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EDITORIAL

Key roles of Src family tyrosine kinases in the integrity of the pulmonary vascular bed

Christophe Guignabert*,#,¶ and David Montani*,#,¶,+

The pulmonary blood vessels have unique structural and functional properties. The pulmonary circulation is a high-flow, low-resistance, low-pressure system, which is mainly explained by two important characteristics of the pulmonary vascular bed: a high compliance of the pulmonary pre-capillary arterioles characterised by thin media and a high capacity to recruit vessels available to cope with an increase in blood flow. Local variations in response to various vasoactive molecules, such as hypoxia and nitric oxide, are well known, but the molecular mechanisms underlying the sensing of those stimuli remain obscure. In contrast to the systemic arteries, the hypoxic stimulus induces vasoconstriction of the pulmonary arteries, an effect that is more pronounced as the vessel diameter decreases [1, 2]. Different potassium channels are expressed and distributed in several types of pulmonary arterial smooth muscle cells (PA-SMCs) and contribute to this large functional diversity. Although voltage-gated potassium channel (K_V)1.2, K_V1.5, K_V2.1, K_V3.1b and K_V9.3 play important roles in the hypoxia-inhibited potassium current found in PA-SMCs, much attention has been attracted by K_V1.5 [3]. In addition to the K_V family, calcium-activated (K_{Ca}) [4], two-pore domain (K2P) [5] and ATP-sensitive potassium channels [6] have been documented to play crucial roles in setting the resting membrane potential (E_m) in PA-SMCs under either basal or hypoxic conditions. TWIK-related acid-sensitive potassium channels (TASK)-1–3 belong to the K2P family. TASK-1 is thought to be a critical element for both homeostasis and pathophysiology. Indeed, TASK-1 channels play a role in the E_m and render these excitable cells sensitive to a variety of vasoactive factors. In addition, TASK-1 channels are constitutively active, and are sensitive to extracellular pH in the physiological range and to volatile anaesthetics such as isoflurane. It has been demonstrated that TASK-1 channels are inhibited by hypoxia but the precise mechanisms remain obscure [7, 8].

In this issue of *European Respiratory Journal*, NAGARAJ *et al.* [9] present the results of a study that provides evidence for a direct link between TASK-1 and the Src family. Tyrosine kinases of the Src family are involved in the regulation of different intracellular signal transduction pathways, and thus play significant role in regulation of vital cellular processes including proliferation, adhesion, motility, differentiation and survival. The Src family comprises nine members: three of them (Src, Fyn and Yes) are ubiquitously distributed and six of them (Blk, Yrk, Fgr, Hck, Lck and Lyn) are variously expressed depending on tissues. c-Src is abundant in vascular tissue [10] and NAGARAJ *et al.* [9] found that human PA-SMCs expressed mRNA for the isoforms c-Src, Fyn and Yes. These nonreceptor protein tyrosine kinases phosphorylate a large number of different substrates in the cytosol or at the inner face of the plasma membrane, or at cell–matrix or cell–cell adhesions. NAGARAJ *et al.* [9] report that TASK-1 and Src are co-localised in the plasma membrane of human PA-SMCs and that Src is required for the functioning of TASK-1. They also note that hypoxia reduces the phosphorylation state of Src and inhibits TASK-1 activity. In addition, they found that Src inhibition significantly attenuates the hypoxia-induced intracellular calcium rise and the potassium current in human PA-SMCs. Finally, they also found that PP2 or dasatinib, two potent Src antagonists, reduce the whole-cell potassium current (K_V and K_{Ca}) and cause a substantial increase in pulmonary vasoconstriction in isolated, perfused lungs from mice. Taken together, these findings clearly established a link between the Src family and TASK-1, supporting the fact that the Src family contributes in modulating the potassium current and, thus, the cell's normal resting E_m in human PA-SMCs.

Using the French Pulmonary Hypertension Registry, we recently reported incident cases of dasatinib-induced pulmonary arterial hypertension (PAH) that highlighted the need of careful follow-up of these patients [11]. However, it is difficult to understand the underlying mechanisms by which dasatinib may induce PAH. First, because dasatinib exhibits a low selectivity and affinity, and modulates multiple protein targets (with >40 kinases as possible targets) and the nonreceptor tyrosine kinase Src is important for many aspects of cell physiology. Secondly, because several types of cell surface or cytoplasmic receptor can activate Src and that several signalling pathways interact and are modulated by the Src family. Both receptor tyrosine kinases (*i.e.* platelet-derived growth factor, epidermal growth factor and fibroblast growth factor-2 receptors) and focal adhesion kinase/Crk-associated protein are able to bind to the SH2 domain and cause the switch of Src from an inactive to an active state, an important process that modulates and facilitates their downstream signals. Although further studies are required, the demonstration of a close relationship between the Src family and TASK-1 may represent at least one of these potential

*INSERM UMR 999, LabEx LERMIT, and #Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, ¶Univ Paris-Sud, Faculté de médecine, and +Assistance Publique Hôpitaux de Paris, Service de Pneumologie et Réanimation Respiratoire, DHU Thorax Innovation, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France.

CORRESPONDENCE: C. Guignabert, INSERM UMR 999, Centre Chirurgical Marie Lannelongue, 133 avenue de la Résistance, 92350 Le Plessis-Robinson, France. E-mail: christophe.guignabert@inserm.fr

mechanisms by which dasatinib may induce pulmonary vasoconstriction and vascular remodelling. However, this hypothesis may appear to contradict a growing literature suggesting that some tyrosine kinase inhibitors (imatinib or dasatinib) reverse established pulmonary hypertension in animal models [12, 13]. One possible explanation for this may be explained by major differences in the structural and functional properties between pulmonary vascular bed from healthy and PAH patients, particularly concerning the function of endothelium-derived vasoactive factors. Therefore, it is clear that a better understanding of the inter-relationships between the Src family and the potassium channel family under physiological and pathophysiological conditions is needed.

STATEMENT OF INTEREST

A statement of interest for D. Montani can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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