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Vascular Mimicry: Concepts and Implications for Anti-Angiogenic Therapy

James M. Dunleavy¹ and Andrew C. Dudley^{1,2,3,*}

¹Department of Cell and Molecular Physiology, The University of North Carolina at Chapel Hill, Chapel Hill, NC

²Lineberger Comprehensive Cancer Center, Chapel Hill, NC

³McAllister Heart Institute, Chapel Hill, NC, USA

Abstract

As in normal tissues, solid tumors depend on vascular networks to supply blood, oxygen, and nutrients. Tumor blood vessels are formed by common processes of neovascularization for example endothelial sprouting. However, some tumors have alternative and unexpected mechanisms of neovascularization at their disposal. In a process termed “vascular mimicry,” tumors create their own, tumor cell-lined channels for fluid transport independent of typical modes of angiogenesis. These tumor cell-lined conduits may express endothelial-selective markers and anti-coagulant factors which allow for anastomosis with host endothelium. In this review, we explore the current status of vascular mimicry research, highlighting recent evidence which strengthens the hypothesis for this unusual ability of tumor cells. Furthermore, we address the theoretical possibility that vascular mimicry provides a mechanism whereby tumors could escape anti-angiogenic therapies.

Keywords

Vascular mimicry; tumor; angiogenesis; tumor endothelial cells; tumor microenvironment

VASCULAR MIMICRY - DISCOVERY AND CONTROVERSY

The ability of solid tumors to initiate and sustain angiogenesis is a cancer hallmark [1]. For years, formation of the tumor vasculature was largely thought to parallel physiological processes of neovascularization, with endothelial sprouting and proliferation being the principal routes of new blood vessel formation. However, it has recently become accepted that tumors have multiple, often unexpected mechanisms of neovascularization. Six modes of tumor angiogenesis are now recognized [2]. These include endothelial sprouting, post-natal vasculogenesis by endothelial precursor cells (EPC), intussusception (vessel splitting), cooption of existing vasculature, tumor cell differentiation into “endothelial-like” cells, and vascular mimicry (VM). In this review, we will briefly discuss VM in its historical context and explore recent advances made in understanding VM biology. The potential mechanisms for VM-mediated resistance to anti-angiogenic therapies will also be presented.

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*Address correspondence to this author at the Dept. of Cell and Molecular Physiology, University of North Carolina at Chapel Hill, 8340C Medical Biomolecular Research Bldg., Chapel Hill, NC 27599, USA; Tel: (919) 966-4419; Fax: (919) 966-6927; acdudley@med.unc.edu.

CONFLICT OF INTEREST

None declared.

VM was initially described in aggressive, uveal forms of melanoma as a process of “dedifferentiation” of tumor cells into an “endothelial-like” phenotype [3]. In these tumors, VM was identified as periodic acid-Schiff (PAS) positive, matrix-associated channels devoid of bona fide endothelium. VM channels appeared to contain erythrocytes and were therefore hypothesized to connect with the existing vasculature. Notably, patients displaying the presence of PAS-positive networks in their tumors had an increased mortality compared to those patients which did not. Following this observation, it was suggested that some tumors were capable of forming their own vascular channels which could carry blood, oxygen and nutrients in collaboration with blood vessels formed by conventional routes of tumor angiogenesis (i.e. sprouting). The clinical implications for VM were clear: VM-forming tumors were more virulent than their non-VM counterparts and VM-lined channels might not respond predictably to conventional anti-angiogenic therapies.

These seminal VM studies were met with criticism at two fronts [4]. First, the novelty of the findings was challenged. For example, tumor cell-lined “blood lakes”, were identified in uveal melanoma over 40 years prior to the work by Hendrix [5–8]. However, it was not understood at that time that these “blood lakes” were not always physically connected with the vasculature; instead, “blood lakes” were typically formed by erythrocytes which had leaked from poorly formed tumor vessels into the surrounding area [9,10]. Second, the relevance of these findings was questioned, considering the possibility that VM channels were not functional. Moreover, there were serious technical limitations in identifying VM channels using conventional immunohistochemistry which was prone to artifacts and not entirely objective.

At the same time VM was identified by Hendrix, an alternative mode of tumor cell-originated vasculature was proposed. “Mosaic vessels”, whereby tumor cells enter the luminal space of host-derived vasculature were initially described in mouse xenografts of labeled human colon cancer specimens [11]. Like VM, the concept of mosaic vessels was controversial. It was unclear whether tumor cells were functioning within the vessel wall or were merely an artifact of tumor cells closely positioned near blood vessels or shed into the circulation. Mosaic vessels contrasted the concept of VM, where an entire vascular channel is lined solely by tumor cells, masquerading as endothelium. As concepts, VM and mosaic vessels are not mutually exclusive, and it is possible that both modes of tumor angiogenesis can co-exist within the same tumor (Fig. 1).

Recently, VM has re-entered the spotlight in angiogenesis research following the publication of three, high-profile research articles on this topic [12–14]; see also commentary by Bautch [15]. Irrespective of these advances, remarkably little is known about the molecular mechanisms and clinical manifestations of VM. Moreover, how VM might impact the effectiveness of anti-angiogenic therapies is not understood.

CHARACTERISTICS OF VASCULAR MIMICRY

Tumors of vascular origin including hemangioma, angiosarcoma, and Kaposi’s sarcoma originate from transformed vascular cells. These tumors, as expected, are highly vascularized, they are pathologically “bloody,” and they are characterized by tangles of poorly formed, atypical vascular structures. In contrast, VM typically designates expression of endothelial factors and acquisition of vascular cell characteristics by tumor cells of a non-vascular origin. Following its initial discovery in uveal melanoma, VM has now been identified in breast [16], ovarian [17, 18], prostate [19], Ewings sarcoma [20], hemangiopericytoma [21], astrocytoma [22], hepatocellular carcinoma [23], glioblastoma [12–14, 24] and lung [25] cancers. Thus, VM has been described in tumors originating from all three germ layers: ectoderm, mesoderm and endoderm. These findings suggest there may

be strong selection pressure for VM within the pool of malignant cells irrespective of cellular ontogeny. A survival advantage may be afforded to tumor cells with greater plasticity and the ability to form their own vascular networks in the face of nutrient and oxygen scarcity characteristic of the tumor microenvironment. Indeed, hypoxic-conditioning of tumor cells promoted their alignment into structures resembling blood vessels and upregulated expression of the endothelial markers vWF and CD31 [14]. Additionally, hypoxic culturing of VM tumor cell lines increases the expression of a number of endothelial-like factors, including laminin 5 γ 2-chain and EphA2 [26, 27].

Here, we have identified three common characteristics of VM networks in cancer that we consider to be cardinal features of the VM phenotype: expression of endothelial-selective makers, expression of anti-coagulant factors, and anastomosis/perfusion with the existing vasculature. While these defining characteristics may be common, unifying features of VM, this list is not all-inclusive. Furthermore, VM tumors need not simultaneously display each of these characteristics. For example, tumor-derived channels which connect with the circulation and carry fluid, even without expression of endothelial-selective markers, would embody the definition.

Expression of Endothelial-Selective Markers

Some tumor cells which participate in VM express typical vascular cell markers [28–30]. Expression of VE-cadherin [31], EphA2 [26], CD34 [14], and CD31 [14] have been described in VM tumors (see Table 1). However, these markers are all selective for and not specific to the vascular endothelium. For example, cells of hematopoietic origin including monocytes, neutrophils, and lymphocytes also express CD31 and CD34. In some cases, expression of these markers by tumor cells may be a “rough attempt” at tumor cell differentiation into vascular-like cells [32]. In support of this possibility, VM tumors do not behave predictably in response to treatment with typical endothelial cell mitogens. For example glioblastoma, with features of VM, lack expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) receptors [14]. The ligands for these receptors are potent endothelial cell mitogens and are indispensable for the survival of bona fide endothelium but may not be necessary for survival of VM tumor cells whose growth is driven by oncogenes. Furthermore, VEGF and bFGF failed to elicit the formation of VM channels, suggesting that factors which are ordinarily pro-angiogenic during development and pathological neovascularization do not necessarily control VM responses [3]. On the other hand, recent work from the Ellis lab demonstrated expression of VEGFR-2 in ovarian cancer, although it was not determined whether this played a direct role in VM [33]. Expression of VEGF receptors (and other “vascular-like” factors) by tumor cells may not necessarily confer a VM phenotype but may instead reflect acquisition of a survival pathway normally related to endothelial function and development. Good examples are members of the Notch/Nodal pathway commonly involved in embryonic morphogenesis but also involved in the regulation of cellular plasticity in aggressive forms of uveal melanoma [34,35].

Expression of Anti-Coagulant Factors

A major function of vascular endothelium is control of hemostasis which is achieved by the expression of anticoagulant proteins including tissue factor pathway inhibitors (TFPIs), heparin sulfate proteoglycans, and thrombomodulin at the luminal surface [36]. Blood will coagulate instantaneously when in contact with most tumor cells in the absence of anti-clotting factors [37]. Thus, it might be predicted that tumor cells which participate in VM would express anticoagulant factors, or otherwise inhibit clotting by another mechanism. Indeed, some aggressive VM-forming tumors, but not their non-VM counterparts, express proteins involved in the coagulation cascade including TFPI-1 and TFPI-2 [38]. Expression

of these factors has been detected in VM networks where it is assumed their activity is necessary to allow blood to flow freely by preventing tissue factor-mediated clotting. The presence of anti-coagulant cell-surface markers, coupled with the identification of circulating erythrocytes in the initial discovery of VM, suggests that these channels may play an active rather than a passive role in fluid transport. While it may be essential that VM channels lined entirely by tumor cells express some proteins of the anti-coagulant system, it is less certain if VM tumor cells which collaborate with host endothelium (e.g. mosaic vessels) require their own anti-coagulant proteins to conduct fluid, or if they can co-opt those of the tumor endothelium.

Anastomosis with Perfused Vasculature

Initial discoveries of VM were met with skepticism because it was not believed that tumor cell-lined channels were physically connected with perfused tumor blood vessels. Instead, VM was mostly dismissed as an artifact of tissue sectioning or was ascribed to pooling of erythrocytes in “blood lakes” which were not physically connected with the vasculature. Definitive proof for functioning VM channels has been difficult to establish due to the low fidelity of imaging systems which does not allow for sufficient resolution. For example, the tumor endothelium is typically “squeezed” by the overlying mass of tumor cells resulting in thin, flattened endothelial nuclei which can be difficult to view under standard microscopy [39]. One common approach for demonstrating VM is through the use of fluorescent dyes injected via the tail vein. In one study, fluorophore-conjugated lectin injected i.v. co-localized with GFAP⁺ glioblastoma cells which is good evidence that the tumor cells were in contact with flowing blood [14]. Recently, several studies have used advanced imaging techniques including MRI and fluorescent dyes to demonstrate that VM channels are definitively anastomosed with the vasculature and they exhibit blood flow [40–42]. Additionally, injected microbubbles viewed with Doppler imaging revealed a functional connection between host vasculature and VM channels [38].

ORIGINS OF VASCULAR MIMICRY

Highly aggressive, uveal forms of melanoma have served as the VM prototype. These tumors display a high degree of plasticity and cellular heterogeneity which has often been interpreted as a recapitulation of the embryonic stages of development related to the de-differentiation of tumor cells into a more primitive phenotype [28–30]. Evidence for this is given by the genetic signature of some uveal melanoma tumors which reveal loss of melanoma-specific markers including melanoma-cell adhesion molecule and microphthalmia-associated transcription factor and gained expression of markers for cells of diverse origins, especially vascular cells. Remarkably, this plasticity is reversible and reprogrammable by transplanting melanoma cells into an embryonic microenvironment [43]. For example, melanoma cells implanted *in ovo* adjacent to the neuronal crest of embryonic chicks did not form tumors and regained expression of a melanocyte-specific phenotype marker (MART-1) and the neuronal marker Tuj1 [44]. Thus, cues within the microenvironment are capable of instructing melanoma cells to reacquire features of cell types derived from the neural crest, their ancestral cell-of-origin.

A second possibility is that putative cancer stem cells (CSCs), which are not lineage restricted, are the cell-of-origin for some tumor cells with VM characteristics. Theoretically, CSCs would have the potential to differentiate to form cells with multiple phenotypes and multiple functions. For example, many of the factors associated with stem cell maintenance and renewal such as Notch, Wnt, ABCB5, CD133, CD166, nestin, and c-kit, are over-expressed in aggressive cancers displaying a VM phenotype [45–49].

Similar to melanoma, CSC or “CSC-like” cells are reported to form blood vessels in aggressive glioblastoma. For example, CD133⁺/CD144⁺ glioblastoma stem-like cells (GSC) were reported to undergo differentiation into endothelium which was blocked by γ -secretase inhibitors or Notch1 silencing [50]. These tumor-derived endothelial cells carried glioblastoma-specific chromosomal aberrations, were not sensitive to VEGF inhibition, and they contributed substantially to the tumor vasculature (range of 20–90%). Moreover, GSC-derived blood vessels were functional because their selective depletion dramatically impaired tumor growth. Because a significant proportion of the vasculature may be of neoplastic origin in some tumor types, it is possible that these tumors would not respond predictably to conventional angiogenesis inhibitors. Moreover, rare CSC with an inherent ability to differentiate and form endothelial-like cells may be selected for in response to angiogenesis inhibition. Thus, it is feasible that VM may underlie tumor escape and vascular rebound following an initial vessel pruning response after treatment with drugs such as Avastin.

CAN VM UNDERLIE RESISTANCE TO ANTI-ANGIOGENIC THERAPIES?

Over 40 years ago it was proposed by Folkman that an effective treatment for cancer would target vascular networks rather than mutable, drug-resistant tumor cells [51]. Anti-angiogenic therapy posited that if the tumor’s “plumbing” could be selectively eliminated, so could access to oxygen and nutrients. Inhibition of tumor-associated blood vessels would also eliminate the principal routes of metastasis. To this end, inhibitors of the VEGF signaling pathway have been investigated exhaustively in pre-clinical and clinical models with varying degrees of success [52]. Disappointingly, tumors appear to develop resistance in response VEGF inhibition just as they do with cytotoxic chemotherapy [53]. Resistance to anti-angiogenic therapy has been “blamed” on a number of counter-responses by both tumor cells and stromal cells [53]. This resistance is puzzling, given that other diseases characterized by unchecked neovascularization (e.g. macular degeneration) respond well to VEGF inhibition [54]. VM offers one attractive and feasible mechanism for a drug resistant paradigm following the use of angiogenesis inhibitors. Indeed, melanoma tube-forming ability was completely unaltered by the prototypical angiogenesis inhibitor, endostatin, whereas normal endothelial cells were strongly inhibited [55].

Initially, anti-angiogenic treatment is successful because it targets and destroys bona fide endothelium. One unexpected consequence of angiogenesis inhibition is that hypoxia is exacerbated which creates selection pressure for hypoxia-tolerant tumor cells and stimulates expression of factors (e.g. VEGF) which support vessel regrowth. Interestingly, VM-positive Ewings sarcoma were closely localized with areas of hypoxia, suggesting the VM may be a response to inadequate vascularization by normal angiogenic processes [20]. Whereas vascular endothelium may be responsive to VEGF inhibition, some tumor cells participating in VM may not be dependent on VEGF for survival, so it is unlikely that therapies which trap and inactivate VEGF would be very effective. In fact, the initial discovery of VM revealed that it was insensitive to VEGF stimulation [3]. In further support of this theory, AG28262 (a selective inhibitor of VEGFR-1, R-2 and R-3) had no effect on *in vitro* tube formation or percentage of glioblastoma tumor-derived vessels *in vivo* [14]. On the other hand, thalidomide, an angiogenic inhibitor which is not believed to interfere with the VEGF pathway, could eradicate VM channels in melanoma [56].

PERSPECTIVE

The concept of VM, initially met with skepticism, has received renewed attention in the field of angiogenesis research. As studies highlight the disappointing, and unexpected consequences of angiogenesis inhibition in tumors, it is tempting to speculate that VM may

be an underlying, perhaps overlooked mechanism of escape to these therapies [38,39]. A Pubmed search of “vascular mimicry” returns ~188 articles dating back to 1999 and in the last two years a burst of high profile studies provide new evidence supporting the existence of VM. Furthermore, while VM was initially described in aggressive forms of uveal melanoma, the list of tumor types displaying characteristics of VM is growing. Still, there are many remaining questions. For example, does VM play a substantial role in metastasis? Do tumor cells form their own lymphatic vessels using processes similar to VM? And finally, if tumors can self-vascularize, is an anti-angiogenic approach for shrinking solid tumors feasible?

As we learn more about the molecular mechanisms and genetic signature of VM, it is possible that tumors could be segregated as likely or unlikely to respond to angiogenesis inhibition. Moreover, it is not expected that all tumor types would have the intrinsic ability to carry out VM and these tumors might respond favorably to anti-VEGF or other anti-angiogenic inhibitors. Thus, VM may not be an intractable problem for cancer therapy but yet another complex adaptation of cancer cells struggling to survive in the face of nutrient and oxygen scarcity.

Acknowledgments

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Fig. 1. Potential modes of vascular mimicry

A) a normal tumor blood vessel lined by vascular endothelial cells **B)** mosaic vessels where tumor cells collaborate with pre-existing endothelium. Tumor cells (shaded) participating as mosaic vessels passively fill in gaps within blood vessel walls. Mosaic tumor cells may co-opt the anti-coagulant properties of existing endothelium and may not express endothelial cell-selective markers **C)** vascular mimicry, whereby tumor cells actively and autonomously create new vessels in the absence of vascular endothelium. These channels are comprised of tumor cells which may acquire features of endothelial cells including expression of endothelial-selective markers, some anti-coagulant properties and ability to transport blood and fluid. Tumor cells, with properties of VM, may also collaborate with co-opted, pre-existing vessels to form hybrid tumor blood vessels.

Table 1

Endothelial-Selective Markers Found in Aggressive, VM-Positive Tumors and their Potential Contribution to VM Channel Formation

Endothelial-Selective Marker	Putative Role in VM	References
VE-cadherin (CD144)	Cell-cell adhesion, collaboration with host vasculature	[3,12,14,26]
PECAM-1 (CD31)	Cell-cell adhesion, signaling	[12,13,14,32]
Laminin 5 γ 2	Adhesion to basement membrane, integrity of VM channels	[27]
EphA2	Migration, remodeling of VM channels	[26]
CD34	Cell-cell adhesion	[14,32]
VEGFR-2	Survival, proliferation	[12]