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Approaching Vessel Co-Option from the Pathologists' Perspective

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Description

Blood vessel formation is a key ingredient of both organogenesis and tissue repair, in which florid endothelial sprouting takes place in the distal parts of the vascular system. This biological process, whose main goal is increasing oxygen and nutrients supply to tissues is called angiogenesis. Importantly, this microvascular development also fuels neoplastic growth. Together with tumor infiltrating lymphocytes, macrophages and cancer associated fibroblasts, endothelia constitute a major component of the tumor microenvironment. The mechanisms by which tumor cells induce angiogenesis have been extensively analyzed [1].

Interestingly, researchers soon noticed that a significant percentage of primary tumors showed no histological evidence of angiogenesis. Since, contrary to expectations, these tumors did not develop hypoxia, it was concluded that they probably resorted to an alternative way of oxygen and nutrients supply. Pezzella, et al. reached this conclusion in 1997, when they noticed that 16% of aggressive stage I non-small cell lung carcinomas in their series of 500 cases lacked features of vascular sprouting. Further evidence accrued in the last decades has confirmed that these non-angiogenic neoplasms are more frequent than previously suspected and tend to display a more aggressive clinical course [2].

Vessel co-option, a term coined by Holash, et al., in 1999 refers to the hijacking of pre-existing vascular networks by neoplastic tissue. This process, which could be considered as a sort of tumor parasitism, guarantees tumor blood supply in the absence of angiogenesis. On the other hand, this phenomenon provides alternative routes for tumor dissemination. Vessel co-option takes place everywhere, albeit it has been preferentially studied in primary and metastatic tumors involving organs such as the brain, lung and liver [3].

Pathologists may detect vessel co-option traits under the microscope, but its identification is difficult and may be overlooked in a context of high diagnostic pressure. It is then of paramount importance to acquaint pathologists with the definitory histologic features of this interesting phenomenon. The issue matters because vessel co-option is responsible for extravascular migratory dissemination of neoplastic cells, a still poorly known mechanism of tumor spreading. Additionally, vessel co-option is associated with lack of therapeutic response to current antiangiogenic drugs [4-6].

The morphological features of vessel co-option have been recently reviewed [3,8]. In the first place, specific organ histology must be kept in mind since wide organ related variations in the microscopic findings of vessel co-option do occur. Thus, Virchow-Robin spaces in the brain, sinusoidal vessels in the liver and perialveolar chicken wire capillaries in the lung, among others, show different histological changes when co-opted. At any rate, the main problem for pathologists is to distinguish immature (angiogenic) from mature (non-angiogenic) vessels in conventional hematoxylin eosin stained slides. Conventional vascular markers such as factor VIII-related antigen, CD31 and CD34 are not useful for this purpose since endothelial cells in both immature and mature vessels are equally immunoreactive.

Fortunately, Smooth Muscle Actin (SMA), which is expressed only in mature vessel pericytes (perivascular niche), is more helpful in this regard. Proliferation index (Ki67) may also be used to detect immature endothelial cells. In this setting, it is crucial to remember that angiogenesis and vessel co-option are not mutually exclusive and may coexist in the same tumor [7-9].

Due to the specific characteristics of brain tissue, its primary tumors and their metastases offer very useful scenarios for the study of vessel co-option. In normal conditions the central nervous system parenchyma lacks connective tissue. This absence favors the development of a diffuse front of tumor infiltration, which is facilitated by co-opting the Virchow-Robin spaces. The mechanism underlying this co-option relies on the intricate interaction of tumor cells, basal membranes and pericytes.

In addition to the common presence of abundant vessel sprouting and vascular proliferation in high grade gliomas, the use of Virchow-Robin spaces as a route of expansion is commonly seen in gliomas and brain metastases [10]. The endothelial sprouting so characteristic of angiogenesis does not take place in the absence of stromal induction, even in the presence of high levels of local vascular growth factors. To better detect co-opting vessel features within the Virchow-Robin spaces, pathologists should focus on the tumor edge of infiltration. If needed, specific immunohistochemical markers may be used to highlight this phenomenon.

Aside from the central nervous system, vessel co-option is a common feature of hepatocellular carcinomas and liver metastases, in which pre-existing sinusoidal vessels are hijacked and of lung carcinomas, in which the perialveolar capillary network is occupied by tumor cells [11]. Melanoma is a typical co-opter by often permeating the virtual perivascular space of local vessels in the skin or the organs to which it metastasizes [12].

Although renal clear cell carcinoma is one of the paradigmatic examples of angiogenic neoplasm, vessel co-option also occurs in this tumor. Of interest, the high density of mature vessels detected in the renal tissue at the tumor edge suggests that a process of pre-co-option vessel remodeling is taking place [13]. These vessels initially keep their pericyte coverage intact, but when co-opted and overrun by the

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tumor expansile growth their pericyte population gradually diminishes until its total disappearance in the necrotic tumor center [14].

Vessel co-option acquired special clinical relevance with the addition of antiangiogenic drugs to oncologic therapeutic protocols. Resistance to this therapy has been well documented in most non-angiogenic tumors. Additionally, some studies have shown that the perivascular niche generated in vessel co-option may also act as a sanctuary for tumor cell dormancy and a facilitator of immune therapy resistance.

Alternative therapies aiming at the inhibition of vessel co-option include the following:

- Suppression of tumor cell motility by knocking down the expression of actin related protein 2/3.
- Blockade of cell adhesion receptors such as L1CAM and cell adhesion receptor β1 integrin.
- Simultaneous inhibition of VEGF and angiopoietin signaling.

At present, however, these and other promising therapeutic alternatives are still under investigation. The successful outcome of these efforts is highly dependent on a better understanding of the vessel co-option phenomenon from the pathologists' perspective.

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Conflict of Interest

The authors declare no conflict of interest.

Author's Contributions

J.I.L. and A.A. designed, wrote and approved the manuscript.

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