Cellular Signalling 26 (2014) 895–902

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Palmitoylated transmembrane adaptor proteins in leukocyte signaling

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ARTICLE INFO

Article history:
Received 18 November 2013
Received in revised form 7 January 2014
Accepted 9 January 2014
Available online 15 January 2014

Keywords:
Adaptor
Palmitoylation
PRR7
SCIMP
LST1
LAT

ABSTRACT

Transmembrane adaptor proteins (TRAPs) are structurally related proteins that have no enzymatic function, but enable inducible recruitment of effector molecules to the plasma membrane, usually in a phosphorylation dependent manner. Numerous surface receptors employ TRAPs for either propagation or negative regulation of the signal transduction. Several TRAPs (LAT, NTAL, PAG, LIME, PRR7, SCIMP, LST1/A, and putatively GAPT) are known to be palmitoylated that could facilitate their localization in lipid rafts or tetraspanin enriched microdomains. This review summarizes expression patterns, binding partners, signaling pathways, and biological functions of particular palmitoylated TRAPs with an emphasis on the three most recently discovered members, PRR7, SCIMP, and LST1/A. Moreover, we discuss in silico methodology used for discovery of new family members, nature of their binding partners, and microdomain localization.

Contents

1. Introduction

The family of transmembrane adaptor proteins (TRAPs) represents a heterogeneous group of proteins that differ in the number and character of interacting partners and expression pattern as well as in their biological role. However, the unifying function of TRAPs is their involvement in the signaling pathways by facilitating protein–protein interactions and recruitment of proteins or protein complexes into specific membrane-proximal compartments and microdomains. The localization of most TRAPs to the plasma membrane predisposes them to act in the proximal events of various signaling pathways, either as positive or negative regulators of signaling. Leukocyte TRAPs can be divided into three subfamilies: immunoreceptor-associated TRAPs (TCRζ, FcRγ, DAP10, DAP12), palmitoylated TRAPs (LAT, PAG/Cbp, NTAL/LAB, LIME, PRR7, SCIMP, LST1/A), and TRAPs that are neither directly associated with any immunoreceptor nor palmitoylated (e.g. LAX, SIT, TRIM) [1–5]. A special case is GAPT which contains a potential pamitoylation motif but whose putative palmitoylation has not been experimentally addressed [6].

This review focuses on the palmitoylated TRAPs (pTRAPs) in leukocytes. Palmitoylation is a reversible lipid modification of juxtamembrane cysteine residues in many transmembrane or soluble cytoplasmic membrane-associated proteins [7]. Numerous proteins involved in

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http://dx.doi.org/10.1016/j.cellsig.2014.01.007

proximal leukocyte signaling are palmitoylated (Fig. 1) [8]. The addition of palmitate to proteins is catalyzed by members of DHHC palmitoyltransferases (23 family members in humans) that reside in plasma membrane or membranes of Golgi or endoplasmic reticulum [9].

Palmitoylation can regulate multiple aspects of protein biology, including protein conformation, membrane microdomain association, protein–protein interactions, and other posttranslation modifications [10]. In case of LAT, a prototypic TRAP, palmitoylation mediates both plasma membrane localization and microdomain targeting [11,12]. Known pTRAPs share the following structural properties: a short N-terminal extracellular part (up to 20 amino acids) without receptor or receptor-like properties, single transmembrane domain, lack of any enzymatic domain, and presence of at least one protein–protein interacting motif in the intracellular part.

Four pTRAP family members were identified by the year 2003 [4]. Recently, the family has expanded by the characterization of three new members in our laboratory [1–3]. Here, we review functional and structural properties of known pTRAPs with the emphasis on the recently discovered family members (Fig. 2) and general features of pTRAPs such as microdomain localization, binding partners, and in silico approaches that were employed to identify the majority of the known family members.

2. "Old" pTRAPs

This chapter briefly summarizes the main findings about the well-established pTRAPs and one putative pTRAP identified before the year 2004. For a more detailed overview, we refer to recent review articles focused on the individual adaptors [13–17].

The first member of the pTRAP family, Linker of activation for T cells (LAT) was identified as a protein expressed in T cells that became strongly phosphorylated upon T-cell receptor (TCR) stimulation [18]. Phosphorylation of LAT, mediated by ZAP70, enables association of LAT with various effector molecules, including Grb2, GADS, PLCγ, and SLP76 [19,20]. LAT is a key component of the TCR signaling pathway that orchestrates formation of a signaling complex where individual molecules interact with each other, leading to the signal propagation and eventual activation of the cell [21]. LAT-deficient Jurkat T cells are unable to respond to the TCR stimulation [22,23]. Mice deficient in LAT have a severe defect in early thymocyte development and are devoid of peripheral T cells [24]. Further analysis demonstrated that LAT is also expressed in NK cells, megakaryocytes, mast cells [25,26], platelets [27,28], and pre-B cells [29]. LAT-deficiency in mast cells leads to markedly decreased responses to FcεRI activation and LAT-deficient mice are therefore resistant to IgE-mediated passive systemic anaphylaxis [30].

The crucial role of LAT in the T cell function prompted research on whether a LAT paralog is present in mature B cells that are practically devoid of LAT. One such candidate termed Non-T-cell activation linker (NTAL alias LAB, LAT2) was independently described by our group and Zhang's [31,32]. NTAL is expressed in B cells, NK cells, monocytes, mast cells, and activated T cells [31–33]. Triggering of B-cell receptor (BCR), Fc receptors, or TCR induces phosphorylation of NTAL mediated by Syk or ZAP70 and enables recruitment of Grb2, Gads and SLP76, but not PLCγ [31,32,34–36]. Initial experiments demonstrated that ectopic expression of NTAL in LAT-deficient Jurkat cells can partially rescue TCR signaling defects [31,37]. Transgenic expression of NTAL enabled murine $LAT^{-/-}$ T cells to pass through thymic selection and these mice subsequently developed severe T cell lymphoproliferative disorders and organomegaly [31,32,34,37]. Interestingly, similar phenotype was described in knock-in mice expressing LAT with mutated PLCγ binding site [38,39]. All these data indicated that ectopically expressed NTAL can substitute for LAT to some extent as a positive regulator of TCR signaling. Therefore, it was surprising that mature B cells derived from NTAL-deficient mice had no overt phenotype [40]. Moreover,

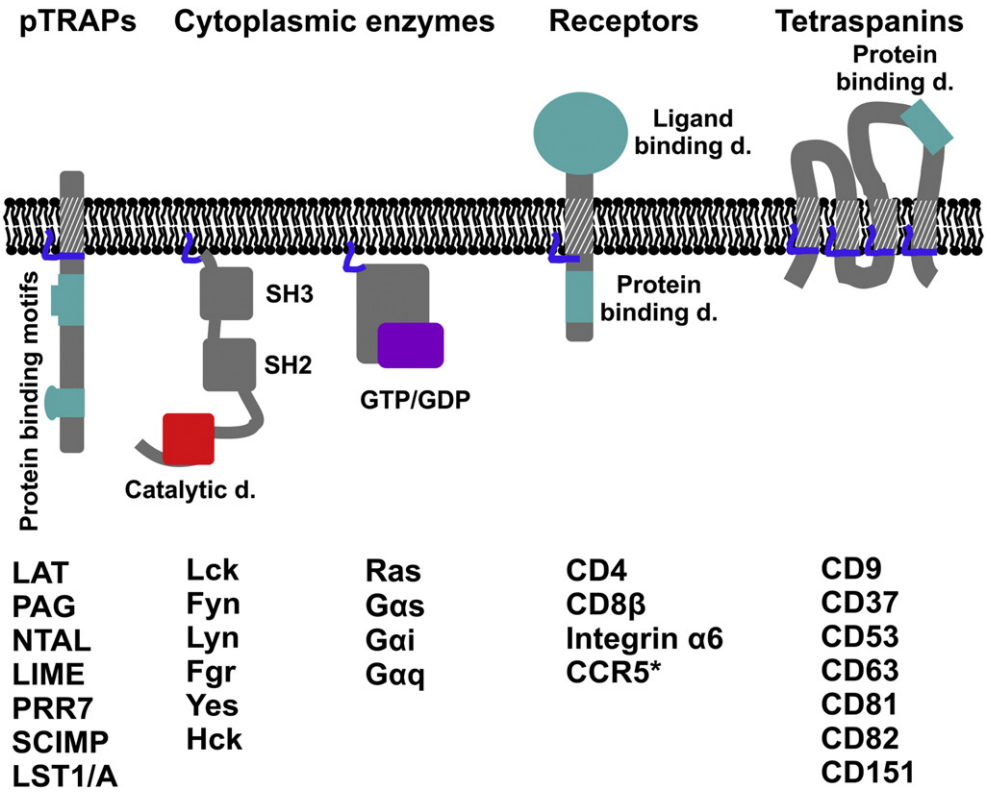

Fig. 1. Important palmitoylated proteins in leukocyte signaling. pTRAPs, soluble cytoplasmic enzymes, receptors, and tetraspanins represent the most important groups of palmitoylated proteins involved in leukocyte signaling. CCR5 has 7 transmembrane domains that are not shown in the scheme. d.: domain.