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Review

P21-activated kinase in inflammatory and cardiovascular disease

Domenico M. Taglieri [a], Masuko Ushio-Fukai [b], Michelle M. Monasky [c,*]

[a] Department of Anesthesia and General Intensive Care Unit, Humanitas Research Hospital, Via Manzoni 56, Rozzano, 20089 Milan, Italy
[b] Department of Pharmacology, Center for Lung and Vascular Biology, Center for Cardiovascular Research, University of Illinois at Chicago, 835S. Wolcott Ave. E403 MSB, M/C868, Chicago, IL 60612, USA
[c] Cardiovascular Research Center, Humanitas Research Hospital, Via Manzoni 113, Rozzano, 20089 Milan, Italy

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ABSTRACT

P-21 activated kinases, or PAKs, are serine–threonine kinases that serve a role in diverse biological functions and organ system diseases. Although PAK signaling has been the focus of many investigations, still our understanding of the role of PAK in inflammation is incomplete. This review consolidates what is known about PAK1 across several cell types, highlighting the role of PAK1 and PAK2 in inflammation in relation to NADPH oxidase activation. This review explores the physiological functions of PAK during inflammation, the role of PAK in several organ diseases with an emphasis on cardiovascular disease, and the PAK signaling pathway, including activators and targets of PAK. Also, we discuss PAK1 as a pharmacological anti-inflammatory target, explore the potentials and the limitations of the current pharmacological tools to regulate PAK1 activity during inflammation, and provide indications for future research. We conclude that a vast amount of evidence supports the idea that PAK is a central molecule in inflammatory signaling, thus making PAK1 itself a promising prospective pharmacological target.

Contents

Abbreviations: AID, Auto-inhibitory domain; ATP, Adenosine-triphosphate; B-cell, B lymphocytes; BLNK, B cell linker protein; CaM, Calmodulin; Cdc, Cell division control protein; cyt b558, Flavocytochrome b558; DUOX1/2, Dual oxidase 1/2; EF hand motif, Helix-loop-helix structural domain; ERK, Extracellular-signal-regulated kinase; ERM, Ezrin/Radixin/Moesin; Fc, Fragment crystallizable; FcεRI, Fc epsilon RI, high-affinity IgE receptor; fMLP, N-formyl-methionyl-leucyl-phenylalanine; GEF, Guanine exchange factors; GTP, Guanosine-5′-triphosphate; GTPases, Guanosine-5′-triphosphate hydrolase; Gβγ, G protein beta-gamma complex; IC_{50}, Half maximal inhibitory concentration; IgE, Immunoglobulin E; IS, Inhibitory switch domain; KI, Kinase inhibitor fragment; LIMK-1, LIM domain kinase 1; MLC, Myosin Light Chain; NADH, Nicotinamide adenine dinucleotide; NADPH oxidase, Nicotinamide adenine dinucleotide phosphate-oxidase; Nck, Non-catalytic region of tyrosine kinase adaptor protein; NFAT, Nuclear factor of activated T-cells; NOX1/2/3/4/5, NADPH oxidase 1/2/3/4/5; PAK1/2/3, p-21 activated kinase 1/2/3; PAKs, p-21 activated kinases; PBD, p21-binding domain; PDE2, Phosphodiesterase 2; PGAM, Phosphoglycerate mutase; PIX, Pak interactive exchange factor; PLCγ2, Phospholipase Cγ2; PLD, Phospholipase D; PP2A, Protein phosphatase 2; Ra2 cells, Microglial cell line; Rac1/2, Ras-related C3 botulinum toxin substrate 1/2; Rho, Rho family of GTPases; RhoA, Ras homolog gene family, member A; ROS, Reactive oxygen species; SH3, SRC Homology 3; SLP-76, SH2 domain-containing leukocyte phosphoprotein; T-cell, T lymphocytes; Vav1, Proto-oncogene vav; WASp, Wiskott–Aldrich syndrome protein.

* Corresponding author at: Cardiovascular Research Center, Humanitas Research Hospital, Via Manzoni 113, 20089 Rozzano, Milan, Italy. Tel.: +39 02/8224 5251; fax: +39 02/8224 5290.
E-mail addresses: domenico.taglieri@humanitas.it (D.M. Taglieri), mfukai@uic.edu (M. Ushio-Fukai), michelle.monasky@humanitasresearch.it (M.M. Monasky).

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1. Introduction

P-21 activated kinases, or PAKs, are serine–threonine kinases activated by the small GTP binding proteins Cdc42 and Rac1 [1,2], and they serve a role in diverse biological functions and organ system diseases [3]. So far, the PAK isoforms identified in mammalian cells are characterized into group I (PAK1-3) and group II (PAK4-6). The first group of PAKs shares a high sequence homology and is highly evolutionarily conserved [3].

Originally discovered in brain tissue [4], PAKs are important regulators of the inflammatory response. To the best of our knowledge, only PAK1 and PAK2, but not PAK3, have been thus far associated with inflammation, immunity, and infective diseases [5–9]. Additionally, PAK1 and PAK2 are the two most abundantly expressed PAK isoforms in white blood cells, including T lymphocytes, neutrophils, macrophages, and mast cells [10–14]. One way in which PAK1 and PAK2 regulate the molecular mechanisms of inflammation is through activation of their downstream target nicotinamide adenine dinucleotide phosphate-oxidase (NADPH oxidase) in neutrophils [15,16]. In the above mentioned cell types, PAK1 is implicated in the regulation of NADPH oxidase activity through several direct and indirect mechanisms, which are described hereafter.

In this review, we describe the role of PAKs in inflammation, with an emphasis on PAK1 and PAK2. PAK signaling has been the focus of many investigations under many different experimental models and conditions. This review aims to piece together what is known about PAK1 across several cell types, highlighting the role of PAK1 and PAK2 in inflammation in relation to NADPH oxidase activation. Also, we will discuss the role of PAK1 as a therapeutic anti-inflammatory target, explore the potentials and the limitations of the current drugs that regulate PAK1 activity during inflammation, and provide indications for future research.

2. PAK structure and activation

P21-activated kinases are a family of enzymes that are central in regulating intracellular signaling and cellular functions [13,17,18]. The actions of PAKs in the context of different cellular functions [19] are tightly regulated and are often achieved as a result of conformational changes in PAK molecular domains. Thus, a clear knowledge of the structure of PAKs is fundamental to understand their regulation and functions. In Fig. 1, we illustrate the primary structure of PAK1, and we show one of the most studied mechanisms of its activation.

The entire PAK structure is incompletely understood, although the crystal structure of PAK1 has been partly resolved. So far, it is known that the N-terminus of Group I PAKs shares a unique proline-rich motif located between amino acids 182–203, which is the binding site of the SH3 domain of PIX, an essential activator of PAK1/2/3 (Fig. 1 A). Thus far, only some parts of the auto-inhibitory domain, located in the N-terminal domain, and the kinase domain, located in the C-terminal domain, of some members of the PAK family have been elucidated [19].

One important key to understanding PAK structure and function is to understand its mechanism of activation. When in the inactive state, PAK1 homodimerizes with another PAK1 molecule through the dimerization segment (DI), the inhibitor switch domain (IS), the kinase-inhibiting segment (KI) domain, and an amino acid segment across the kinase domain (Fig. 1 B). The IS domain overlaps with the protein binding domain (PBD), which binds the GTPases Rac1/cdc42 and the auto-inhibitory domain (AID). The binding of GTPases to the PBD induces a conformational change in the kinase inhibitor (KI) fragment located within the AID. This is first followed by the dissociation of the IS from the kinase domain, then by PAK autophosphorylation of the T-loop, resulting in the activation of PAK1.

An ATP binding pocket (where ATP is the native ligand) exists and lies between the N-lobe and the C-lobe of the PAK1 kinase domain. This niche has been recently exploited to achieve pharmacological modulation of PAK1. A molecular analysis of the kinase domain structure using a Q-site finder technique has illustrated that molecular niches exist that could nest small pharmacological molecules. In fact, most PAK non-native ligands (e.g. 3Q53 [20], 3FXZ [21], 3FY0 [21], and 2HY8 [22]) bind to the ATP binding pocket, nurturing hopes that modulation of PAKs can be pharmacologically achieved.

Additional studies are required to fully understand the mechanism of PAK activation, especially across multiple organs and cell types. There remains a limited understanding of the effects of PAK regulation of the inflammatory process. A better understanding of both the role of PAK in multiple systems, as well as the relationship between the PAK structure and function, will provide the necessary knowledge to design activators or inhibitors that bind to PAK and modulate its functions in the inflammatory process.

3. Mechanisms of PAK activation

Besides activation via the small Rho GTPase Rac1, PAK1 can alternatively or synergistically be activated by other molecules, including membrane lipids [23] or receptor agonists [24]. Recently, we have understood that a vast number of important regulators of the inflammatory process act upon PAK1 as a downstream target and exert their effects through PAK1. In this section and in Fig. 2, we describe some recent advances in the understanding of signaling mechanisms involved in the activation of PAK during inflammation.

3.1. Lipid-mediated and receptor tyrosine kinase-mediated activation of PAK1 and NADPH oxidase

Long chain sphingoid bases, sphingosine, phosphatidic acid, and phosphatidyl inositol produce stimulatory effects on PAK1 through a domain that is similar to the GTP-ase binding domain [25]. On the

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