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Molecules in focus

NTAL/LAB/LAT2

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Abstract

Non-T cell activation linker (NTAL)/linker for activation of B cells (LAB), now officially termed LAT2 (linker for activation of T cells 2) is a 25–30 kDa transmembrane adaptor protein (TRAP) associated with glycolipid-enriched membrane fractions (GEMs; lipid rafts) in specific cell types of hematopoietic lineage. Tyrosine phosphorylation of NTAL/LAB/LAT2 is induced by FcεRI aggregation and Kit dimerization in mast cells, FcγRI aggregation in monocytes, and BCR aggregation in B cells. NTAL/LAB/LAT2 is also expressed in resting NK cells but, unlike the related TRAP, LAT, not in resting T cells. As demonstrated in monocytes and B cells, phosphorylated NTAL/LAB/LAT2 recruits signaling molecules such as Grb2, Gab1 and c-Cbl into receptor-signaling complexes. Although gene knock out and knock down studies have indicated that NTAL/LAB/LAT2 may function as both a positive and negative regulator of mast cell activation, its precise role in the activation of these and other hematopoietic cells remains enigmatic.
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Keywords: NTAL; LAB; LAT2; Transmembrane adaptor protein; Mast cells

1. Introduction

NTAL (non-T cell activation linker) was originally identified in 2002 in the laboratory of Vaclav Horejsi (ASCR, Prague, Czech Republic) following sequencing of a previously unidentified tyrosine phosphorylated protein of 30 kDa found in the glycolipid-enriched membrane (GEM or lipid rafts) fractions isolated from the THP-1 myeloid cell line (Brdicka et al., 2002). The molecule was subsequently also described and given the name LAB (linker for activation of B cells) by the group of Weiguo Zhang in 2003 (Duke University, NC, USA) following human genome database search for LAT (linker for activation of T cells) homologs in B cells and other cell types (Janssen, Zhu, Zhang, Koonpaew, & Zhang, 2003). The molecule has now been given the official name LAT2 by the Human Genome Organization Nomenclature Committee based on the structural similarity of this molecule to LAT (Gilfillan & Iwaki, 2006). To avoid confusion we will use the NTAL/LAB/LAT2 designation for this molecule in this article.

2. Structure

The human NTAL/LAB/LAT2 gene is located on chromosome 7 (7q11.23) and is identical to the *wbscr5* gene, which is part of a gene locus deleted in Williams–Beuren syndrome (Brdicka et al., 2002; Gilfillan & Iwaki, 2006; Janssen et al., 2003). This

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gene consists of 11 exons and encodes a 243 amino acid protein with a molecular weight of approximately 30 kDa (Brdicka et al., 2002; Gilfillan & Iwaki, 2006; Janssen et al., 2003). Both longer and shorter alternatively spliced isoforms, however, have been reported at the cDNA level (Gilfillan & Iwaki, 2006). The murine form is a protein of 203 amino acids with a molecular weight of approximately 25 kDa (Brdicka et al., 2002). Human NTAL/LAB/LAT2 has a short 4 amino acid extracellular domain, a single 18 amino acid transmembrane span and a 221 amino acid cytosolic domain (Brdicka et al., 2002; Gilfillan & Iwaki, 2006; Janssen et al., 2003). The cytosolic juxta-membrane region of NTAL/LAB/LAT2 has a -CVRC- palmitoylation site (Fig. 1) which results in this molecule being targeted to reside in the GEMs/lipid rafts (Brdicka et al., 2002; Janssen et al., 2003). Contained within the cytosolic domain of NTAL/LAB/LAT2 are 10 tyrosines which are potential targets for tyrosine kinases. Six of these tyrosines are found within five YXN motifs (one of these motifs is $Y^{118}Y^{119}N$) which are recognized as putative binding sites for the cytosolic adaptor molecule Grb2 following the phosphorylation of these tyrosines (Brdicka et al., 2002; Koonpaew, Janssen, Zhu, & Zhang, 2004). One of the YXN motifs ($Y^{233}VN$, human NTAL/LAB/LAT2 sequence) in LAT has been recognized as a binding site for the Grb2-related cytosolic adaptor molecule, GADS (Gilfillan & Tkaczyk, 2006), however, as yet, phosphorylated NTAL/LAB/LAT2 has not been demonstrated to bind this molecule.

In addition to these potential binding sites, Y^{110} is part of a YIDP sequence also found in Kit which, in this latter molecule, is recognized as a putative Src kinase/SHP-1 binding site (Linnekin, 1999). Again, whether such interactions occur with NTAL/LAB/LAT2 is currently unknown. The remaining three tyrosines do not appear to be part of recognized binding motifs. NTAL/LAB/LAT2 however does posses three RXXK motifs which, although not yet demonstrated for NTAL/LAB/LAT2, may permit constitutive binding of SH3 domain-containing signaling molecules such as Src kinases (Gilfillan & Tkaczyk, 2006). Unlike

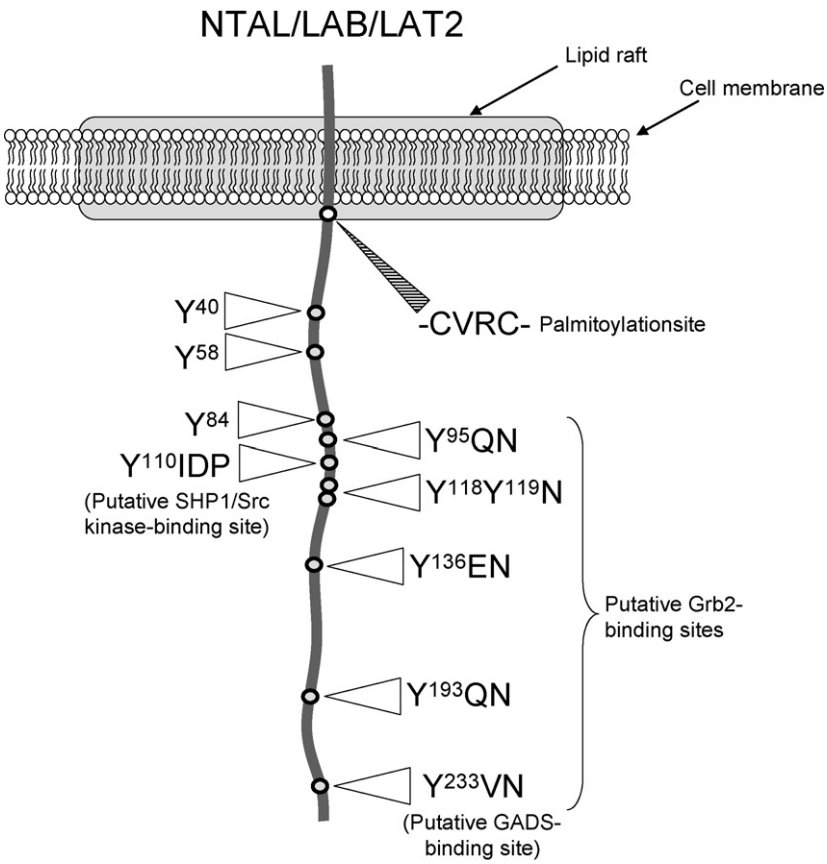

Fig. 1. Representation of the structure and location of human NTAL/LAB/LAT2. The striped triangle designates the position of the juxta-membrane palmitoylation site, and the open triangles designate the position of the potential tyrosine phosphorylation sites.