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Title: TNFα mediates ectodomain shedding of BMPR-II: A potential role in pulmonary arterial hypertension

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Body: Background: Mutations in BMP type II receptor (BMPR-II) account for 70% of heritable pulmonary arterial hypertension (PAH) cases, but low penetrance (~20%) in mutation carriers implies a ‘second hit’ is required for disease initiation. Inflammation has been implicated, yet the molecular mechanisms by which it influences pathology are unclear. Aim: To investigate a possible molecular link between a key mediator of inflammation, tumour necrosis factor alpha (TNFα), and BMPR-II. Methods: Human pulmonary arterial smooth muscle cells (PASMCs) were stimulated with TNFα (1ng/mL). Immunoprecipitation, western blotting, quantitative PCR, plasmid DNA transfection, site-directed mutagenesis, RNA interference and pharmacological inhibitors were used to assess the impact of TNFα on BMPR-II and BMP signalling pathways. Results: TNFα stimulation reduced BMPR-II mRNA and protein expression, leading to loss of BMP signalling, as evidenced by abrogated Smad 1/5 and ID1 activation. Notably, a low molecular weight form of BMPR-II accumulated in PASMC lysates following prolonged TNFα exposure: identified as a C-terminal cleavage product of BMPR-II. Furthermore, the N-terminal ectodomain of BMPR-II could be immunoprecipitated from conditioned media. TNFα increased expression of two A Disintegrin and Metalloproteinase Domain-containing proteins (ADAMs); ADAM10 and ADAM17. Pharmacological blockade and RNA interference revealed both proteases were capable of BMPR-II cleavage. Mutation of the putative cleavage site restored BMP signalling. Conclusions: We identified a novel mechanism by which TNFα impairs BMP signalling. These findings highlight TNFα as a potential therapeutic target in PAH.