Abstract ID: 93420

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Area of Research: Metabolism, circulation and inflammatory diseases

PhD Programme: PhD Molecular Medicine (MolMed)

Semester: 4

Unraveling the Role of Epigenetic Mechanisms as Potential Driver of Female Predominance in Pulmonary Arterial Hypertension

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Gender bias is observed in numerous conditions and diseases, however exact mechanisms underlying this predisposition are often unclear. Pulmonary arterial hypertension (PAH) is a rare lung vascular disease with female predominance. It is characterized by vessel well thickening and lumen narrowing, resulting mainly from pulmonary artery smooth muscle cells (PASMCs) expansion and matrix deposition. Despite improved therapy, PAH still represents a severe and progressive disorder in which the causative mechanism is not entirely understood. We investigated whether normal epigenetic inactivation of the second chromosome X in females might be disturbed in PAH patients. We hypothesized that the resulting aberrant biallelic expression of X-linked genes could thus drive PAH pathogenesis and female predominance.

Genes escaping X chromosome inactivation (escapees) were identified using a combination of single cell RNA sequencing and whole exome sequencing in PASMCs isolated from donors and PAH patients, eight subject in each group. Escapees were identified based on a cutoff of 5% or higher for biallelic expression that was found in at least 4% of the sequenced cells. Our preliminary results show that on average 11% of genes expressed in PASMCs under normal condition escape chromosome X inactivation, while in diseased samples this averaged to 9%. Most of the escapees are common and shared between conditions (53%). PAH-unique escapees (21% of all detected escapees) were defined by enrichment mainly in protein metabolism and biosynthesis processes. Within them only MAOA and SMS genes were already connected with PAH pathogenesis. Rest of identified escapees in PAH group could represent novel research target.

Obtained data revealed that disturbances in chromosome X inactivation pattern are unlikely to be the cause of female predominance in PAH, however it provides a valuable contribution to understanding PAH pathogenesis.