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Review

Negative regulation of immunoreceptor signaling by protein adapters: Shc proteins join the club

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ABSTRACT

Protein adapters couple surface receptors to multiple intracellular signaling modules by acting as scaffolds for the assembly of multimolecular complexes responsible for the coordination and amplification of signals. Through the spatiotemporally controlled recruitment of mediators with opposite activities (e.g. protein tyrosine kinases and phosphatases), adapters are implicated not only in signal initiation and propagation, but also in feedback loops for signal extinction. Moreover, adaptors specialized in preventing or dampening signaling have been more recently discovered. Here we shall present of brief overview of the principal adaptors which act as negative regulators of TCR and BCR signaling, with a focus of the mechanisms underlying this function. We shall then discuss our recent findings implicating p66Shc and Rai, two members of the Shc family of cytosolic protein adapters, in the negative control of antigen receptor signaling, and their role as gatekeepers of autoimmunity and leukemia.

1. Introduction

In the last decade molecular adapters have emerged as key participants in immunoreceptor signaling. While not directly implicated in the initiation of the signaling cascades triggered by immunoreceptors, adapters provide the scaffolds required for the activation, integration and fine-tuning of multiple signaling modules, accounting for the complexity and plasticity of immunoreceptor signaling and for the strikingly diverse biological outputs. Adapters have moreover been implicated in termination of signaling through the temporally controlled recruitment of negative regulators, such as proteins and lipid phosphatases and ubiquitin ligases, close the activated receptor. Accumulating evidence, obtained principally in genetically manipulated mice, has more recently underscored a previously unappreciated role of adapters in dampening the signals triggered by immunoreceptors, thereby preventing potentially dangerous pathological outcomes resulting from uncontrolled lymphocyte hyperreactivity to both self and foreign antigen. This applies not only to "dedicated" adapters (e.g. phosphoprotein associated with glycosphingolipid-enriched domains, PAG), but also to adapters previously believed to only mediate positive signals (e.g. non-T-cell activation linker, NTAL).

Here we shall summarize our present understanding of the mechanisms of attenuation of T cell receptor (TCR) and B cell receptor (BCR) signaling by molecular adapters and discuss the pathological outcome of their deficiency, with a focus on our recent findings implicating specific members of the Shc (Src homology domain containing) family of protein adapters as negative regulators of antigen receptor signaling, autoimmunity and cancer.

2. The role of protein adapters in the negative control of antigen receptor signaling

Antigen receptor signaling is coordinately regulated by two classes of adapters, grouped on the basis of their subcellular localization. Cytosolic adapters essentially consist of an array of protein/protein and protein/lipid interaction domains and can include one or more phosphorylatable tyrosine residues. At variance, transmembrane adapters lack the typical interaction domains of their cytosolic counterparts. Rather, they are provided of a long cytosolic tail which includes several tyrosine residues which, when phosphorylated, become docking sites for proteins provided of phosphotyrosine binding domains (Src Homology 2 domain, SH2, and phosphotyrosine-binding domain, PTB). These adaptors form large scaffolds ideally suited for assembling

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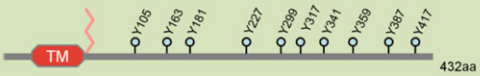
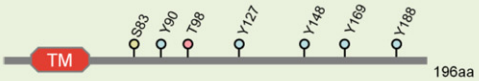
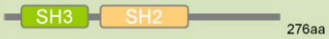
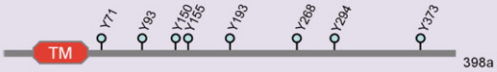
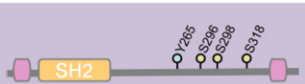
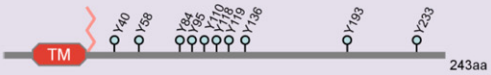
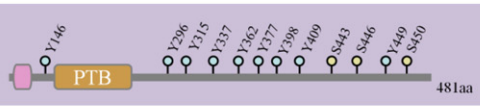
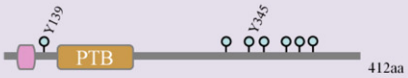
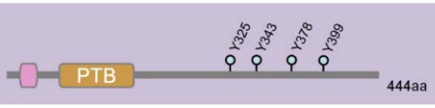
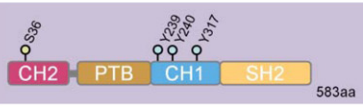
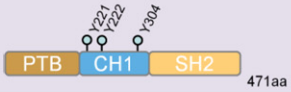
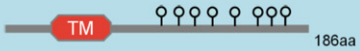
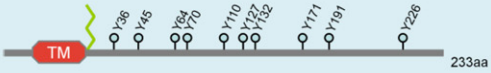
multimolecular complexes, which in many instances include cytosolic adaptors, thereby extending the combinatorial potential of the scaffold itself. Both classes of adapters include members implicated in the negative control of antigen receptor signaling.

Table 1
Negative regulatory adapters in TCR and BCR signaling.[a]

Adapter	Structure	Expression	Interactions	Ref.
PAG		ubiquitous	Csk, Fyn, Lyn, RasGAP	[3]
SIT		B, T cells	Grb2, SHP1, SHP2, SHIP-1	[3]
SLAP		T, B, myeloid cells	CD3ζ, LAT, Lck, SLP-76, Syk, Vav, ZAP-70, PI-3K, c-Cbl, Igα	[9]
LAX		T, B, NK, monocytes, BMMC	ALX, Grb2, Gads, PI-3K	[3]
ALX		T, B cells	LAX, Lck	[3]
NTAL/LAB		B, NK, monocytes, mast cells, stimulated T cells	Grb2, SHP-1, Sos1, Gab1, c-Cbl	[3]
Dok-1		B, T cells, macrophages, neutrophils	Abl, Crk, CrkL, Lyn, Nck, PI-3K, PLCγ1, RasGAP, CD3ε, Dok-1, Dok-2, SHIP-1, CD3ζ	[19]
Dok-2		T, B, myeloid cells	Abl, Crk, CrkL, Lyn, Nck, RasGAP, CD3ε, Dok-1, Dok-2, SHIP-1, CD3ζ	[19]
Dok-3		T, B, myeloid cells	Abl, Dok-3, SHIP-1, Csk, Grb2	[19]
Dok-4		T cells	-	[19]
p66Shc		T, B, myeloid cells	Grb2, ZAP-70	[29]
Rai		T, B, myeloid cells	-	[29]
TRIM		T, NK cells	CD3ζ, CD2, CD3, CD4, CD5, CD8, CTLA-4, Grb2 PI-3K	[3]
LAT		T, pre-B, NK, megakaryocytes, platelets, mast cells	PLCγ1, Grb2-Sos, Gads-SLP-76, Grap, Gab2, Vav, PI-3K, Cbl-b, 3BP2, Shb	[25]

[a] Background colours highlight the classes of adapters described in Sections 2.1–2.3. p66Shc and Rai are included among the adaptors dampening antigen receptor signaling. Aminoacid residues refer to the human proteins.