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Modulation of the tumor vasculature and oxygenation to improve therapy

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ABSTRACT

The tumor microenvironment is increasingly recognized as a major factor influencing the success of therapeutic treatments and has become a key focus for cancer research. The progressive growth of a tumor results in an inability of normal tissue blood vessels to oxygenate and provide sufficient nutritional support to tumor cells. As a consequence the expanding neoplastic cell population initiates its own vascular network which is both structurally and functionally abnormal. This aberrant vasculature impacts all aspects of the tumor microenvironment including the cells, extracellular matrix, and extracellular molecules which together are essential for the initiation, progression and spread of tumor cells. The physical conditions that arise are imposing and manifold, and include elevated interstitial pressure, localized extracellular acidity, and regions of oxygen and nutrient deprivation. No less important are the functional consequences experienced by the tumor cells residing in such environments: adaptation to hypoxia, cell quiescence, modulation of transporters and critical signaling molecules, immune escape, and enhanced metastatic potential. Together these factors lead to therapeutic barriers that create a significant hindrance to the control of cancers by conventional anticancer therapies. However, the aberrant nature of the tumor microenvironments also offers unique therapeutic opportunities. Particularly interventions that seek to improve tumor physiology and alleviate tumor hypoxia will selectively impair the neoplastic cell populations residing in these environments. Ultimately, by combining such therapeutic strategies with conventional anticancer treatments it may be possible to bring cancer growth, invasion, and metastasis to a halt.

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1. Introduction

In the development of a cancer, the transformation into a neoplastic and progressively invasive tumor occurs though a multitude of etiologies. Oncogenic lesions, coupled with inhibition of tumor suppressors, together contribute to cellular transformation. Genomic, proteomic, post-translational, and epigenetic mutations are responsible for activating oncogenes and inhibiting tumor suppressor genes. Several essential characteristics are present in malignancies; a key element of malignant

Abbreviations: IFP, interstitial fluid pressure; HIF-1, hypoxia inducible factor 1; VEGF, vascular endothelial growth factor; TIC, tumor initiating cell; CTSL, cysteine protease cathepsin L; CTL, cytotoxic T lymphocyte; PD-L1, programmed cell death ligand-1; AI, angiogenesis inhibitor; VDA, vascular disrupting agent; EPO, erythropoietin; HCR, hypoxic cytotoxic ratio.

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transformation being the loss of regulatory control mechanisms. Cancer cells not only possess heightened rates of cell proliferation and aberrant cell cycle checkpoints, but also lose contact-inhibited growth regulation.

The developing tumor contains a distinct cellular compartment that retains stem-like cell characteristics, namely multipotency, self-renewal and proliferation potential, and this in turn drives oncogenesis and tumor progression. Thus a discrete subset of cells within a tumor possesses the capability of self-renewal and multipotency that gives rise to a heterogeneous population of cancer cells. Although cancer stem cells can vary by definition, they generally comprise less than 10% of the population of a tumor. Still, cancer stem cells have been implicated as a key component in the formation and spread of human cancers to distant sites.

In addition to the variety of neoplastic cells, many other cell types are present in the tumor milieu. Examples include fibroblasts, endothelial cells, hematopoietic-derived cells, and immune cells, which normally monitor this environment for foreign bodies. In cancer, particularly at the later stages of transformation and invasion, normal immune functions are subverted, leading to recognition of the tumor as part of the host, rather than as an invading foreign entity.

This cellular heterogeneity coupled with key physical and structural tissue components which form the extracellular matrix define the tumor microenvironment. The matrix is deposited as a mix of such proteins as collagens, fibronectin, laminins, hyaluronan, plasminogens, proteases, and numerous others which collectively form an inflexible scaffold to which cells attach. In addition, other secreted cellular proteins such as cytokines and extracellular matrix remodeling proteins normally reside in the extracellular matrix and contribute to its turnover regulation.

The tumor microenvironment is not static, but rather highly variable depending on tumor type and stage of cancer development. A critical factor impacting variations in the tumor microenvironment is the tumor supportive blood vessel network. The abnormal tumor vasculature and its physiologic consequences serve as an over-arching modulator of the tumor microenvironment affecting the composition and interaction of its constituents to impact tumor progression, cell dissemination, response to anticancer therapeutics, and cancer patient outcomes.

The deleterious effects of the tumor microenvironment on cancer therapy outcomes were first recognized in the 1950s when the possible negative consequences of tumor hypoxia for radiotherapy efficacy were postulated. Unfortunately, this issue has not been resolved. Indeed it has become abundantly clear that the effect of the tumor microenvironment is far more insidious than initially anticipated; now known to impact all conventional anticancer therapies, fundamental cancer cell biology, gene expression, and metastatic incidence. This review provides a historical context to our current perspectives of interventions strategies seeking to overcome the negative therapeutic consequences of the aberrant tumor microenvironment.

2. Physiological characteristics of the tumor microenvironment

2.1. Aberrant vascular networks

Survival of tumor cells and subsequent tumor development require an adequate supply of oxygen and nutrients. These are initially supplied from the host vascular system, but the demand for these critical factors soon exceeds the supply from this source, thus tumors develop their own functional vascular supply (Folkman, 1986) from the normal host vascular network by the process of angiogenesis (Bergers & Benjamin, 2003). Despite the importance of this neo-vasculature, the system that actually develops is far from adequate. Endothelial cells divide at a slower rate than tumor cells (Denekamp & Hobson, 1982) and thus the developing tumor vasculature is unable to keep pace with the expanding neoplastic cell population. The tumor vasculature formed is also very different from that of normal tissues (Vaupel et al., 1989; Vaupel, 2004). Structurally, it is chaotic, there is a loss of hierarchy, vascular density is abnormal, and the vessels have contour irregularities, are tortuous, dilated, and elongated (Fig. 1A). The vessels also are very primitive in nature, having incomplete or missing basement membranes and endothelial lining, and lacking pericytes, smooth muscle, and pharmacological receptors. In addition, there are numerous functional abnormalities, including unstable speed and direction of blood flow, high vascular resistance, increased vascular fragility, red blood cell sludging, leukocyte sticking, and blockage of vessels by circulating white blood cells, platelet aggregates, or tumor cells. All these factors result in the development of areas within the tumor that are characterized by glucose and energy deprivation, high lactate levels and extracellular acidosis, and oxygen deficiency (Vaupel et al., 1989; Vaupel, 2004).

2.2. Elevated interstitial pressure

The primitive nature of tumor blood vessels results in them being leakier than those of normal tissues. This, coupled with a lack of a functional lymphatic system (Fukumura & Jain, 2007) leads to a significant flow of free fluid in the interstitial space. Consequently, there is a build-up of interstitial fluid pressure (IFP) (Gutmann et al., 1992; Milosevic et al., 2001). Although IFP within tumors may fluctuate (Vaupel, 2011), it is generally uniformly high throughout the center of tumors reaching values of 50–100 mm Hg (Vaupel, 2011). However, it drops steeply at the tumor periphery (Boucher et al., 1990), presumably because these areas tend to obtain their blood supply from the normal tissue vessels from which angiogenesis originates.

2.3. Acidic pH

Tumor cells receive essential oxygen and nutrients via diffusion from the vascular supply. But, as these are utilized, gradients are established. For nutrients, especially glucose, these gradients result in energy deprivation at distances from blood vessels (Vaupel et al., 1989). Tumor pH gradients are also found (Helmlinger et al., 1997), with cells distant from vessels being more acidic. Oxygen gradients also occur and regions of low oxygenation (hypoxia) can further influence tumor pH by causing a shift in the balance of cellular energy production toward glycolysis with the subsequent generation of lactate (Vaupel, 2009). Several clinical studies have indeed reported high lactate levels in tumors (Brizel et al., 2001; Walenta & Mueller-Klieser, 2004). This results in tumor acidosis, although ATP hydrolysis, glutaminolysis, carbon dioxide production, and bicarbonate depletion, can play important roles (Vaupel, 2009).

2.4. Oxygen deprivation

The microenvironmental parameter that has been the most extensively investigated is hypoxia. Generally, hypoxia is considered to be either chronic or acute in nature (Horsman et al., 2012; Fig. 1B). Chronic hypoxia was first suggested by Thomlinson and Gray (1955) and results from a diffusion limitation of oxygen from the blood supply, while acute hypoxia was identified later (Chaplin et al., 1987) and shown to occur due to transient fluctuations in tumor blood flow. This concept of chronic and acute/fluctuating hypoxia is now considered to be an over-simplification (Bayer et al., 2011). Acute hypoxia can result from a total or partial shut-down in perfusion (Kimura et al., 1996); a complete shut-down would starve cells of oxygen and nutrients and result in ischemic hypoxia, which would not be the case for a partial shut-down where plasma flow, thus nutrient supply, can occur. For chronic hypoxia the picture is even more complicated. It can result from a diffusion limitation under “normal” conditions, or be due to reduced oxygen availability as seen in anemic patients or smokers. One also has to consider the level of oxygenation; cells close to the vessel could be slightly hypoxic, while cells next to necrosis could even be anoxic. Using a variety of measurements including microelectrodes, hypoxic markers, and