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Review

Cycling hypoxia: A key feature of the tumor microenvironment

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ABSTRACT

A compelling body of evidence indicates that most human solid tumors contain hypoxic areas. Hypoxia is the consequence not only of the chaotic proliferation of cancer cells that places them at distance from the nearest capillary but also of the abnormal structure of the new vasculature network resulting in transient blood flow. Hence two types of hypoxia are observed in tumors: chronic and cycling (intermittent) hypoxia. Most of the current work aims at understanding the role of chronic hypoxia in tumor growth, response to treatment and metastasis. Only recently, cycling hypoxia, with spatial and temporal fluctuations in oxygen levels, has emerged as another key feature of the tumor environment that triggers different responses in comparison to chronic hypoxia. Either type of hypoxia is associated with distinct effects not only in cancer cells but also in stromal cells. In particular, cycling hypoxia has been demonstrated to favor, to a higher extent than chronic hypoxia, angiogenesis, resistance to anti-cancer treatments, intratumoral inflammation and tumor metastasis. These review details these effects as well as the signaling pathway it triggers to switch on specific transcriptomic programs. Understanding the signaling pathways through which cycling hypoxia induces these processes that support the development of an aggressive cancer could convey to the emergence of promising new cancer treatments.
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1. Introduction

Cancer has long been termed as a disease characterized by transformed cells acquiring the capabilities of autonomous proliferation, immortalization and invasion [1]. Next, emerging evidence have led to redefine cancer as a disease involving complex heterotypic multicellular interactions between incipient transformed cells and their normal neighbors collaborating to favor malignant growth [2]. Indeed, the unique proliferation of transformed cells does not lead to cancer unless it arises in a permissive environment able to support tumor development, termed the tumor microenvironment [3]. It encompasses both the physicochemical microenvironment and the cellular microenvironment. Changes in the tumor microenvironment have profound effects on cancer progression [4].

Among these changes, a main feature altering the tumor microenvironment is the reduction of oxygen level called hypoxia. The tumor level of oxygen fluctuates in a spatio-temporal way within a same tumor, delimitating multiple sub-microenvironments with specific characteristics and different cell behaviors. Intratumoral hypoxia results on one hand from the diffusion-limited O_2 delivery and on the other hand from the inconstant erythrocyte flux circulating into the dysfunctional tumor vascular network. The so-called chronic hypoxia, describes a deficit in O_2 for a continuous period of time (at least several hours) while cycling hypoxia describes a fluctuating situation between periods of deep hypoxia and moderate hypoxia, more commonly associated to a hypoxia-reoxygenation pattern. Importantly, the generic term of chronic hypoxia also gathers different levels of reduced pO_2 from anoxia to mild hypoxia. Nonetheless, the severity of hypoxia highly determines the cell response and thus the intracellular signaling mechanisms initiated in the exposed cells. In contrast to chronic hypoxia that affects cells distant from blood vessels, cycling hypoxia affects cancer and stromal cells immediately adjacent to inefficiently perfused blood vessels. The endothelial cells lining these blood vessels are thus also exposed to cycling hypoxia. The rapid drop of oxygen level is severe as no more oxygen molecule is delivered to the cells constituting and surrounding the unperfused blood vessel. Afterwards, when the blood flow is restored, the hypoxia period is followed by a reoxygenation period. Thus, in addition to the cellular adaptations orchestrated by the hypoxia periods, the periods of reoxygenation can instigate specific responses in cells exposed to cycling hypoxia. Reoxygenation periods are for instance prone to reactive oxygen species (ROS) generation which is associated with the induction of specific transcriptomic program, and require the reactivation of energy-costing machineries such as the ones used for transcription and translation. The review aims to describe these processes.

2. Tumor hypoxia

In solid tumors, O_2 availability is reduced due to structural abnormalities of the tumor vascular network resulting in a disturbed microcirculation leading to deficiencies in O_2 transport. Numerous areas of low O_2 tension exist in solid tumors. These microregions are heterogeneously distributed within the tumor mass and may be located next to regions with normal O_2 tension [5]. Moreover, the range of hypoxia in malignant tumors also widely varies in a spatio-temporal manner. Altogether, tumor hypoxia defines oxygen partial pressure ranging from <0.1 mm Hg (anoxia) to 15 mm Hg imposed either through a continuous or cycling manner to the various cells present in the tumor microenvironment [6,7].

Two types of hypoxia are distinguished within the tumor tissue. Chronic hypoxia results from the limited diffusion of O_2 through the tissue and is the first mode of hypoxia to occur during tumor development. Indeed, because of tumor cell proliferation, the density of the blood vascular network becomes rapidly too low for supporting the perfusion of the whole tumor. As a consequence, some tumor cells are placed far away from existing blood vessels to receive a sufficient O_2 supply (Fig. 1). This phenomenon was initially described by Thomlinson and Gray in 1955 when they observed the presence of necrotic areas within tumors. These necrotic areas were surrounded by intact tumor cells, thus appearing as rings in tumor sections. They suggested the existence of a falling gradient in O_2 tension between the periphery and the center of tumor islets. Moreover, these authors estimated, by evaluating the respiratory quotient throughout the tumor mass, that complete anoxia would be expected at the center of any tumor sphere with a radius larger than 150 μm [8]. Furthermore, they were also the first to connect the histological structures of tumors and radioresistance as they had previously reported that anoxic cells at the time of irradiation were much less damaged by a given dose of X- or γ-radiation compared to those well oxygenated [9].

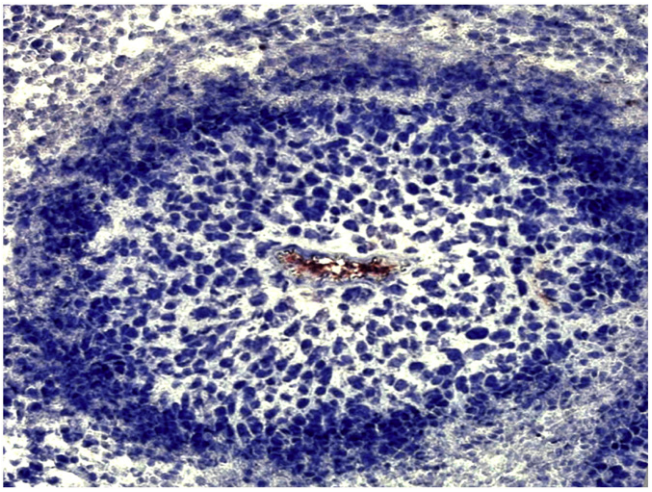

Fig. 1. Islet of cancer cells detected within a larger mouse tumor section. DAPI counterstained nuclei (blue) show that cancer cells are not viable at some distance (>150–200 μm) from the blood vessel (CD31-immunostained, red-brown).

In order to adapt to hypoxia, we know today that tumors develop their own blood vessel network through the dysregulated production of angiogenic factors mainly *via* the activation of the HIF (hypoxia-inducible factor) transcription factors. However, this tumor blood neovasculature remains structurally and functionally abnormal. The immaturity of the tumor blood vessel network results in an inefficient perfusion of the tumor, with a level of O_2 availability still below that of healthy tissues (Fig. 2). Moreover, O_2 consumption by stromal and cancer cells also influences the tumor oxygenation state. Even for cancer cells that convert most of the captured glucose into lactate, other energy substrates including glutamine and fatty acids can be used to fuel the TCA cycle and sustain oxidative phosphorylation [10]. Tumor O_2 availability is also highly dependent on the presence of (myeloid) inflammatory cells that are known to be avid O_2-consuming cells.

Seven features have been reported to influence the global oxygenation state of tumors [11]. These interrelated features contribute to a poor O_2 availability within the tumor tissue. In particular, the perfusion in tumor blood vessels can also be unstable, leading to another type of hypoxia that named cycling hypoxia [11]. In 1979, Brown firstly evoked this form of hypoxia initially denoted as acute hypoxia and proposed to result from variations in the tumor tissue O_2 perfusion [12]. The chaotic and poorly hierarchical structure of the tumor blood vessel network causes indeed an irregular tumor tissue perfusion. These fluctuations in the perfusion lead to periods of poor and better oxygenation that depend on the feeding vessel, and thus expose cells to periods of hypoxia followed by periods of reoxygenation in a cyclic manner. Chronic hypoxia and cycling hypoxia thus represent distinct pathophysiological entities that have different biological and therapeutic consequences.

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