This issue of Cell Adhesion & Migration has a special focus that contains reviews that explore different aspects of the interplay between vascular endothelial growth factor (VEGF), vascular and non-vascular cells with examples of impacts on tissue function. (VEGF-A) is a key regulator of developmental, physiological and pathological neovascularization, including tumor growth and metastasis. Alternative splicing of VEGF-A results in the production of several VEGF isoforms with different heparin-binding affinity. Interaction between VEGF and its endothelial receptors, VEGF-R1 (Flt-1), VEGF-R2 (KDR/Flk-1) and neuropilin-1 (NRP-1), stimulates receptor-associated kinase activity and initiates signaling pathways leading to angiogenesis. Our knowledge of the significance of VEGF, and/or VEGF isoforms, in vascular remodeling and in non-vascular cells is less known.

Two reviews focus on the interplay between VEGF, angiogenesis and vascular remodeling. Angiogenesis involves complex cellular events comprising sprouting, proliferation, migration and lumen formation, dynamic regulation of cell-cell contacts with endothelial cells together with the establishment of connections with mural cells. Sprouting during developmental and pathological angiogenesis requires the coordinated behavior of endothelial cells, leading “tip” cells and training “stalk” cells, under the control of VEGF/VEGFR and Dll4-Notch signaling pathways. Endothelial tip cells are induced and guided by an extracellular gradient of VEGF. Gerhardt and Ruhrberg have initiated a series of studies showing that the combinatorial expression of a soluble and a heparin-binding VEGF isoform is sufficient to induce the formation of a normal branching pattern. Mettouchi reminds us how extracellular matrix (ECM) is a multifaceted substrate, which behind a classical structural role hides a powerful conductor function for the patterning of vessels. ECM, by interacting with VEGF, modulates its availability, its gradient organization. By engaging a specific array of integrins, ECM can indirectly signal through the Notch pathway by controlling Dll4 ligand expression. Also, ECM mechanically influences cellular tension and cytoskeleton organization inducing cell shape and transcription. Thus, ECM contributes importantly to the branching pattern of angiogenic vessels. In their review, Breuss and Uhrin discuss the interplay between VEGF-initiated angiogenesis and the uPA/uPAR system. In particular how VEGF initiates uPA/uPAR activation through VEGFR2, subsequent redistribution of uPAR to the leading edge of endothelial cells, and activation of proteolysis to the invasive front of endothelial cells.

VEGF is secreted by several cell-types and may act on non vascular cells during development. Tillo et al. discuss emerging roles for two families of neural and vascular guidance cues in synapse development, maintenance and elimination, the semaphorins and the VEGFs. Their contribution to synapse formation and function add a new facet to the spectrum of overlapping roles for these molecules in development.

Two reviews focus on the autocrine role of VEGF-secreting cells in different physio-pathological conditions such as

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Dr Perrot-Applanat obtained degrees at the University of Paris and from Ecole Normale Superieure in Physiology-Biochemistry. She received her PhD in Endocrinology from the University of Paris in 1981. Under the supervision of Professors E.E. Baulieu and E. Milgrom, she studied the mechanism of action and physiopathology of estrogen and progesterone receptors. In 1993 she joined the Professor P. Kelly lab as senior researcher in the field of prolactin receptors. Dr Perrot-Applanat joined the CNRS in 1977, where she is now Directeur de Recherche since 1988. After her participation to the first Gordon Conference on Angiogenesis in 1994, Dr Perrot-Applanat developed her team “Angiogenesis and Hormones” with the support of the Fondation de Recherche Medicale. Dr Perrot-Applanat began working on angiogenesis in the human endometrium, demonstrating that estradiol and progesterone modulate VEGF expression. In 2002, she demonstrated that VEGF 189, a spliced isoform of VEGF-A, was specifically expressed in endometrial decidual cells during the secretory phase of the menstrual cycle, pointing out the importance of VEGF isoforms in physiological angiogenesis. She has also focused on early angiogenesis in breast tumors, studying the role of estrogens, agonists and antagonists. She has recently demonstrated that different VEGF-A isoforms may have specific roles on adhesion, proliferation and survival of tumor cells. This finding was exploited to analyze the mechanisms that mediate autocrine functions of VEGF-A on tumor cells. More generally, understanding the mechanisms that mediate autocrine and paracrine VEGF-A signaling is of primary importance due to the growing therapeutic use of cancer inhibitors.
tumorigenesis. Deregulated VEGF-A expression contributes to the development of solid tumors by promoting tumor angiogenesis and metastasis. The discovery of multiple VEGF isoforms raised the possibility that individual isoforms might have different functions, affecting different aspects of tumor progression. In recent years, an emerging area of importance in cancer biology relates to the presence of VEGF receptors in tumor cells, suggesting that VEGF-A also promotes a wide range of other functions, both in vitro and in vivo. Perrot-Applanat and Di Benedetto report that VEGF-A secreted by different types of cancer cells acts through an autocrine signaling pathway mediated by VEGF receptors and/or NRPs to promote tumorigenesis. VEGF can promote proliferation, survival, adhesion, migration and chemotaxis of breast cancer cells, independently from angiogenesis. The review also discusses the role of VEGF-A isoforms in breast cancer progression. In particular how VEGF189 is involved in increased adhesion, but decreased migration and survival of cancer cells as compared with VEGF165. Using an in vitro model (MDA-MB-435 breast cancer cells), Goel and Mercurio discuss how neuropilins (NRPs), a distinct class of VEGF receptors, enable the function of specific integrins that contributes to tumor initiation and progression. Understanding the mechanisms underlying autocrine and paracrine VEGF/VEGFR/NRP signaling has become/will be increasingly important due to the growing use of therapeutic inhibitors for cancer treatment.

The discovery of novel splice variants of VEGF with antiangiogenic properties (VEGFxxx) about a decade ago has made this growth factor even more fascinating and complex. In her review, Peiris-Pagès focuses on VEGF165b physiological expression and function, VEGF165b regulation and its role in various physio-pathological conditions including fertility control and pregnancy, eye and renal diseases and cancer. An upregulation of the pro-angiogenic VEGFxxx variants has been widely reported in human tumors. This upregulation brings about a loss in the balance of isoforms, which causes a drop in the proportion of VEGFxxx levels. The author argues that the VEGFxxx/VEGFxxxb ratio seems to have an effect on the sensitivity of cells to bevacizumab, an anti-VEGF antibody licensed for its use in treatment cancer.

The mechanisms by which metastases develop are not entirely understood. Tumor cells are generally thought to acquire features affecting their metastatic potential during tumor progression. These features include greater survival, invasive and migratory capacities. Stromal cells and the tumor cell-stroma interaction have also been reported to play a very important role in these different steps.

In recent years, immunotherapy has emerged as a viable and effective treatment for a range of cancers through the administration of therapeutic antibodies as drugs. Antiangiogenic treatments targeting VEGF or its receptors have been developed with consistent results in some metastatic cancers including colorectal cancer, but not in others. The refractory reaction to angiogenic therapies might be due to tumor cell acquisition of resistance to VEGF therapies by means of the recruitment of circulating endothelial progenitors, or could be due to a resistance of tumor cell themselves to the treatment. Eveno and Pocard provide evidence that, despite the proposal of new drugs for treatment, new concepts, such as the tumor microenvironment and metastatic niche have not yet reached surgical practice.

Thus, refining our knowledge of VEGF/VEGF isoforms signaling pathways in tumor cells, of the recruitment of endothelial progenitors or stem cells, should help us understand why the current use of therapeutics targeting the VEGF pathway in cancer is not proved universally effective in inhibiting metastasis tumors and provide additional avenues for future therapies.

References

1. Mettouchi A. The role of extracellular matrix in vascular branching morphogenesis. Cell Adhes Migr 2012; 6:528-34; PMID:23257831; http://dx.doi.org/10.4161/cam.22862
2. Breuss JM, Uhrin P. VEGF-initiated angiogenesis and the uPA/uPAR system. Cell Adhes Migr 2012; 6:535-40; PMID:23076133; http://dx.doi.org/10.4161/cam.22243
3. Tillo M, Rohrborg C, Mackenzie F. Emerging roles for semaphorins and VEGFs in synaptogenesis and synaptic plasticity. Cell Adhes Migr 2012; 6:541-6; PMID:23076132; http://dx.doi.org/10.4161/cam.22408
4. Perrot-Applanat M, Di Benedetto M. Autocrine functions of VEGF in breast tumor cells: Adhesion, survival, migration and invasion. Cell Adhes Migr 2012; 6:547-53; PMID:23257828; http://dx.doi.org/10.4161/cam.23332
5. Goel HL, Mercurio AM. Enhanced integrin function by VEGF/neuropilin signaling: Implications for tumor biology. Cell Adhes Migr 2012; 6:554-60; PMID:23076131; http://dx.doi.org/10.4161/cam.22419
6. Peiris-Pages M. The role of VEGF165b in pathophysiology. Cell Adhes Migr 2012; 6:561-8; PMID:23076130; http://dx.doi.org/10.4161/cam.22439
7. Eveno C, Pocard M. VEGF levels and the angiogenic potential of the microenvironment can affect surgical strategy for colorectal liver metastasis. Cell Adhes Migr 2012; 6:569-73; PMID:23257830; http://dx.doi.org/10.4161/cam.23247