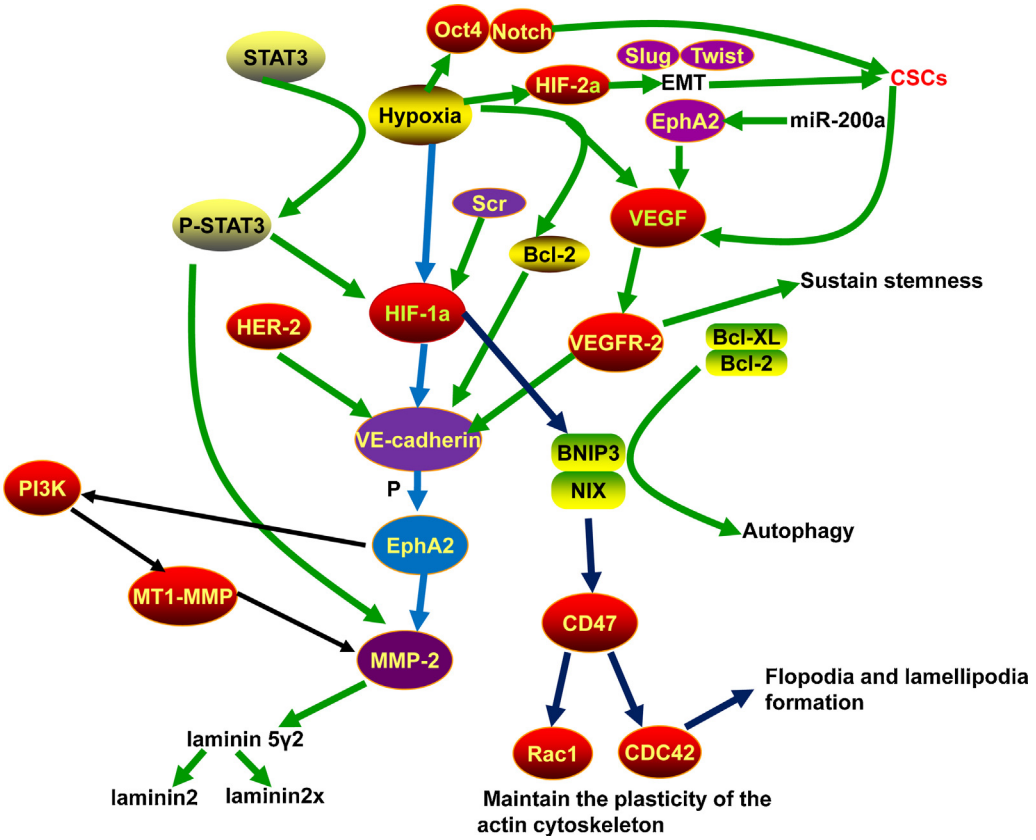

Fig. 1. Schematic model of formation mechanisms and signaling pathways in tumor vasculogenic mimicry (VM).