Pulmonary arterial hypertension and the Enigma code of smouldering inflammation

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Anti-interleukin-1 treatment for pulmonary arterial hypertension: are we there yet?

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More than any other cytokine family, the [interleukin]-1 family is closely linked to innate inflammatory and immune responses.

DINARELLO [1]

“What causes fever?” was the question that prompted the work that led to the discovery of the “leukocyte pyrogen”, eventually named interleukin (IL)-1, in the late 1970s [1]. However, despite the rapid understanding of innate and adaptive immune responses and inflammation during the 1980s, it was not until 1995 that HUMBERT *et al.* [2] reported that both IL-1 and IL-6 levels were increased in the plasma of patients with idiopathic pulmonary arterial hypertension (PAH), thus revealing an inflammatory component in the pathogenesis of severe PAH. Ever since the first report by HUMBERT *et al.* [2], the role of inflammation as a cause or consequence of PAH has remained controversial [3] and this ongoing debate has perhaps prevented the pragmatism to design clinical trials to test novel anti-inflammatory therapies in patients with PAH.

In the current issue of the *European Respiratory Journal*, PARPALEIX *et al.* [4] provide one more mechanistic piece of evidence to solve the enigma of aseptic inflammation in PAH and offer another rationale to justify the clinical evaluation of IL-1-based treatment strategies for PAH. The authors demonstrated that the levels of the IL-1 receptor 1 (IL1R1) protein and its adaptor protein MyD88, required for downstream signalling, are increased in the lung tissue samples from patients with idiopathic PAH. They also showed that in mice with chronic hypoxia-induced PAH and in rats with monocrotaline-induced PAH, treatment with anakinra, a recombinant IL1R1 antagonist, decreased pulmonary vascular muscularisation, right ventricular systolic pressure and right ventricular hypertrophy. The study by PARPALEIX *et al.* [4] confirmed earlier studies that had demonstrated the increased expression of IL-1 α and IL-1 β protein levels in monocrotaline-induced pulmonary hypertensive rat lungs and that chronic treatment with anakinra prevented the development of monocrotaline-induced PAH [5]. To further assess causality, PARPALEIX *et al.* [4] challenged both IL1R1 and MyD88 knock-out mice with chronic hypoxia, and showed that genetic ablation of the IL-1 β canonical signalling machinery ameliorated the pulmonary vascular response to hypoxia. *In vitro*, they showed how pulmonary vascular smooth muscle cells treated with anakinra had reduced IL-1 β -induced cell proliferation, NF- κ B activation (a major inflammatory regulator) and IL-6 expression (an IL-1 β -inducible cytokine linked to increased mortality in PAH [6, 7]). Moreover, supernatants from M1-polarised macrophages resulted in pulmonary vascular smooth muscle cell proliferation, partly *via* IL1R1/MyD88 signalling. However, some questions remain unanswered. For example, 1) what is the mechanism whereby

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IL-1 β induces vascular smooth muscle cell growth? 2) Are there additional MyD88-dependent cytokines involved in the development of hypoxic pulmonary hypertension? 3) How much of the effect of anakinra resulted from blocking IL-1 α ?

The work of PARPALEIX *et al.* [4], along with the publication by TIAN *et al.* [8], suggests that macrophages may play a significant role in the still enigmatic signalling cascades of inflammatory reactions involved in the pathogenesis of PAH. Whereas the work by TIAN *et al.* [8] discovered a novel action for macrophage-released leukotriene B4 as an inducer of endothelial cell apoptosis, the work by PARPALEIX *et al.* [4] suggests that macrophages may also contribute to pulmonary vascular inflammation and proliferation, at least partly *via* IL-1/IL1R1 signalling. Thus, it appears that both the “leukocyte pyrogen” IL-1 and the “leukocyte-triene” eicosanoid LTB4 are elements of a code that we need to decipher in order to understand the multicellular interactions between macrophages, endothelial cells and other immune cells, which culminate in pulmonary vascular disorders.

While the focus of research in the setting of PAH has been on IL-1 β , little is known about the role of IL-1 α ; however, it should not be overlooked because “all autoimmune diseases have a significant inflammatory component that is due to production of both of IL-1 β as well as IL-1 α from myeloid cells, particularly macrophages) [...] B cells produce IL-1 β and there is IL-1 α from T cells” [1]. IL-1 α is an “alarmin” [9], a DNA-damage sensor [10] and, most importantly, it is highly abundant in endothelial cells [11]. It has been postulated that apoptosis of pulmonary microvascular endothelial cells may be the critically important initiating event in PAH pathogenesis [12] and it is now known that endothelial apoptotic bodies contain IL-1 α [11] that, upon release, could contribute to vascular remodelling. Now that both IL-1 β [4] and IL-1 α [5] have been found to be elevated in the lung tissue from pulmonary hypertensive humans and rodents, we should attempt to understand the potential nonredundant roles of these two cytokines in lung vascular diseases. For instance, in murine models of inflammatory bowel disease, IL-1 α mediates inflammation whilst IL-1 β mediates healing [13, 14]; a similar phenomenon could occur in the lung circulation. Nevertheless, IL-1 α induces IL-1 β , and both IL-1 α and IL-1 β share a single type I signalling receptor, making it difficult to dissect the role of the individual cytokines *in vivo* [14].

Increasing evidence has suggested that high levels of IL-1 β predict a worse outcome in patients with severe PAH [5, 6, 15]. However, despite its prognostic value, no prospective study has explored whether treatment with PAH-specific pharmacotherapies lowers IL-1 β or whether lowering cytokine levels can affect survival. Anakinra has been proven to be effective in treating multiple autoinflammatory as well as autoimmune conditions [1]. Among clinical trials, there are some examples of small cohort studies in patients with acute myocardial infarction [16] and acute decompensated or chronic heart failure [17, 18] that have begun exploring the treatment effects of anakinra in cardiovascular diseases, and another large controlled clinical trial is presently underway to probe the inflammatory underpinnings of atherosclerotic diseases [19, 20]. Perhaps these studies could provide a blue print for the design of IL-1-targeting PAH trials. We believe that pre-clinical PAH trials, like the current study by PARPALEIX *et al.* [4], should no longer be seen only as academic, *l'art pour l'art* exercises. Instead, they should lower the threshold for the design and conduct of clinical pilot trials. To us, it appears the time is right for the start of anti-IL PAH trials. The safety profile of anakinra has been assessed and found to be acceptable [21], and thus the risk/benefit balance may be tilted towards potential benefits.

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