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Pulmonary arterial hypertension (PAH) is a progressive disorder with high blood pressure in the arteries of the lungs [1]. Patients with PAH would have small pulmonary arteries because they increase the resistance to blood flows through the lungs [2]. In order to overcome such high resistance, pressure would increase in the pulmonary arteries and in the right ventricle, which pumps the blood into the pulmonary arteries [1]. Every year in the United States, about 1,000 patients are diagnosed with PAH [2]. Mutations in the Bone Morphogenetic Protein Receptor type II gene (*BMPR2*) confers about a 17% chance of developing PAH in a carrier's lifetime [3]. After PAH diagnosis, the mean survival time of PAH patients is about 2.8 years [4]. According to the clinical data, females are diagnosed twice higher than males [2]. However, **it is unclear why there is a higher female prevalence for PAH.**

The **primary goal** of this study is to elucidate why females are more often diagnosed with PAH than males. It is **hypothesized** that the expression of *BMPR2* is more predominant in females presumably due to the different expression level of certain hormones in the blood, such as estrogen.

Specific Aim 1: To investigate how *BMPR2* gene is expressed at different levels in females and males in our *in vitro* study using adult human adipocytes.
Approach: To compare the level of *BMPR2* expression between females and males, the adipocytes from females and males humans with PAH will be used as an experimental group. The adipocytes from males and females who have not had PAH will be also used as a control to compare. The cells will be then cultured in the adequate cell culture medium that can well support these cell lines over one week. After one week, by using DNA microarray, the expression of *BMPR2* gene will be quantitatively measured and compared to see if such difference exists between male and female as expected. Not only measuring the level of gene expression of our interest, it would be possible that whether *BMPR2* gene is expressed as proteins in the cell. Thus, the cell lines can be lysed and subject to western blot to see if the antibodies specific to *BMPR2* genes can detect the difference in the level of protein expression of *BMPR2 in vitro* between males and females.
Hypothesis: The difference of the sex hormone between different sexes may potentially act as an activator or repressor of *BMPR2*, a novel gene responsible for causing PAH in the human, in our *in vitro* study.

Specific Aim 2: To determine if the level of estrogen in the blood regulates the expression of *BMPR2*.
Approach: The mice will be used for our model organism in this study. Different concentrations of estrogen will be injected on daily basis to the different groups of mice and the gene expression of *BMPR2* will be recorded as described previously. To further confirm its direct and/or indirect interaction using biochemical assay, mass spectrometry-based screen (using Tap tag then mass spec) can be used as a preliminary screening tool to determine if estrogen and *BMPR2* interact each other or if there are other protein partners interacting with either estrogen or *BMPR2*. For direct interaction of such duplex, it can be further confirmed by immunoprecipitation or pull-down assay. For indirect interaction, the level of *BMPR2*, its interacting partner, and estrogen can be further examined when the level of estrogen is increased in the blood.
Hypothesis: High concentrations of estrogen may lead to the down-expression of *BMPR2* directly or indirectly by interacting with its potential partners.

References

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