A possible role for Smurf1 in pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a progressive disease, marked by shortness of breath and fatigue which can be fatal if untreated. Increased pressure in the pulmonary artery and its branches is associated with dysfunctional growth control of endothelial and smooth muscle cells leading to excessive thickening of the blood vessel wall, obliteration of the lumen and right heart failure.

BMP (bone morphogenetic protein) receptors play an important role in preventing excess growth of vascular cells. Some individuals with PAH have mutations in BMP receptor (type II). Mutant, and to a lesser extent wild type, receptors are thought to decline in response to disease associated factors such as hypoxia and cytokines. However, the mechanisms leading to the decline in these receptors are not understood.

In the July 2010 issue of *Experimental Biology and Medicine*, Drs. Murakami, Mathew, Huang, Farahani, Peng, Olson and Etlinger at New York Medical College in Valhalla, NY found that a protein called Smurf1 is elevated in animal models of PAH. This protein is a ubiquitin ligase which can covalently attach ubiquitin to BMP receptors as well as regulate downstream signaling molecules. Such ubiquitin "tagging" leads to receptor endocytosis and degradation by proteasomes and/or lysosomes. Recent studies on cancer cell metastasis have linked Smurf1 with the RhoA/ROCK signaling pathway which has also been implicated in vasoconstriction and vascular remodeling in PAH. Thus, Smurf-1 may have even a broader role in PAH pathogenesis.

The researchers produced PAH in rats by treating with a chemical monocrotaline and in mice by exposure to hypoxia, two well established animal models for the disease. Increased levels of Smurf1 appeared in vascular tissue and could be visualized in endothelial and smooth muscle cells with a time course consistent with a casual role in PAH. Studies with cultured cell lines confirmed Smurf1 dependent degradation of BMP receptors. A mutated Smurf1 which lacked the ability to ligate ubiquitin was able to block BMP receptor degradation acting in a dominant negative manner. Murakami said "these results suggest that Smurf1 may be an attractive therapeutic target to block with agents like dominant negative Smurf-1 mutant or with siRNA constructs etc." Currently treatments for PAH can offer some amelioration of symptoms but no cure is available. Interfering with Smurf1 may offer promise in this regard but future research will need to confirm the role of Smurf1 in human PAH as well as explore the specificity of its actions.

Steven R. Goodman, Editor-in-Chief of Experimental Biology and Medicine said "Murakami et al have demonstrated an elevation of Smurf 1, a ubiquitin ligase, in rat models of pulmonary arterial hypertension (PAH). Further they have demonstrated that Smurf1 can degrade BMP receptors that have a known relationship to PAH. This suggests that elevation of Smurf1 may play a role in the molecular basis of PAH".

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