Leukocyte Adhesion Deficiencies

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KEYWORDS

• Inflammation • Leukocytes • Leukocyte adhesion deficiency • β integrins • LAD-I • LAD-II • LAD-III • Kindlin-3

KEY POINTS

- During inflammation, leukocytes play a key role in maintaining tissue homeostasis by elimination of pathogens and removal of damaged tissue.
- Leukocytes migrate to the site of inflammation by crawling over and through the blood vessel wall, into the tissue.
- Leukocyte adhesion deficiencies (ie, LAD-I, -II, and LAD-I/variant, the latter also known as LAD-III) are caused by defects in the adhesion of leukocytes to the blood vessel wall, due to mutations in the genes encoding β2 integrin (*ITGB2*), a GDP-fucose transport protein (*SLC35C1*) and kindlin-3 (*FERMT3*), respectively.
- Patients experience recurrent nonpussing bacterial infections and neutrophilia, often preceded by delayed separation of the umbilical cord, and additional symptoms depending on the subtype.
- For LAD-I and LAD-III, the only curative treatment is hematopoietic stem cell transplantation. In case of LAD-II, oral fucose supplementation may invert the immune defect, but additional mental retardation is hardly improved.

INTRODUCTION

Leukocyte Recruitment and Extravasation

During inflammation, circulating leukocytes migrate to the site of infection following a gradient of chemotaxins in a process called *chemotaxis*.[1] Chemotaxins may be derived from either the infected tissue or local complement activation, or directly from the pathogens themselves, and diffuse within the tissue into the local vasculature.[2] These gradients of chemotaxins recruit the leukocytes in interplay with factors expressed locally on the luminal side of blood vessel endothelial cells. Neutrophils are short-living leukocytes that are recruited early in the inflammatory response.

Leukocytes following the chemotaxin gradient toward the site of infection must leave the bloodstream, in a process called *extravasation* (**Fig. 1**).[1,3] Extravasation is

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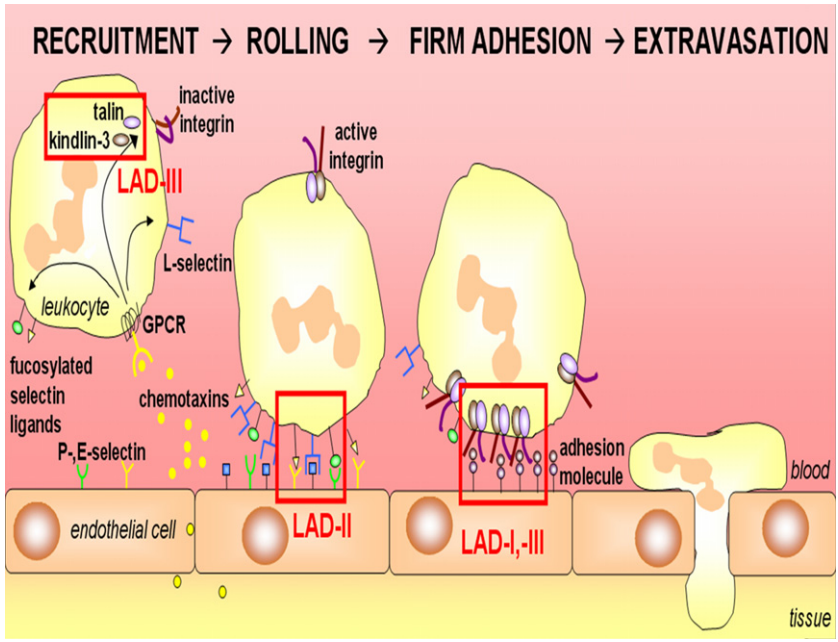

Fig. 1. Leukocyte recruitment and extravasation. Leukocytes migrate to the site of inflammation following a gradient of chemotaxins. The cells slow down because of transient interactions between selectins and their glycosylated ligands, which are defective in LAD-II. Next, stable adhesion by leukocyte integrins, absent in LAD-I, to ligands on the endothelium results in leukocyte arrest. Activation of blood cell integrins is decreased in LAD-III. Healthy neutrophils extravasate after firm adhesion.

a multistep process involving adhesion molecules, in which chemotaxins function as activating agents or (pro-) inflammatory mediators. The first step of extravasation consists of initial contact between endothelial cells and leukocytes marginated by the fluid flow of the blood. L-selectin (CD62L) on leukocytes plays a role herein, contacting several cell adhesion molecules on endothelial cells.[4] Within the local environment of an inflammatory tissue reaction, the endothelium begins to express the adhesion molecules P-selectin (CD62P) and later E-selectin (CD62E). The low-avidity interaction of these selectins with their fucosylated ligands on the opposite cells forces the leukocytes to slow down and start a rolling movement along the vessel wall (see **Fig. 1**).[4,5]

In contrast to the low-avidity binding of leukocytes to selectins, the final step of firm adhesion and subsequent migration depends on stable interaction between integrins on the leukocytes and their ligands on the endothelial cells.[1,6] Integrins are type 1 transmembrane glycoproteins that form heterodimers via noncovalent association of their α and β subunits, with sizes of 120 to 170 kDa and 90 to 130 kDa, respectively.[7] In mammals, 18 α and 8 β subunits form 24 known combinations, each of which can bind to a specific repertoire of cell-surface, extracellular matrix or soluble protein ligands. The β_2 integrin receptor subfamily is selectively expressed on leukocytes and comprises 4 different heterodimeric proteins, each of which contains a different α subunit: $\alpha_L\beta_2$ (LFA-1; CD11a/CD18), $\alpha_M\beta_2$ (CR3; CD11b/CD18), $\alpha_x\beta_2$ (gp150,95; CD11c/CD18); and $\alpha_D\beta_2$ (CD11d/CD18), the latter only being expressed on macrophages. The β_2 integrins bind to adhesion molecules on endothelial cells (intercellular