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Review

The role of the osteoprotegerin/tumor necrosis factor related apoptosis-inducing ligand axis in the pathogenesis of pulmonary arterial hypertension ☆

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ABSTRACT

Pulmonary arterial hypertension (PAH) is a fatal condition driven by a progressive remodelling of the small pulmonary arteries through sustained vasoconstriction, and vascular cell proliferation. This process causes a substantial reduction in luminal area increasing pulmonary vascular resistance and blood pressure leading to right heart failure. Current medical therapies can alleviate some symptoms and reduce the vasoconstrictive aspects of disease but new treatments are required that target the vascular cell proliferation if we are to develop new therapies. Expression of the tumour necrosis factor related apoptosis-inducing ligand (TRAIL) and osteoprotegerin (OPG) proteins are increased in IPAH. Specifically OPG is increased within the serum of patients with idiopathic pulmonary arterial hypertension (IPAH) and has prognostic utility, and both OPG and TRAIL are increased within pulmonary vascular lesions of patients with IPAH, and are mitogens for pulmonary artery smooth muscle cells in vitro. We have demonstrated that genetic deletion, or antibody blockade of TRAIL prevents, and critically reverses the development of PAH in multiple rodent models. The role OPG plays in this process both through interacting with TRAIL, and indirectly through other mechanisms is currently unclear these but data highlight the critical importance of this pathway in PAH pathogenesis, and its potential for future therapies.

Contents

1. Introduction

Pulmonary hypertension (PH) describes a group of progressive conditions each with a different origin but sharing a common haemodynamic diagnosis of mean pulmonary artery pressure greater than or equal to 25 mm Hg at rest [1]. The World Health Organisation (WHO) classification segregates PH into six groups based on aetiology and pathology that are — 1. Pulmonary arterial hypertension; 1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis; 3. PH due to left heart disease; 4. PH due to lung diseases and/or hypoxia; 4. Chronic thromboembolic pulmonary hypertension; and 5. PH with unclear and/or multifactorial mechanisms [2]. The work

Abbreviations: BM, bone marrow; BMDC, bone marrow derived cells; BMT, bone marrow transplant; MCT, monocrotaline; SuHx, sugen 5416 & hypoxia; OPG, osteoprotegerin; PAH, pulmonary arterial hypertension; PASMC, pulmonary artery smooth muscle cell; PCNA, proliferating cell nuclear antigen; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; SMC, smooth muscle cell; TRAIL, tumor necrosis factor related apoptosis-inducing ligand; TUNEL, TdT-mediated dUTP nick-end labelling.

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highlighted in this article is primarily focused on addressing the pathogenesis of group 1 pulmonary arterial hypertension (PAH) where the haemodynamic alterations are driven by progressive pulmonary vascular remodelling.

PAH is a rare disease with approximately 3000 prevalent cases in the UK [3] that often affects the young, with a 1:2.3 female gender bias. The disease significantly limits physical capacity and confers a life expectancy of 2.8 years without treatment [4]. Pathologically, PAH is characterised by sustained vasoconstriction and a progressive obliteration of small resistance pulmonary arteries and arterioles through a process of medial thickening, intimal fibrosis and the formation of angioproliferative (plexiform) lesions [5]. Endothelial dysfunction and pulmonary artery endothelial cell (PA-EC) apoptosis/dysfunction are thought to play an important early role in disease pathogenesis. Subsequent proliferation and migration of medial cells including smooth muscle cells (PA-SMC), fibroblasts and PA-EC [5] drive the pulmonary vascular remodelling. Current treatments target the sustained pulmonary vasoconstriction via either the prostacyclin, endothelin or nitric oxide pathway [6] in isolation or combination, but do little to address the underlying proliferative vascular disease. Subsequently, there is still no curative treatment for PAH other than transplantation, and the 3 and 5 year survival for PAH in its idiopathic form remains low at 38% and 17% respectively [7].

The last 10–15 years have seen some major breakthroughs in our understanding of the pathobiology of PAH. There are now well-established mechanistic insights into disease pathogenesis, for example, bone morphogenetic protein receptor type II (BMP-RII) mutations, the involvement of serotonin pathway, inflammation, mitochondria metabolism and many others [8,9]. These have manifested in many preclinical and small clinical studies evaluating the 'therapeutic potential' of manipulating new pathways implicated in vasoconstriction and/or the progressive remodelling of the pulmonary vasculature, such as vasoactive intestinal peptide (VIP) [10], Rho kinases [11], serotonin [12], apelin [13], the innate and acquired immunity system [14], epidermal growth factor [15,16], and peroxisome proliferator-activated receptor (PPAR)γ/β-catenin complex [17,18], and fatty acid omega three [19]. Despite these important insights, the precise cell and molecular mechanisms leading to disease manifestation, and driving pathogenesis remain poorly understood. Dissecting the molecular mechanisms underlying PAH is therefore crucial if effective treatments for a condition that has a worse prognosis than many malignancies are to be developed.

2. Tumor necrosis factor (TNF) related apoptosis inducing-ligand

Tumor necrosis factor (TNF) related apoptosis inducing-ligand (TRAIL, Apo2L), is a type II transmembrane protein that is widely expressed and detected in a variety of human tissues, most predominantly in spleen, lung, and prostate [20]. TRAIL can be alternatively spliced to produce a number of different isoforms [21] although little is known about their function. In humans there are four transmembrane TRAIL receptors, death receptor 4 (DR4, TRAIL-R1) [22], DR5 (TRAIL-R2) [22–25], decoy receptor 1 (DcR1, TRAIL-R3) [26–28], DcR2 (TRAIL-R4) [29–31] and the soluble protein osteoprotegerin (OPG) [32]. Both TRAIL-R1 and TRAIL-R2 contain a conserved death domain (DD) motif and mediate the extrinsic apoptosis pathway by TRAIL [33], TRAIL-R3 lacks an intracellular domain and TRAIL-R4 has a truncated DD, both are therefore considered decoy receptors to antagonize TRAIL-induced apoptosis by competing for ligand binding along with OPG [28,33,34] (Fig. 1).

TRAIL was initially heralded as an anti-cancer therapy [35] due to its apparent selective ability to induce apoptosis in a variety of transformed or tumour cells while leaving normal, untransformed cells unaffected [20,36]. Unfortunately many cancer cells have subsequently been found to be resistant to TRAIL-induced apoptosis [35] via a variety of mechanism thought to include the regulation TRAIL receptor expression by genetic [37] and epigenetic mechanisms [38], as well as modulation of OPG expression [39,40].

TRAIL has also been shown to be important in the early resolution of inflammation through regulating inflammatory cell clearance by apoptosis [41–43] and to have immunosuppressive and immunoregulatory functions that are important for lymphocyte homeostasis and the transition between innate-to-adaptive immunity [44]. Interactions between inflammation and vascular cells are a key aspect of vascular injury/repair and are considered to have an important role in cardiovascular disease. TRAIL mRNA and protein expression has previously been described in normal human pulmonary arteries [45]. We have demonstrated that TRAIL protein is associated with concentric and plexiform pulmonary vascular lesions from patients with IPAH [46] and from a

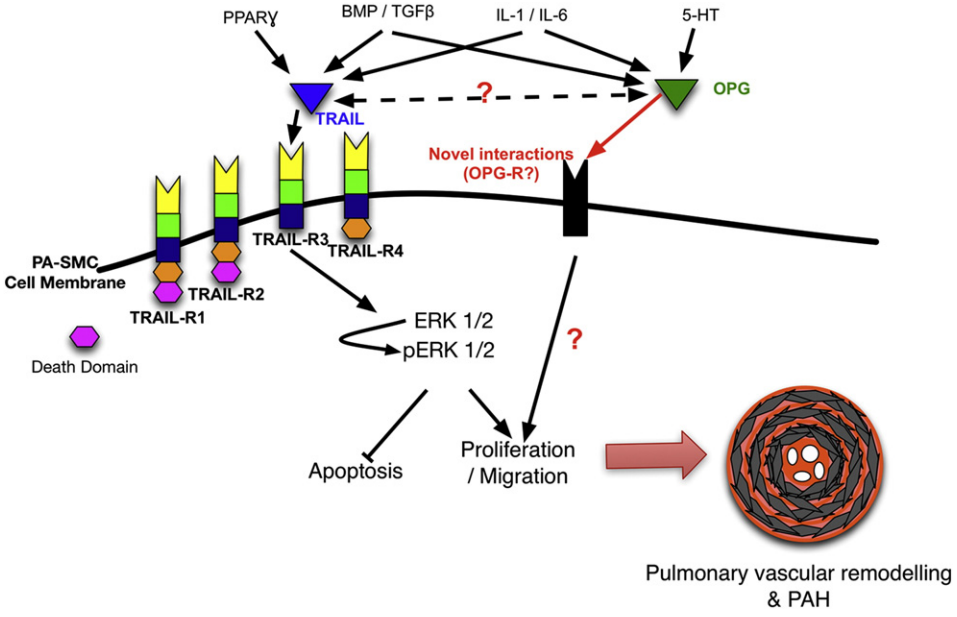

Fig. 1. Multiple signalling pathway implicated in PAH pathogenesis can feed into, and cause an increase in recruitment/expression of OPG and/or TRAIL. TRAIL binds to TRAIL-R3 on the cell surface of pulmonary artery smooth muscle cells (PA-SMC) and activates the phosphorylation of ERK 1/2 driving a pro-proliferative phenotype. OPG, either by interaction with TRAIL, or another un-associated cell surface receptor similarly mediates a pro-survival phenotype by a yet to be defined mechanism.