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Review

RTK SLAP DOWN: The emerging role of Src-like adaptor protein as a key player in receptor tyrosine kinase signaling☆

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ABSTRACT

SLAP (Src like adaptor protein) contains adjacent Src homology 3 (SH3) and Src homology 2 (SH2) domains closely related in sequence to that of cytoplasmic Src family tyrosine kinases. Expressed most abundantly in the immune system, SLAP function has been predominantly studied in the context of lymphocyte signaling, where it functions in the Cbl dependent downregulation of antigen receptor signaling. However, accumulating evidence suggests that SLAP plays a role in the regulation of a broad range of membrane receptors including members of the receptor tyrosine kinase (RTK) family. In this review we highlight the role of SLAP in the ubiquitin dependent regulation of type III RTKs PDGFR, CSF-1R, KIT and Flt3, as well as Eph family RTKs. SLAP appears to bind activated type III and Eph RTKs via a conserved autophosphorylated juxtamembrane tyrosine motif in an SH2-dependent manner, suggesting that SLAP is important in regulating RTK signaling.

Contents

1. Introduction

Intracellular signal transduction involves the assembly of multi-protein complexes in a spatially and temporally regulated manner. The formation of signaling complexes is facilitated by adaptor proteins, which consist of modular protein-protein or protein–lipid interaction domains, but lack intrinsic enzymatic activity of their own. The Src-like adaptor proteins, SLAP and SLAP2, are highly expressed in hematopoietic tissues, and have been most extensively studied for their role in lymphocyte signaling. The importance of SLAP and SLAP2 in regulating the signaling, ubiquitination, and trafficking of components of the T

Abbreviations: AML, acute myeloid leukemia; BCR, B cell receptor; BMM, bone marrow-derived macrophage; CSF-1R, colony stimulating factor-1 receptor; CRC, colorectal cancer; Flt3, Fms-like tyrosine kinase 3; NMDAR, *N*-methyl-D-aspartate receptor; PDGFR, platelet derived growth factor receptor; RTK, receptor tyrosine kinase; SLAP, Src-like adaptor protein; SFK, Src family kinase; SH, Src-homology; TKBD, tyrosine kinase binding domain; TCR, T cell receptor.

☆ The authors declare no conflict of interest.

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cell receptor (TCR) and B cell receptor (BCR) antigen receptor complexes is well established and has been thoroughly reviewed elsewhere [1]. However, mounting evidence suggests that SLAP/SLAP2 also play an important role in signaling by receptor tyrosine kinases (RTKs). Growth factors mediate their signaling responses by binding to RTKs, which induces receptor dimerization and catalytic activation. Activated receptors phosphorylate tyrosine residues within their cytoplasmic domains, thereby creating binding sites for SH2-containing proteins including Src family kinases (SFKs) and adaptor proteins, and leading to a signaling response (reviewed in [2]). It is imperative that these signaling complexes are activated and subsequently downregulated at appropriate times (reviewed in [3]). This review focuses on emerging

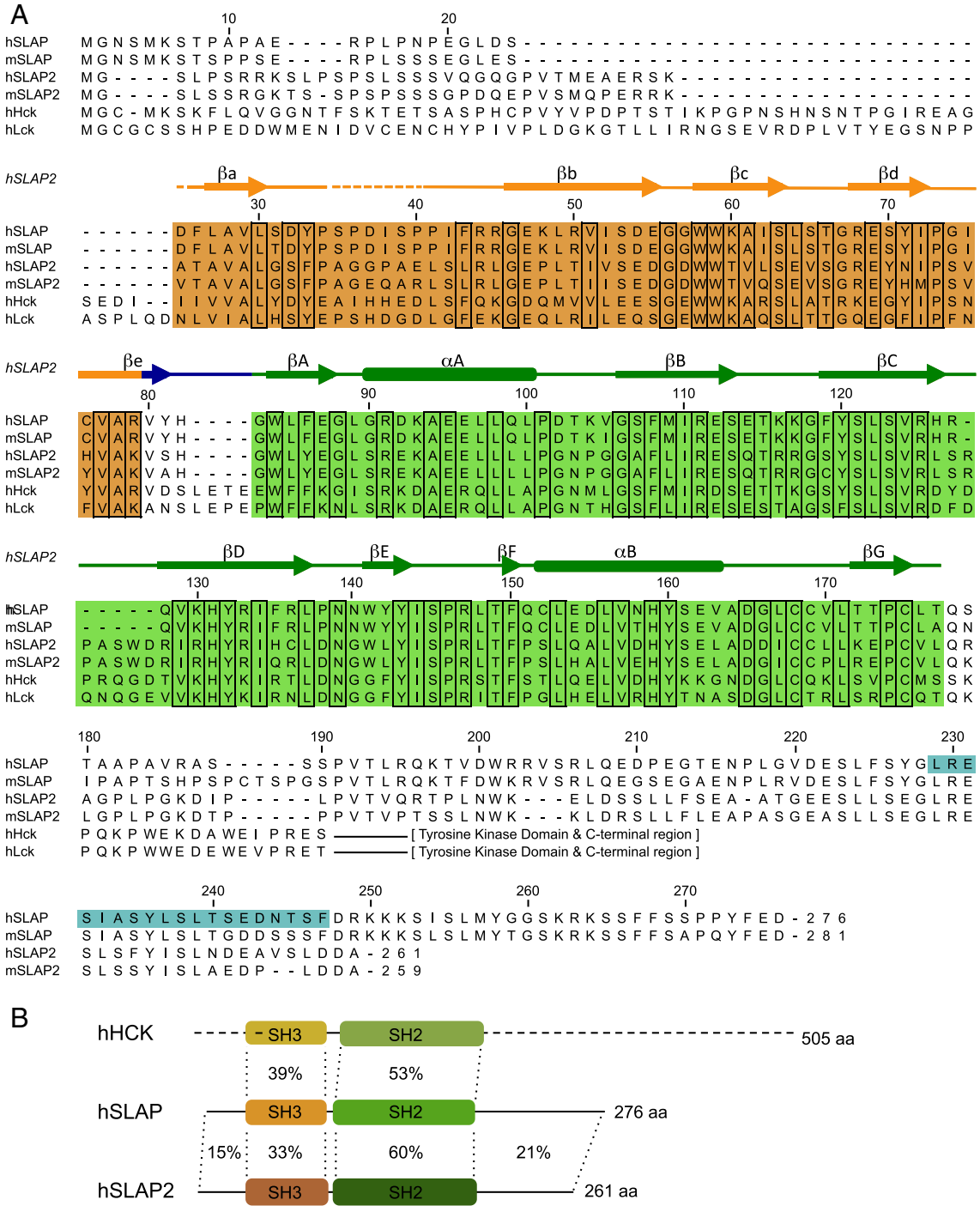

Fig. 1. SLAP and SLAP2 are highly similar in sequence and domain structure to Src family kinases. (A) Structure-based sequence alignment of Src-like adaptor proteins with the SH3 and SH2 domains of human Hck and human Lck, with residue numbering based on human SLAP. The secondary structure elements of human SLAP2 are indicated based on PDB id 4M4Z, with the SH3, SH3-SH2 connector, SH2, and C-terminal tail colored orange, blue, and green, respectively. Residues that are identical between hSLAP and hHck are marked with a black box. The Cbl interaction site as mapped by Tang *et al.* is highlighted in cyan [6]. (B) Schematic representations of human Hck (SH3 and SH2 domains only), SLAP, and SLAP2. The percent amino acid identity between the individual regions is indicated. The hatched lines at the N- and C-termini of Hck indicate regions that are not similar to SLAP/SLAP2 in sequence and/or domain structure.

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