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Review

Hemodynamic parameters regulating vascular inflammation and atherosclerosis: A brief update

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Abstract

Atherosclerosis is a chronic lipid-driven inflammatory disease of the arteries. Early lesions (fatty streaks) contain monocytes and T lymphocytes which are recruited from the circulation by adhesion to activated vascular endothelial cells (EC). This process is described as the leukocyte adhesion cascade. Atherogenesis occurs predominantly at branches and bends of the arterial tree that are exposed to relatively low or re-circulating blood flow. Here we briefly review the effects of blood flow and shear stress on the leukocyte adhesion cascade and endothelial cell function.

Keywords: Atherosclerosis; Blood flow; Shear stress; Endothelium; Leukocyte adhesion

1. Introduction

Atherosclerosis causes heart attack and stroke and is the disease with the highest mortality in the western world. Although atherosclerosis is known to be a lipid-driven disease, recently, two other factors, namely inflammation and blood flow/shear, have generated considerable interest as alternative or complementary explanations for plaque formation [1,2].

The effect of blood flow in atherosclerosis is based upon the observation that vascular inflammation and plaques are distributed at near side branches, i.e. where blood flow is non-uniform, or at the lesser curvature of bends, i.e. where blood flow rates are relatively low. Here we review the multiple effects of blood flow and shear stress on the leukocyte adhesion cascade and endothelial cell function.

2. The leukocyte adhesion cascade

The vascular endothelium mediates inflammation by regulating both the adhesion and subsequent infiltration of leukocytes into tissue (see Fig. 1).

Blood flow modulates the expression levels of components of the leukocyte adhesion cascade, influences the spatial distribution of leukocytes within the vessel lumen (margination) and regulates the rolling speed of inflammatory cells on the endothelium.

2.1. Selectin-mediated capture and rolling

To date, three selectins have been characterized, namely P-, L- and E-selectins. They share a common structure; an N-terminal lectin domain, epidermal growth factor (EGF)-like domain, short consensus repeats, transmembrane domain and a short cytoplasmic tail. It is the number of consensus repeats that differs, with P-selectin containing 9, E-selectin 6 and L-selectin 2.

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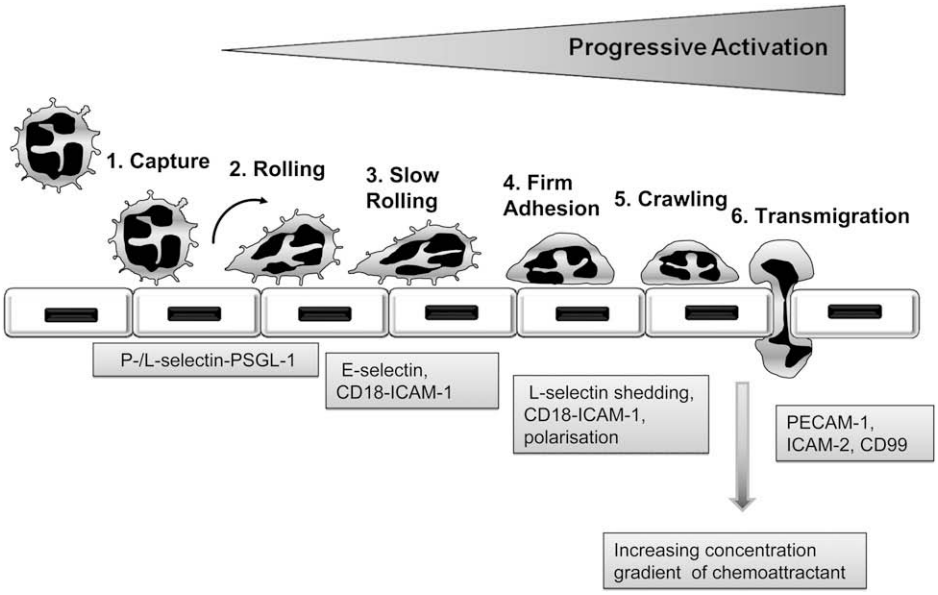

Fig. 1. The leukocyte adhesion cascade.

Leukocytes typically flow too fast to allow their capture (1–10 mm/s). However, they scour the vessel wall and interact with it if it is adhesive. The initial stage of the adhesion cascade, capture or tethering of leukocytes, may then occur through P- or L-selectin-ligand interactions on the microvilli of leukocytes and on the endothelium [3,4] (Fig. 1, step 1). The ability of these bonds to be formed under flow conditions is due to their high on (formation)- and off (breakage)-rates [5] and without flow rolling cells detach from the endothelium [6]. This phenomenon has been termed the shear threshold effect and is thought to prevent unsolicited leukocyte adhesion at areas of low flow. High on-rates result in rapid bond formation allowing the capture of cells moving at high velocities whereas high off-rates under flow facilitate labile bond formation resulting in leukocyte rolling (Fig. 1, step 2).

Once rolling, leukocytes begin to move at velocities considerably lower than free flowing blood cells resulting in increased transit times. E-selectin is known to play a critical role in the slower rolling observed after longer periods of endothelial stimulation [7]. The slower velocities of E-selectin-dependent rolling may be significant in the exposure of leukocytes to endothelial presented chemoattractants leading to the development of firm adhesion as the transition between rolling and firm adhesion is much less efficient in the absence of E-selectin [7]. Rolling triggers transmembrane signaling coupled with the formation of shear-resistant adhesion bonds, enabling cells to become arrested before migration [8]. Although previously thought to be mediated by E-selectin, it is now known that slow rolling of leukocytes also involves engagement of CD18 (β_2 integrins) [9] (Fig. 1, step 3).

2.2. Chemokine-induced activation

The transition from rolling to firm adhesion or arrest is rapidly triggered by the expression of chemokines or other chemoattractants on the luminal surface of the endothelium [10]. Chemokines are a specific type of cytokine that attract leukocytes to areas of low shear stress, injury or infection. They can bind to glycosaminoglycans (GAGs) present in the glycocalyx [11]. This is thought to enable chemokines to remain anchored to the endothelial lumen resisting flow, thus obtaining a high local concentration and increasing the likelihood of leukocyte exposure and driving the formation of a haptotactic concentration gradient. Chemokines bind to specific G protein-linked receptors (GPLRs) that cluster at the leading edge of the leukocyte and mediate directional movement of the cell towards higher concentrations of chemokine. GPLR ligation leads to rapid intracellular signaling resulting in integrin activation, making this system particularly apposite for leukocyte arrest under flow.

Inflammatory stimuli including IL-8, C5a and PAF can also stimulate rapid shedding of L-selectin. Impairment of L-selectin shedding from the surface of leukocytes resulted in markedly less efficient recruitment of leukocytes to the site of inflammation [12].

2.3. Integrin mediated firm adhesion

Integrins are a large family of divalent cation-dependent heterodimeric proteins widely expressed on leukocytes (Fig. 1, step 4). Patients with leukocyte adhesion deficiency I (LADI) show various mutations in the gene encoding β_2 [13], demonstrate marked leukocytosis and can succumb to life-threatening infections within 2 years of life.

Integrins require activation through exposure to chemoattractants. It is thought that inactive integrins have a bent conformation and exposure to inflammatory stimuli allows extension of this conformation in a switch-blade or flick-knife manner exposing the ligand binding site [14]. This alters the affinity and avidity of the integrin for its ligand and influences