Investigating SOCS3 as a new target for drugs to treat pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a fatal disease caused by the walls of the small blood vessels that supply the lungs walls becoming thicker (Fig. 1) and unable to adapt to changes in blood flow, resulting in high blood pressure within these vessels. This results in changes to the structure of the heart as it adapts to the increased blood pressure. Although initially beneficial, these changes cannot be sustained and eventually cause heart failure which is the main cause of death in PAH patients.

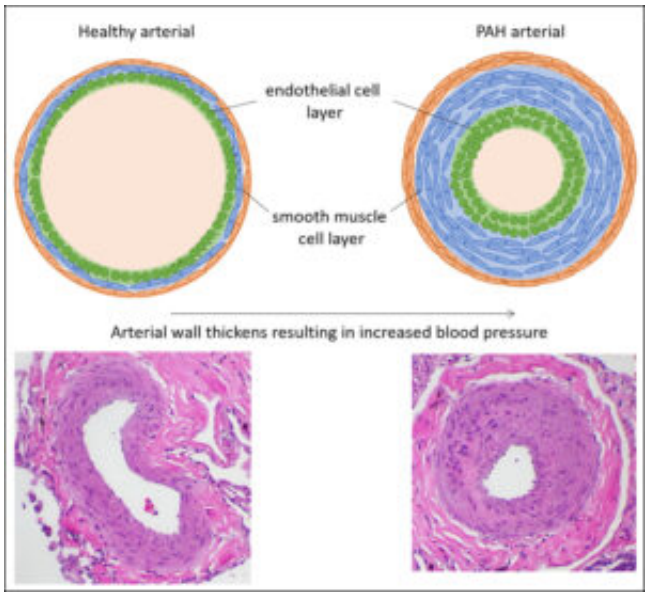

Fig. 1. PAH is caused by thickening of pulmonary blood vessels, resulting in a vessel less able to adapt to changes in the blood flow and causing increased blood pressure.
This figure is adapted from an image with a creative commons license (Yale Rosen/Wikimedia Commons/ CC BY-SA 2.0).

The development of PAH is associated with numerous changes that affect the local area such as genetic mutations, changes in the ability of blood vessels to expand, or dilate, and chronic inflammation. Current treatments for PAH consist of drugs that enable the small blood vessels that supply the lungs to dilate and adapt to the increased blood pressure. However, while these drugs relieve the symptoms of PAH, they have little effect slowing the processes responsible for disease progression. Thus, there is a need for new therapies that specifically target the molecular changes responsible for the blood vessel thickening and chronic inflammation responsible for PAH.

One potential target is interleukin (IL)-6, a circulating factor whose levels are increased in blood

from PAH patients and which is known to cause inflammation in disease. IL-6 levels have been shown to negatively correlate with survival rates and positively correlate with blood vessel deterioration in the lung, suggesting IL-6 plays a key role in PAH progression. In addition, numerous studies in animal models of PAH have shown that reducing IL-6 protects against the vascular changes and lung inflammation characteristic of PAH.

SOCS3 (suppressor of cytokine signalling 3) is a potent intracellular inhibitor of IL-6 function. Given the role of IL-6 in the development of PAH, we propose that enhancing SOCS3 function may be one way to reduce IL-6 activity and inhibit blood vessel thickening and chronic inflammation responsible for PAH. Typically, IL-6 increases SOCS3 expression, resulting in inhibition of IL-6 function (Fig. 2). However, SOCS3 can also be induced by the intracellular messenger cAMP. The only drug currently used for PAH treatment which has been shown to improve survival rates is epoprostonol, a prostanoid drug which acts via increasing cAMP to relax blood vessels and ease the symptoms caused by high blood pressure in the lungs. We suggest epoprostonol may also be able to inhibit IL-6 activity through a cAMP-mediated increase in SOCS3 expression (Fig. 2) and that this may explain why epoprostonol slows disease progression unlike other drugs used for PAH, and it further supports our hypothesis that enhancing SOCS3 function is a potential strategy to combat PAH.

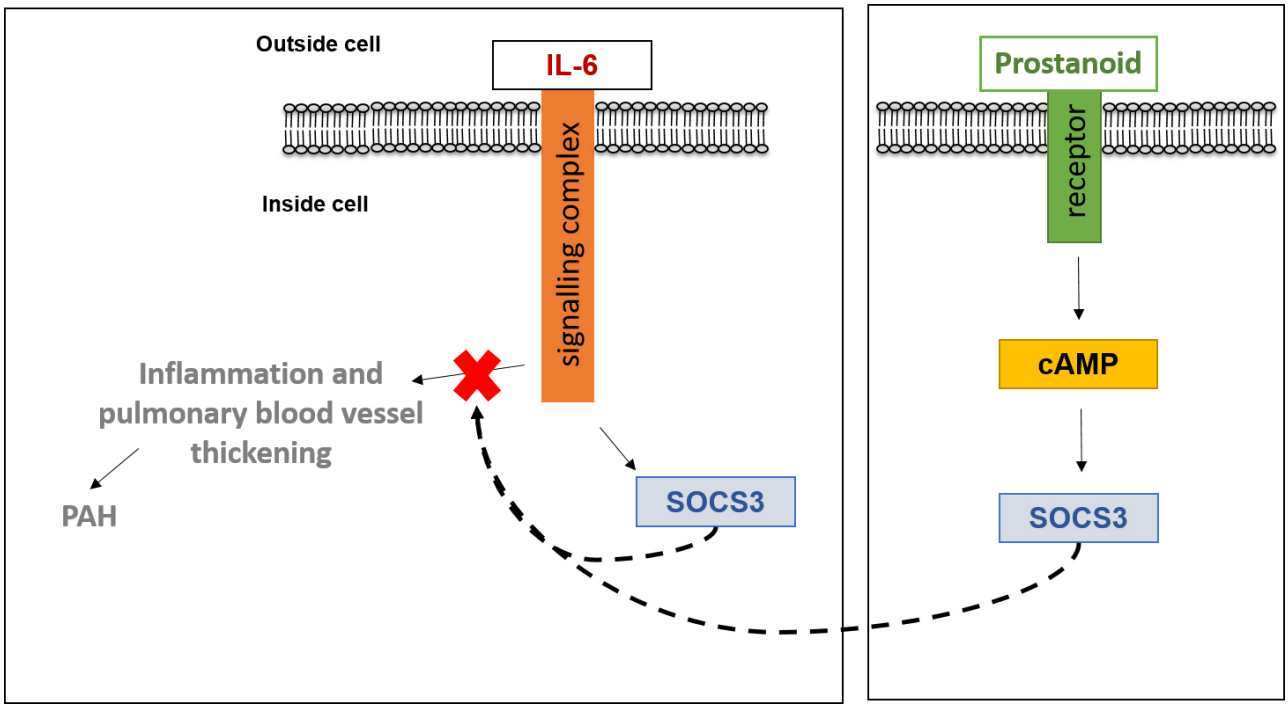

Fig. 2. IL-6 stimulates inflammation and pulmonary blood vessel thickening which contributes to PAH. However, IL-6 also stimulates SOCS3 which prevents further IL-6 action. Prostanoid drugs are also able to increase SOCS3 via cAMP-signalling. Thus, we propose SOCS3 produced in this manner can also contributes to the inhibition of IL-6 and may be beneficial in the treatment of PAH.

We propose comparing the clinical deterioration and quality of life of PAH patients receiving tradition PAH treatment with those also receiving IL-6 limiting drugs such as the antibody drug tocilizumab (approved for the treatment of arthritis) to investigate if inhibiting IL-6 activity is therapeutically beneficial. In addition, we discuss how pre-clinical PAH models could be used to investigate the protective effects of SOCS3 expression in PAH. We envisage future treatment of PAH will benefit from the development of novel SOCS3-based therapies.

Gillian A. Durham, Timothy M. Palmer
Centre for Atherothrombosis and Metabolic Disease, Hull York Medical School, University of Hull, Hull HU6 7RX, United Kingdom

Publication

Is there a role for prostanoid-mediated inhibition of IL-6 trans-signalling in the management of pulmonary arterial hypertension?
Gillian A Durham, Timothy M Palmer
Biochem Soc Trans. 2019 Aug 30