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Review Article

F-actin remodeling defects as revealed in primary immunodeficiency disorders

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ABSTRACT

Primary immunodeficiencies (PIDs) are a heterogeneous group of immune-related diseases. PIDs develop due to defects in gene-products that have consequences to immune cell function. A number of PID-proteins is involved in the remodeling of filamentous actin (f-actin) to support the generation of a contact zone between the antigen-specific T cell and antigen presenting cell (APC): the immunological synapse (IS). IS formation is the first step towards T-cell activation and essential for clonal expansion and acquisition of effector function. We here evaluated PIDs in which aberrant f-actin-driven IS formation may contribute to the PID disease phenotypes as seen in patients. We review examples of such contributions to PID phenotypes from literature, and highlight cases in which PID-proteins were evaluated for a role in f-actin polymerization and IS formation. We conclude with the proposition that patient groups might benefit from stratifying them in distinct functional groups in regard to their f-actin remodeling phenotypes in lymphocytes.

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Contents

1. Introduction

Currently, more than 250 human primary immunodeficiencies (PIDs) have been reported [1,2]. PIDs represent a heterogeneous group of diseases caused by genetic defects that culminate in

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malfunction of the immune system [3]. These defects can obstruct a variety of processes, including the initiation of the adaptive immune system branch, as required for high affinity antigen-specific immunity and the induction of recall immune responses. Adaptive immune activation commences with the presentation of antigenic peptide/major histocompatibility complexes (MHC) to antigen-specific T cells. The process of antigen-specific T cell activation starts by the productive binding of a cognate T cell receptor (TCR), which triggers the assembly of a molecular structure at the T cell surface, the immunological synapse (IS) [4,5] (Fig. 1). Considering the importance of stable IS assembly to the generation of effective adaptive immune responses, for selected PIDs, defects in IS assembly may contribute to the disease phenotype observed (Table 1).

When cell surface molecules are triggered, associated signaling molecules transmit signals that induce f-actin remodeling. Here, f-actin monomers rearrange to form polymers, which helps to recruit additional cell surface molecules to the IS, and mediate T cell activation [7,8]. Considering the importance of signaling molecules in early T cell signaling, we explored a selective group of PID-associated signaling molecules for contribution to IS formation defects and the clinical PID phenotype (Figs. 1 and 2). First, we discuss upstream signaling molecules that transmit the antigen ligation-induced signal from the TCR inward. Second, we describe downstream signaling molecules that promote stable IS formation via f-actin polymerization and adhesion molecules. Third, we consider downstream actin-regulatory molecules, which induce tightly regulated f-actin remodeling.

2. Upstream signaling molecules

Lymphocyte-specific protein tyrosine kinase (LCK), ZAP70, class IA phosphatidylinositol 4,5-bisphosphate 3-kinases (PI3K), and interleukin-2-inducible T cell kinase (ITK) are PID-related kinases that are involved in f-actin remodeling and IS formation. In the next sections we discuss these upstream PID-related signaling molecules in more detail (as depicted in Fig. 2).

2.1. Upstream signaling molecules and PID phenotype

2.1.1. LCK and UNC119

Currently, three PID patients with reduced LCK expression have been reported [10,15,16]. However, in only one of these patients a mutation in the LCK gene was determined [10]. On a molecular level, this patient displayed reduced phosphorylation of early signaling molecules, including CD3ζ, ZAP70, LAT, and 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase (PLC)γ1 [10]. PLCγ1 is important for calcium mobilization, which is required for f-actin remodeling and thereby mature IS formation [17]. Consequently, LCK-mutant cells show no calcium fluxes [10], impaired f-actin remodeling [18], and reduced T cell/APC synapse formation [18]. Furthermore, LCK serves as upstream mediator of integrin recruitment and activation, processes that are also dependent on f-actin remodeling [18–20]. In line with the crucial role of LCK in early T cell signaling, the LCK mutation patient displayed a severe phenotype including $CD4^+$ T cell lymphopenia, recurrent infections, autoimmunity, autoinflammation, and T cells originating from a small number of clones and showing little surface expression of CD4 and CD8 [10]. Thus, in LCK-deficient cells or cells expressing mutant LCK, PID disease may involve a failure to direct integrin alpha-L/beta-2 (LFA1) to the IS, thereby disturbing T cell adhesion to APCs [18].

Uncoordinated 119 homolog A (UNC119) is required for LCK activation and localization to the plasma membrane [9,21]. Since UNC119 is expressed at low levels in murine thymocytes, PID disease in UNC119-gene variant patients may not be related to LCK activation during thymic development of T cells [21]. Instead, in peripheral T cells, in which UNC119 expression is increased and essential to target LCK in an f-actin-dependent manner to the developing IS, UNC119 may contribute to early activation of mature T cells [9]. In support, a mutation in UNC119 hampers the protein's association with LCK, thereby causing impaired LCK activation and localization in peripheral T cells. Because T cell development in UNC119-gene variants is likely intact, clinical PID manifestations in UNC119 variants exhibits $CD4^+$ T cell lymphopenia and a variety of bacterial, viral, and fungal infections [21]. Taken

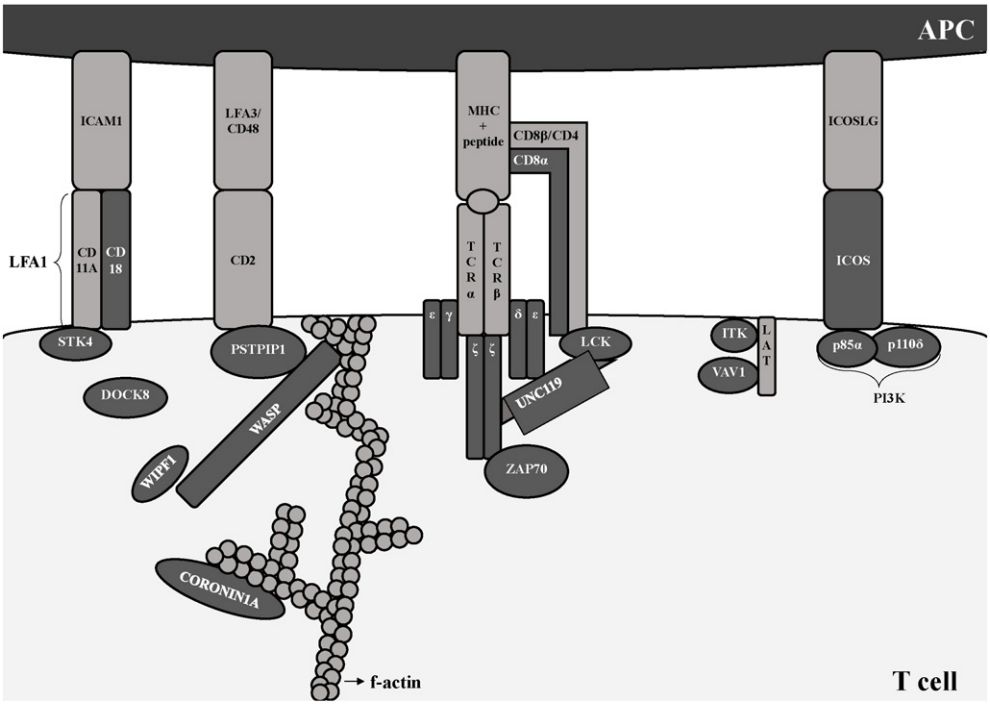

Fig. 1. Overview of the immunological synapse between a $CD4^+$ or $CD8^+$ T cell and an APC. Examples of PID-proteins that are linked to IS formation and discussed in this article are depicted in dark-gray.

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