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A Focus on Vascular Malformations

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Our understanding of vascular morphogenesis and angiogenic growth has progressed considerably during the last few decades. Today the field has gained significant clarity on the framework of interacting signaling pathways, extracellular regulatory proteins and participating physical forces involved in the process of endothelial cell sprouting, lumen formation, and vascular remodeling. This knowledge has provided an excellent platform in which to seek molecular mechanisms associated with vascular malformations. In fact, in the last two decades the field of vascular biology has witness significant expansion in the identification of monogenic causes, cellular effects and signaling pathways involved in vascular malformations. The purpose of this series of reviews is to shed light on some recent developments in this area, including both new discoveries and therapies that surfaced from basic scientific inquiry.

The emergence of the vasculature occurs early in the development with the direct differentiation of mesenchymal cells into angioblasts. These cells initially form tight clumps (blood islands) that include endothelial and hematopoietic progenitors. Individual blood islands connect with one another to form a vascular plexus. Subsequently, the uniformed plexus is reorganized into a hierarchical vascular tree where larger arteries, branch into capillaries which merge into veins. This organization enables broad exposure of blood to tissues facilitating exchange of nutrients while also controlling blood velocity and pressure. Loss-of-function mutations in members of the Bone Morphogenic Protein (BMP) signaling pathway (namely *ACVRL1*, *ENG*, and *SMAD4*) perturb this organization promoting the direct connection of arteries to veins bypassing capillaries. The high-pressure arterial flow impacts the thin walled veins that become enlarged and frequently rupture. Depending on their extent and location, these vascular anomalies referred to as hereditary hemorrhagic telangiectasia (HHT), can be life-threatening (1). The exact mechanisms by which aberrant arterial-to-vein connections take place are starting to emerge and include aberrant response to shear stress, increase sprouting, and changes in cell shape. Importantly, another group of vascular malformations, namely cerebral cavernous malformation (CCM) also show deregulation in the BMP signaling pathway (1). As reviewed by Bautch, a cohort of recent publications has uncovered a role for BMP signaling in the regulation of endothelial cell junctions (2). These findings are of paramount importance because of the critical role of junctional complexes in angiogenesis, permeability, endothelial-to-mesenchymal transition and regulation of critical transcription factors like YAP/TAZ and beta-catenin. Thus, at this

point, it is important to take stock and consider how deregulation of junctional complexes might pivot some of the multiple cellular and molecular abnormalities in HHT and how this new findings can inform therapeutic directions.

A recent highlight also related to HHT was the identification of missense mutations in the *DROSHA* gene in a cohort of patients afflicted by the disease. *DROSHA* is a critical enzyme in the processing of micro-RNAs, thus this subset of HHT patients are also compromised in their ability to process micro-RNAs. The combination of mutations is likely to impact disease burden, clinical presentation and response to treatment. In this series, Hata provides a comprehensive review of the recent publications on *DROSHA* and HHT and offers prospective on how these mutations might further affect vascular function (3).

The search for genetic causes of vascular malformations has recently yield two newcomers: *PIK3CA* and *GNAQ*. The former codes for the p110alpha isoform of PI3K lipid kinases that plays a critical role as second messenger downstream many receptor kinase pathways. *PIK3CA* was already of interest in cancer, as several carcinomas show mutations in this gene. Importantly, a few years ago, it became clear that a large percentage of lymphatic malformations also harbor mutations in *PIK3CA*. More recently, additional studies indicated that this gene is also mutated in approximately 20% of venous malformations. The impact of these findings has been evaluated in a comprehensive review by Castillo and colleagues in this series. The group offers an excellent review on *PIK3CA* signaling in vascular cells placing this information in the context lymphatic and venous malformations (4). New somatic missense mutations in *GNAQ* were recently identified in capillary malformations. The gene codes for the Gαq subunit of heterotrimeric G-proteins, which play critical roles in vascular cells. G-proteins are known to convey systemic information to endothelial and smooth muscle cells, controlling vasoreactivity, homeostasis and regulating angiogenic responses. In this series, Bichsel and Bischoff take account of the mutations reported in capillary malformations, discuss the cells affected and examine the impact of the mutation in cell signaling (5).

It is extremely satisfying to witness the translation of basic science discoveries into the clinic. In this series, Seront and colleagues discuss how information on the signaling pathways that are deregulated venous malformations, namely PI3K-AKT-mTOR, resulted in selecting rapamycin as a potential drug to treat these disorders. The authors summarize the outcome of phase 1–3 clinical trials assessing the clinical efficacy of rapamycin in patients with venous malformations and discuss patient stratification to best identify individuals who might best benefit from the treatment (6).

In addition to the classical vascular anomalies associated with lymphatics, capillaries and venules, a subgroup of vascular pathologies that mostly affect medium-to-small size arterioles has been referred to as “small vessel disease”. This cohort of vascular pathologies are not as easy to spot, as they do not promote tissue growth, like lymphatic or venous malformations, nor they appear as red lesions due to the accumulation of blood like in HHT or capillary malformations. Instead, small vessel disease is mostly due to drastic alterations in function rather than structure, and while not deforming, the resulting disease is equally devastating. The best understood monogenic form of small vessel disease is CADASIL

(cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). It is due to mutations in *NOTCH3* and while it affects vascular smooth muscle cells across the entire arterial tree, symptoms are more severe in the brain causing progressive loss of gray matter and promoting vascular dementia. Recent developments in the clinic and in basic science are reviewed in this series by Ferrante and colleagues (7).

A growing group of additional mono and polygenic causes of small vessel disease have been recently identified. Much like CADASIL, the disorders are not exclusive to the brain, but most are more severely manifested in this organ likely because of its low tolerance for oxygen deprivation and like CADASIL they result in dementia. The most recent advancements in this area were discussed by Romay and colleagues in this issue (8).

Through these series our objective was to bring readers a condensed view of some of the new developments, exciting therapeutic advances, and promising directions which may pave the way to translational opportunities.

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