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PPARγ Agonist Induces Regression of Pulmonary Arterial Hypertension in Mice

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Pulmonary arterial hypertension (PAH) is characterized by a variable degree of vasoconstriction and vascular obstruction, leading to increased pulmonary vascular resistance and eventually to right-sided heart failure and death. Treatment options are limited, as is the knowledge about what initiates and sustains the disease. When mutations in the bone morphogenetic protein receptor II (BMPR-II) were linked to PAH, research into the molecular mechanisms underlying PAH intensified. In PAH patients, BMP-mediated activation of specific transcription factors is impaired, one of them being PPARγ. PPARγ is a nuclear hormone receptor and transcription factor that is closely linked to insulin resistance and other metabolic processes. Several transcriptional targets of PPARγ, but not PPARγ itself, have been shown to play a role in the pathobiology of PAH, for instance Endothelin-1 and ADMA.
The aim of this study was to investigate whether PAH and insulin resistance are linked through PPARγ. In a novel animal model used for this study, male ApoE deficient mice on high fat diet developed severe pulmonary arterial hypertension and insulin resistance. We hypothesized that in this animal model a PPARγ agonist will not only reverse insulin resistance, but also PAH. As PPARγ is downstream of the BMPR-II mutation, activation of PPARγ through Rosiglitazone might be able to compensate for the mutation's inhibiting effect on PPARγ. As a result, PPARγ agonists like Rosiglitazone might be able to rescue the signalling cascades downstream of BMPR-II in a BMPR-II mutation, thus preventing or even reversing PAH.

In this study, 15-week old control and insulin-resistant ApoE-/- mice, all on high fat diet, were treated with the PPARγ agonist Rosiglitazone for 4 and 10 weeks respectively. After both time

points a significant decrease in right ventricular systolic pressure, right ventricular hypertrophy, and peripheral muscularization of pulmonary arteries in Rosiglitazone-treated ApoE-/- mice was observed when compared to non-treated littermates. This reversal of PAH was accompanied by improved insulin sensitivity and an 8-fold increase in plasma levels of the adipocytokine Adiponectin.

Subsequently, cell culture experiments were conducted to support and explain the phenotypic changes observed in our animal model. Different target genes of PPARγ were examined for their potential role in the pathobiology of PAH. The influence of PPARγ on mRNA and protein expression levels of these target genes was investigated in human pulmonary artery smooth muscle cells (PA SMC). Furthermore, assays were performed to assess whether Rosiglitazone and selected targets of PPARγ inhibit proliferation of PA SMC, a key feature of PAH. For these proliferation assays, a potent mitogen known to stimulate proliferation in PAH was used: platelet-derived growth factor (PDGF). The cell culture experiments show that both Rosiglitazone and Adiponectin, an adipocytokine up-regulated under Rosiglitazone treatment, inhibit PDGF-induced proliferation in human PA SMC. Thus at least part of the regression of the PAH phenotype could result from the elevated Adiponectin levels induced by administration of Rosiglitazone.