HAEMANGIOMAS AND VASCULAR MALFORMATIONS

MOLECULAR PATHOGENESIS OF PORT WINE STAIN BLOOD VESSELS

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Introduction: Port-wine stain (PWS) is a vascular malformation characterized by progressive dilatation of postcapillary venules, but the molecular pathogenesis remains obscure.

Objectives: To characterize the molecular phenotypes of PWS endothelial cells (ECs).

Methods: Immunohistochemistry and transmission electron microscopy (TEM) were used to characterize the ultrastructure and molecular phenotypes of PWS blood vessels. Sequential windowed acquisition of all theoretical fragment ion mass spectra (SWATH-MS) was used to identify differentially expressed proteins in PWS lesions followed by confirmative studies with immunoblot and TEM.

Results: PWS ECs showed stemness properties with expression of endothelial progenitor cell markers CD133 and CD166. They also expressed dual venous/arterial identities, ephrin-B1 (EphB1) and ephrin-B2 (EfnB2). Co-expression of EphB1 and EfnB2 in normal human dermal microvascular ECs led to the formation of PWS-like vasculatures in vitro, e.g. larger-diameter and thick-walled capillaries. In addition, 107 out of 299 identified proteins showed differential expressions in PWS lesions as compared to normal skin, mainly involving the functions of biosynthesis, membrane trafficking, cytoskeleton and cell adhesion/migration. The confirmative studies showed that expressions of membrane trafficking/exocytosis related proteins such as VAT1, IQGAP1, HSC70, clathrin, perlecan, spectrin α1 and GDIR1 were significantly increased in PWS blood vessels as compared to normal ones. Furthermore, TEM studies showed there is a significant upregulation of extracellular vesicle exocytosis from PWS blood vessels as compared to control.

Conclusions: PWS ECs are differentiation-impaired, late-stage endothelial progenitor cells with a specific phenotype of CD133+/CD166+/EphB1+/EfnB2+, which form immature venule-like pathoanatomical vasculatures. The disruption of normal EC–EC interactions by coexistence of EphB1 and EfnB2 contributes to progressive dilatation of PWS vasculatures. Furthermore, the biological process of membrane trafficking and exocytosis is enhanced in

PWS blood vessels, suggesting that the extracellular vesicles released by lesional endothelial cells may act as potential intercellular signaling mediators to contribute to the pathogenesis of PWS.