What brings pericytes to tumor vessels?

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Paracrine signaling via platelet-derived growth factor B (PDGFB), expressed by endothelial cells, and its receptor PDGFR-β, expressed by pericytes, plays a central role in blood vessel maturation. A new study (see the related article beginning on page 1142) reveals that it is not just the presence of PDGFB, but how it is presented to pericytes, that determines the quality of the endothelium-pericyte interaction.


Tumor vessels are enigmatic. Their wall structure and branching patterns are abnormal (1). The mural cells (MCs) — pericytes and VSMCs — are either absent or loosely associated with the tumor endothelium. This abnormality contributes to the leakiness of the vessels, which, counterintuitively, poses a challenge for drug delivery (2). At the same time, this very absence of MCs renders the vessels vulnerable to antiangiogenic therapies. Thus, an understanding of the molecular mechanism of MC recruitment to tumor endothelial cells (ECs) is important for cancer treatment.

The tumor vascular network is formed by vasculogenesis (de novo vessel formation from angioblasts or stem cells) as well as angiogenesis (sprouting, bridging, and intussusceptive growth from existing vessels). VEGF signaling initiates the formation of new vessels by recruiting ECs to form tubes. VEGF also triggers a chain of molecular and cellular events that stabilize the EC tubes by recruiting MCs and generating an ECM. At least four molecular pathways are involved in the regulation of this process, and the key components of these include (a) platelet-derived growth factor B (PDGFB) and PDGFR receptor β (PDGFR-β); (b) sphingosine-1-phosphate-1 (S1P1) and endothelial differentiation sphingolipid G-protein–coupled receptor 1 (EDG1); (c) Ang1 and Tie2; and (d) TGF-β (1). Based on the phenotype of PDgfb- and PDgfr-β-null mice, Hellstrom et al. previously demonstrated that paracrine signaling via PDGFB (expressed by ECs) and its receptor PDGFR-β (expressed by MCs) plays a central role in MC recruitment and blood vessel stabilization (3). However, the precise mechanism underlying the recruitment of MCs to ECs is shrouded in mystery.

In this issue of the JCI, Abramsson et al. (4) propose that it is not just the presence of PDGFB but how it is presented to MCs that determines the quality of EC-MC interactions. They offer compelling evidence for the hypothesis that an extracellular gradient of PDGFB, adjacent to the ECs, coaxes MCs into close contact with vessels (4). Because technical difficulties precluded the direct measurement of extracellular PDGFB concentration gradients in vivo, Abramson et al. (4) disrupted these gradients by a series of clever approaches (Figure 1) and monitored the effect on MC recruitment.

The PDGFB molecule contains a “retention motif,” a region that mediates binding to proteoglycans at the cell surface and in the ECM. Presumably, this motif helps to localize PDGFB in or near the secreting ECs (Figure 1, a and b). Abramsson et al. (4) demonstrate that when T241 fibrosarcoma cells, which do not express PDGFB, are implanted in wild-type mice, the resulting tumor vessels are invested with MCs. When the same tumor cells are transplanted into pdgfb-ret/ret mice — transgenic mice that express a form of PDGFB that lacks the retention motif (5) — they have fewer vessel-associated MCs and looser attachment between MCs and ECs (4). This is presumably because the modified PDGFB is free to diffuse throughout the ECM and does not form sharp, EC-associated gradients (Figure 1c). If tumor cells expressing PDGFB are used, the number of recruited MCs increases, but since the extra PDGFB is not concentrated around the ECs, the EC-MC attachment in pdgfb-ret/ret mice does not improve (Figure 1d). Finally, exogenous cells that do not express PDGFR-β are unable to form contact with ECs (Figure 1e).

**Pericyte coverage: bad or good?**

These findings have important clinical implications, not only for cancer, but also for other diseases characterized by abnormal EC-MC interactions (6). The host cells (possibly MCs) that surround the tumor vessels are known to produce VEGF (7, 8) (Figure 1f), which is a survival factor for ECs. Thus it seems reasonable to speculate that MCs serve as a private source of VEGF for the adjacent ECs (9). If the MCs were absent or could not produce VEGF, the endothelium would become vulnerable to VEGF blockade. Indeed, this is the case for both normal and pathological vessels (10). Furthermore, tyrosine kinase inhibitors, which block multiple kinases including PDGFR-β, enhance the effect of VEGF inhibitors (11). This enhancement may be a result of disrupted EC-MC contact, or it may be caused by the reduced production of VEGF and/or tumor matrix molecules by PDGFR-β-positive perivascular cells.
When antiangiogenic therapy prunes away tumor vessels with little or no MC coverage, it may leave behind a “normalized” network of MC-invested vessels. This normalization process could be exploited for the improved delivery of drugs to tumors (12). Because recent clinical trials suggest that, for the near future, antiangiogenic therapies must be combined with cytotoxic therapies to achieve the best therapeutic response (13), the normalization of tumor vasculature — and the role of MCs in that normalization — is a fertile area of research.

Although recent efforts have focused on destabilizing tumor vessels by interfering with EC-MC communication, the other side of the coin — enhancing EC-MC communication — is equally important in medicine. The formation of a mature, well-organized, stable vasculature is a key goal in tissue engineering, regenerative medicine, therapeutic angiogenesis, and the treatment of vascular diseases such as diabetic retinopathy (1, 6).

Unanswered questions
As any good study does, the present work (4) raises many questions. For example, where do the MCs in tumors come from? Does TGF-β (or another trigger) prompt fibroblasts at the tumor/host interface to differentiate into myofibroblasts and then into pericyte-like cells (1, 14, 15)? How do the PDGF gradients produce a close association between ECs and MCs? Do they direct subcellular localization of adhesion molecules, localized ECM production, or other factors, as Abramsson and colleagues suggest (4)? Vessels in most tumors either lack MC coverage or have abnormal MC coverage. Is this due to the presence of nonretained isoforms of PDGFB? Or is it that PDGFB levels in tumors are so large that they overwhelm the peri-EC gradients? Is this due to the presence of nonretained isoforms of PDGFB? Or is it that PDGFB levels in tumors are so large that they overwhelm the peri-EC gradients? Finally, how does the PDGFB/PDGFR-β pathway interact with the other molecular pathways that are known to play a role in EC-MC interactions? These include VEGF, TGF-β, ephrins, Ang1 and Tie2, and S1P1 and EDG1 (1).

An even more fundamental question is: What is the structural and
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Receptor “cross talk” in innate immunity

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Toll-like receptors (TLRs) recognize microbial molecular signatures and can initiate innate immune responses against invading pathogens. A new study (see the related article beginning on page 1234) reports how TLR2 expression by endothelium is locally upregulated by the action of activated polymorphonuclear neutrophils via an unprecedented mechanism involving cell-cell interaction and NAD(P)H oxidase. The report reveals yet another way in which the primordial innate immune system is remarkably complex.


In this issue of the JCI, Fan et al. report on receptor “cross talk” between members of the Toll-like receptor (TLR) family (1). This elegant study confirms previous observations that inflammation via TLR4 results in the enhanced expression of TLR2 (2, 3). However, Fan et al. elucidate a new mechanism of enhancement of endothelial TLR2 expression that may have important physiological consequences. Polymorphonuclear neutrophils (PMNs) that have been activated by endotoxin (LPS) can instruct endothelium to upregulate TLR2 and thus sensitize endothelium to TLR2 ligands. This message is sent to endothelial cells by the release of free oxygen radicals as the result of a CD14-dependent cell-cell interaction. TLR2 expression in endothelium, for example, was dramatically enhanced when endothelium was co-incubated with activated PMN from normal mice but not mice with a targeted lesion in TLR2.

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Nonstandard abbreviations used: Toll-like receptor (TLR); polymorphonuclear neutrophil (PMN).


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