Research experience and latest discoveries in HHT

Michelle Letarte

Professor Emeritus, Hospital for Sick Children and Department of Immunology, University of Toronto, Toronto, Canada

We identified endoglin 30 years ago as a membrane glycoprotein expressed predominantly in endothelial cells of all blood vessels and in the placenta. We cloned the human and mouse genes and identified endoglin as an auxiliary receptor for several members of the TGF-β superfamily including TGF-β1 and several BMPs. Endoglin is thus a component of the receptor complex for these ligands and modulates their responses. Through collaborative studies, we identified endoglin as the gene mutated in hereditary hemorrhagic telangiectasia type 1 (HHT1). Soon after, ACVRL1 (or ALK1), coding for a type I receptor that binds TGF-β1 and BMP9, was recognized as the gene mutated in HHT2. SMAD4, a downstream mediator of all TGF-β superfamily ligands is affected in a small percentage of HHT patients, in a syndrome combined with Juvenile Polyposis. Recently, BMP9 mutations were found in a few families with an HHT-like syndrome. The pathways mediated by these various proteins are likely the ones affected in HHT and several groups are studying how mutated proteins can lead to the generation of arteriovenous malformations (AVMs).

We generated the first animal model of HHT1, the endoglin heterozygous (Eng+/−) mouse that developed signs of HHT on the 129/Ola strain but minimal disease in the C57BL/6 strain. This suggested that modifier genes contributed to the variable penetrance. Recently, the PTN14 phosphatase gene was found to be associated with the risk of pulmonary AVMs in HHT patients. Interestingly, the Eng+/− mice do not show pulmonary AVMs but develop with age signs of pulmonary arterial hypertension (PAH). We observed that superoxide, generated through the uncoupling of endothelial NO synthase (eNOS), was responsible for this phenotype that was prevented by treatment with anti-oxidant. We showed that endoglin associates with eNOS and regulates its activation. We also showed that the rarefied peripheral lung vasculature of Eng+/− mice is in part due to an increase in the angiostatic factor TSP-1 and is reversed by anti-VEGF treatment, suggesting that an angiogenic imbalance is associated with HHT1.

Mouse models where endoglin is conditionally knocked out in endothelial cells during neonatal life develop spontaneous AVMs. However, the generation of AVMs in adult mice requires a wound or an angiogenic trigger in combination with the inducible loss of endoglin. In these models, AVMs are observed reproducibly and can be studied to unravel factors contributing to the progression of HHT and to test potential therapies. Progress has also been made in the identification of endoglin as an adhesion molecule interacting with the α5β1 integrin on adjacent endothelial cells or on circulating leukocytes, and in the maintenance of endothelial barrier function. HHT is a complex disease requiring much more research that will also contribute to our understanding of the rules regulating vascular functions.