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Review article

# Monocyte adhesion to the endothelium is an initial stage of atherosclerosis development

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ABSTRACT

The formation of atherosclerotic plaque is a long and very complex process. The first signs of development of atherosclerosis occur in areas where the blood vessels are strongly stressed. Although it clinically manifests from middle age, the first signs of plaque formation are detectable at a very early age [1]. Although the endothelium consists of only one layer of cells, it plays an important role in the development of atherosclerosis. The endothelium produces a wide range of factors that influence vascular tone, cellular adhesion, vessel wall injury, thromboresistance and smooth muscle cell proliferation. Adhesion and migration of monocytes occur at the beginning of atherosclerotic plaque formation. These cells later differentiate into tissue macrophages and this leads to the development and stabilisation of local inflammation and their transformation into foam cells.



## Contents



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## Introduction

The endothelium lines a number of organs, but here we focus only on the lining of the blood vessels. It is a multifactorial organ involved in metabolic, immunologic and numerous cardiovascular processes. This 'organ' covers a large surface area (approximately 350 $m^2$), has a comparatively small total mass (approximately 110 g) [2] and is actively involved in vital functions of the cardiovascular system, including regulation of perfusion, fluid and solute exchange, haemostasis, coagulation, inflammatory responses, vasculogenesis and angiogenesis [3]. A healthy endothelium regulates activity and affects both the lumen and the vascular wall. It separates the space from the subendothelial part of the artery. It also integrates influences and signals from the lumen and from the bloodstream with those generated directly in the vessel wall and its immediate vicinity, thus contributing to their harmonious cooperation.

Endothelial cells (ECs) produce many bioactive substances, one of which is nitric oxide (NO). NO is crucial for the correct function of a healthy endothelium. NO is generated by oxidation of L-arginine by eNOS (endothelial NO synthase) [4]. The discoverers of NO as a signal molecule (Robert F. Furchgott, Louis J. Ignarro and Ferid Murad) were awarded the Nobel Prize in 1998. This substance has a wide range of biological properties that maintain vascular homeostasis, including modulation of vascular dilator tone, regulation of local cell growth and protection of the vessel from injurious consequences of platelets and cells circulating in the blood. Through these processes it plays a crucial role in normal endothelial function [5]. Endothelial dysfunction is linked to eNOS (endothelial NO synthase) dysfunction. eNOS physiologically produces NO, but it can also produce superoxide instead of NO [6]. eNOS downregulation leads to a reduction of the amount of endothelium-derived NO, which is required for vascular relaxation and endothelial cells (ECs) proliferation and survival [7]. The cofactor tetrahydrobiopterin (BH4) is an important factor which regulates the balance between NO and production of superoxides (eNOS coupling) [8,9]. However, BH4 can be influenced by oxidative stress, during which it can be converted by dihydrofolate reductase to 7,8-dihydrobiopterin (BH2), which in turn promotes eNOS uncoupling [9]. The dysfunction of NO production is connected to changes in the expression of vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and/or E-selectin [10–12], which further affect the ability of leukocytes to adhere to the endothelium [13]. It can locally increase their infiltration in the intima, which supports pro-inflammatory conditions and growth of atherosclerotic plaque.

## The endothelium and monocytes

The vascular endothelium plays a central role in modulating the inflammatory response of the arteries. It works by attracting inflammatory cells, activating the coagulation and complement systems and increasing vascular permeability [10]. Monocyte recruitment from the blood stream is probably the initial stage in the process of atherosclerotic plaque formation, activated by a regulated multistep process and mediated by chemoattractants, cell adhesion molecules and their receptors. Extravasation may occur due to the nature of its completely physiological defence against infection, but in this pathophysiological event it leads to development of atherosclerosis. There are several stages involved in leucocyte recruitment into vascular tissue: (1) initial selectin-dependent tethering and rolling; (2) triggering of adhesion via chemokines and their receptors or through selectin binding to P-selectin glycoprotein ligand-1 (PSGL-1); (3) integrin-dependent adhesion and adhesion strengthening by integrin clustering; (4) and transmigration across the endothelium [14].

### *The adhesion cascade*

Initially, activation of endothelial cells leads to stimulation of the expression and subsequent production of selectin molecules. L-, P- and E-selectins are C-type lectins that bind to sialylated and fucosylated carbohydrate ligands, which are presented by sialomucins. They also mediate initial capture, tethering and rolling along the endothelium [14]. Capture, the initiation stage of the adhesion cascade, is mediated mainly by P-selectin and its ligand, P-selectin glycoprotein ligand-1 (PSGL-1) [15]. P-selectin (as well as ICAM-1) is strongly expressed by the endothelium and overlie active atherosclerotic plaques, unlike their unactivated form [16]. Expression of P-selectin is even increased in human umbilical vein endothelial cells (HUVEC) of the newborns of parents with a strong family history of myocardial infarction [1,17], which suggests there is a strong genetic predisposition to the development of cardiovascular diseases [1,18].

In any case, under normal blood flow, selectin-mediated bonds are not able to block the rolling of leukocytes. It is clear that signalling and activation of other bonds, which are usually mediated by integrins, occur through selectin [19]. The weak adhesion is mediated by PSGL-1 and selectins. PSGL-1 is the dominant ligand for all three types of selectin (P-, L- and E-selectin). This interaction can enable leucocyte activation by displaying cytokine and chemoattractants for the purposes of rolling and firm integrin-mediated adhesion [19]. The signalling properties of PSGL-1 are activated via Src kinase [20], mitogen-activated protein kinase [21] and spleen tyrosine kinase [22] pathways. Specifically, the binding and cross-linking of PSGL-1 by P-selectin or E-selectin augments the adhesion of neutrophils, via β2-integrins, to fibrinogen [19] and ICAM-1 [23]. Firm adhesion of leucocytes to endothelium is the most important step requiring special interaction between integrins (very late antigen-4 integrin) and ICAM and VCAM [24,25].

In the last few years, interest has turned to the role of the glycocalyx. The luminal side is covered with a layer of the glycocalyx, which is important for immune response, vascular permeability and induction of thrombosis [26–29]. The carbohydrate antigens carried by glycoconjugates (e.g. glycoproteins, glycosphingolipids and proteoglycans), which are mainly presented on the cell surface, serve not only as marker molecules but also as functional molecules [30]. This can be important for regulating the inflammatory cascade site, with the concept being that proinflammatory stimuli (e.g. TNF-α