

Tumor Angiogenic Switch Determines Sustained Proliferative Malignant Transformation in Tumorigenesis and Overlaps with Para-inflammatory Phenomena

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Abstract

Both inflammation and tumorigenesis are analogous counterpart phenomena in overlap dynamics determining angiogenesis within reactive microenvironments and as angiogenic switch in tumorigenic expansion and progression. In this regard, the counter-effects of pro-angiogenesis and of anti-angiogenesis reconstitute a series of endothelial cell activation steps or apoptosis of these cells. In close parallel, apoptosis of endothelial cells in response to inhibitory angiogenic factors may reflect in some measure apoptosis of tumor cells related to such sprouting endothelial cell tubes. Further to such measures, multi-potent bone marrow mesenchymal cells induce a plethora of effects relative to the migrating endothelial progenitor cells in terms of the ongoing promotion of angiogenesis and of the angiogenic switch. Indeed, angiogenesis of tumors may prove a central modulator in emergence of malignant potentialities in tumorigenic lesions.

Keywords: tumorigenesis, angiogenic switch, inflammation, growth factors, chemotaxis.

1 Introduction

Tumor Angiogenesis refers to the pre-existence of host blood vessels in the first instance in a manner that specifically implicates the sprouting of neo-vessels within an avascular and hence hypoxic micro-deposit tumor of tumor cells. Angiogenesis-modulating proteins are ideal biomarkers for studying tumor pathophysiology [1]. It is the breakdown of the basement membrane of such host pre-existent vessels that is determinant, in critical manner, to the subsequent migration of proliferating endothelial cells, endothelial progenitor cells, hematopoietic multi-potent progenitor cells and also the infiltration by macrophages of the extracellular matrix.

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HYPOXIA

Particular influences exerted by the evolving hypoxia and concurrent stimulation of hypoxia-inducible factor- α 1, within the essential extra-cellular tumor matrix, act as powerful inducers to a whole concerted series of responsive elements, including in particular the paracrine stimulating effects of vascular endothelial growth factor (VEGF), and also of basic fibroblast growth factor, and of placental inhibitor factor and of platelet-derived growth factor.

ANGIOGENESIS

The central stage phenomena of pro-angiogenic and anti-angiogenic system actions clearly delineate a highly dynamic series of pathway effects that promote both upregulation and downregulation of agonist effects in terms of endothelial proliferation and migration. miR-125a regulates the paracrine of VEGF-A in gastric cancer and thereby controls angiogenesis of the tumor [2]. Selectin E, which is a leukocyte adhesion molecule, also calls into operation an essential series of chemotactic influences that particular in essential ways towards the establishment of sprouting of neovessels within angiogenic switch evolution of the nascent micro-tumor.

Performance patterning and organizational biology in the progression of tumor angiogenesis is a dysfunctional attribute of the production of vascular growth factors involving especially production of vascular endothelial growth factor by endothelial cells and also by stromal fibroblasts in particular. Benzyl butyl phthalate adversely influences the efficacy of chemotherapy by remodeling the tumor microenvironment of breast cancer [3].

PROTEASE ACTIONS

Protease degradation of the extracellular matrix, on the one hand, and of the vascular basement membrane is itself a requisite and critical determinant in angiogenic patterning in tumor evolution. The use of bevacizumab to reduce angiogenesis improves clinical outcome in colorectal cancer [4]. Metalloproteinase 2 and 9 in particular contribute to possible emergence of endothelial cell migration from the pre-existing vessels, particularly with reference to the capillary-venous interface. Visualization of abnormal vascular tortuosity may render possible a better understanding of changes in the vascular microenvironment during tumor progression [5]. In such manner, also, degradation of the extracellular matrix progresses concurrently with the protease-induced degradation of the vascular basement membrane within shifting systems of enhanced angiogenesis. Such a phenomenon is also partly regulated by protease-induced liberation of vascular endothelial growth factor that is bound to matrix proteins.

INHIBITORY PATHWAYS

Further to such progression, a series of inhibitory pathways operate to better orchestrate the angiogenesis phenomenon. The cleavage in particular of collagen IV, which is the most abundant component of the vascular endothelial basement membrane, creates various domain residues with potential anti-angiogenic effects. Thus endostatin and tumstatin have significant anti-angiogenic action and are derived from the cytoplasmic globular terminal of the non-collagenous domain of the collagen type XVIII molecule. Endostatin action is significant particularly in view of the direct inhibition of expression of VEGF and of vascular permeability.

Pattern formulation in tumor angiogenesis is dominantly influenced by “outside-inside” and “inside-outside” signaling induced by integrin receptors, in particular, by molecules α -v- β 3 and α -v- β 5 integrins. Antibodies against α -v- β 3 on endothelial cells inhibit binding to basic fibroblast growth factor, whereas antibodies to α -v- β 5 integrin inhibit binding to VEGF.

Also, particular significant are the interactions of integrin molecules with extracellular matrix, and they play an essential role in the migration of activated endothelial cells in angiogenic sprouting,

The creation of soluble receptor factions such as the VEGF-2 receptor flk-1 has also been found to operate as powerful inhibitors in angiogenesis.

RECONSTRUCTIVE OPERABILITY

Dimensional reconstruction of operability implicate an overall patterning formulation that is integral to the evolving tumor angiogenic process in a specific manner inducing the cooperative institution of arrays of proliferating or partly hypoxic tumor cells in association with the sprouting endothelial cell tubes. It is significant to recognize hypoxic effects that are indeed powerful stimulants in the paracrine production of VEGF by both endothelial cells and tumor cells. Hypoxia-inducible factor 1 promotes the initiation, progression, metastasis and resistance to treatment of the majority of solid tumors [6].

The vascular basement membrane and also integral tissue components, which include extracellular matrix components, hence cooperatively determine dominant positive and dominant negative pathway effects in the migration, proliferation of endothelial cells and in the formation of endothelial cell tubes. In this regard, the subsequent deposition of a basement membrane to the spouting endothelial cell tubes establishes maturation attributes to the tumor cell bed in a manner that may also allow enhanced permeability in regions of this vascular bed.

EMBRYONIC VASCULARIZATION PARALLELS

It is especially significant to recognize essential parallel formulations of vascular growth factor actions in tumor vascular beds with the embryonic process of vasculogenesis early in development. Bone marrow mesenchymal cells that are pluripotent cell elements play a vital process in embryonic development of the cardiovascular system and such process overlaps significantly in the subsequent emergence of tumor angiogenesis that arises necessarily as sprouting from pre-existent vessels.

Primary predominance of dominant action in interactions of integrins with the extra-cellular matrix proteins is a critical series of pathway effects that allows cell-matrix communication. In like manner, beta-cadherin and focal adhesion factor allow for cell-cell interaction in establishing the vascular sprouting and migration of the activated endothelial cells. Fibroblast growth factor is identified as a candidate cancer biomarker in many types of cancer [7].

INFLAMMATION

Particular relevant to tumor angiogenesis is the overlap of system pathways as integral to inflammation and immune cells. p38 mitogen-activated protein kinase not only plays a central role in induction and regulation of innate and adaptive immunity but also promotes tumor invasion, metastasis and angiogenesis [8]. Interleukin-1 α and interleukin 6 are implicated also in the angiogenic switch of developing and expanding

masses of tumor cells. Inflammation induces an extensive series of networks in chemotaxis in a manner that operatively determines in multi-faceted dimensional angiogenesis in tumors. In this regard, macrophages and bone marrow mesenchymal cells are also implicated in the activation of the vascular endothelial cells that subsequently migrate into the matrix. The proteases of the tumor matrix are constitutive and endogenous operants in delineating in a dominant fashion the cooperative overlap of inflammatory dynamics and also in hypoxic tumor micro-deposits. Glycogen Synthase Kinase-3beta regulates mTOR/p70S6K1 signaling pathway and exerts growth and angiogenesis-inhibitory effects in glioma progression in vivo [9].

VASCULAR HYPER-PERMEABILITY

Dominant targeting performance is an integral mechanism in the construction of tumor angiogenic networks that include in significant manner hyper-permeable vessels along with more mature vascular elements. Endothelial cell proliferation is influenced by both soluble factors and mechanical forces; reduced expression of the mechanosensitive ion channel TRPV4 in tumor endothelial cells induces abnormal angiogenesis [10]. Interactivities are formulas in the interventional behavior of heparin-sulphate glycoproteins and extracellular matrix component proteins in the initiation and sustainment of pathway induction and activation of various cellular subsets. The outline significance of endogenous stimulation and counter-active inhibitory influences is further evidenced by the participation of chemotaxis that is promoted initially as concurrent degradation of the vascular basement membrane and activation of the lining endothelial cells. The emergence of endothelial progenitor cells is also a system targeting mechanism that appears to promote enhancing influence of mesenchymal bone marrow cells.

Blood perfusion of the tumor vascular bed is evidenced as factor formulation in the developing tumor angiogenesis in terms of determined targeting and dynamics of both the proliferating and also partly dormant tumor cell fractions within the neoplastic micro-deposits. This vascularization also is instrumental in establishing future metastasizing potentialities early in tumorigenesis.

TARGETING STRATEGY

Inhibition of tumor angiogenesis is hence an attractive targeting strategy in controlling tumorigenesis. Wogonoside, derived from *Scutellaria baicalensis* Georgi, decreases intracellular Wnt3a, increases expression of GSK-3beta, AXIN, and promotes the phosphorylation of beta-catenin for proteasome degradation in breast carcinoma [11]. Many degradation products of the vascular basement membrane such as endostatin, tumstatin, canstatin appear to exert inhibitory or pro-apoptotic effects not only on sprouting endothelial cells but also on related tumor cell bed. Apoptosis is evidenced by VEGF insufficiency in view of an essential role of this growth factor in the survival and proliferation of endothelial cells. In this regard, the hyper-permeability of the vascular wall in the tumor cell bed that is induced by VEGF is a central series of mechanistic pathways in the expansion of the tumor mass that is inherently hypoxic and multifocally ischemic or avascular. A spheroid-plug model resembles natural tumor progression and relies on in vitro formation of tumor spheroids followed by subcutaneous injection of single tumor spheroids in matrigel matrix [12].

Tumor inflammation is a potent positively inducing mechanism in promoting the vascularization of the tumor cell bed in the first instance and has been implicated in the

active tumorigenesis that is progressively enhancing in terms of subsequent alignment of the neoplastic cells in close apposition to the developing vascularity of the lesion.

In such terms, angiogenesis is a mediator in the dynamic turnover and proliferation of tumor cells that adapt to dynamics of migratory endothelial cell proliferation or possible focal apoptosis. Inflammation-related tumor necrosis factor-alpha induces the tumor suppressor protein promyelocytic leukemia to accumulate; resulting nuclear bodies mediate cancer cell death and inhibit migration and capillary tube formation by endothelial cells [13]. It is with regard to apoptosis of endothelial cells in response to sub-maximal doses of chemotherapeutic agents such as cyclophosphamide or vinblastine that an especially targeted series of susceptibility phenomena can be created within foci of emerging tumorigenesis.

2 Concluding Remarks

Discriminatory criteria as parameters determining the dynamics of angiogenesis and of tumor angiogenic switch would recapitulate the embryonic processes involved in vasculogenesis as evidenced also by participation of endothelial progenitor cells and also of pluripotent cells of bone marrow mesenchymal origin. The plethora of factors such as thrombospondin-1, angiopoietins, urokinase plasminogen activator, multiplicity of vascular growth factor sub-types, and the central roles of effect as exerted by integrin receptors and of secreted soluble receptor variants attest to a series of paramount influences that dictate especially the dynamics of the tumor cell proliferation and of the evolving tumorigenesis. CXCR7, a chemokine receptor, modulates proliferation, apoptosis and invasion of papillary thyroid carcinoma, and, in general terms, effects on metastasis and angiogenesis [14]. In such terms, inflammatory analogy to the turnover and dynamics of influence attest to an angiogenic switch that dominantly incorporates, in real measure, the integral malignant transformation process and ensures the sustained tumorigenesis phenomenon per se.

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