Biochimica et Biophysica Acta 1828 (2013) 157–166

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

Connexins in atherosclerosis ☆

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ARTICLE INFO

Article history:
Received 8 February 2012
Received in revised form 26 April 2012
Accepted 4 May 2012
Available online 15 May 2012

Keywords:
Gap junction
Connexin
Hemichannel
Atherosclerosis

ABSTRACT

Atherosclerosis, a chronic inflammatory disease of the vessel wall, involves multiple cell types of different origins, and complex interactions and signaling pathways between them. Autocrine and paracrine communication pathways provided by cytokines, chemokines, growth factors and lipid mediators are central to atherogenesis. However, it is becoming increasingly recognized that a more direct communication through both hemichannels and gap junction channels formed by connexins also plays an important role in atherosclerosis development. Three main connexins are expressed in cells involved in atherosclerosis: Cx37, Cx40 and Cx43. Cx37 is found in endothelial cells, monocytes/macrophages and platelets, Cx40 is predominantly an endothelial connexin, and Cx43 is found in a large variety of cells such as smooth muscle cells, resident and circulating leukocytes (neutrophils, dendritic cells, lymphocytes, activated macrophages, mast cells) and some endothelial cells. Here, we will systematically review the expression and function of connexins in cells and processes underlying atherosclerosis. This article is part of a Special Issue entitled: The Communicating junctions, roles and dysfunctions.

Contents

1. Introduction

Atherosclerosis is a multifactorial inflammatory disease of the vessel wall of medium to large-sized arteries. It is the leading cause of mortality in industrialized countries, and its incidence is rapidly increasing in the developing nations [1]. Atherosclerosis is characterized by specific

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0005-2736/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbamem.2012.05.011

lesions of the intimal layer of arteries, called atheromas, where the traditional components of a chronic inflammatory response such as the extravasation and accumulation of leukocytes, the presence of necrotic debris, the deposition of extracellular matrix, and the apparition of angiogenesis, can all be found [2] (Fig. 1). This disease progresses over decades. In fact, the earliest atheromatous plaques can be found in teenagers, and most of the consequences are generally apparent after the 4th decade of life. Atherosclerosis can thus be viewed as a model of a slowly progressing inflammatory disorder.

Atherosclerosis starts with a dysfunction of the endothelial cells (ECs) lining an artery, which start to express increased levels of adhesion molecules [2,3]. At the same time, lipid particles, such as low density lipoprotein (LDL)-cholesterol, accumulate within the vessel wall and become oxidized. The traditional cardiovascular risk factors

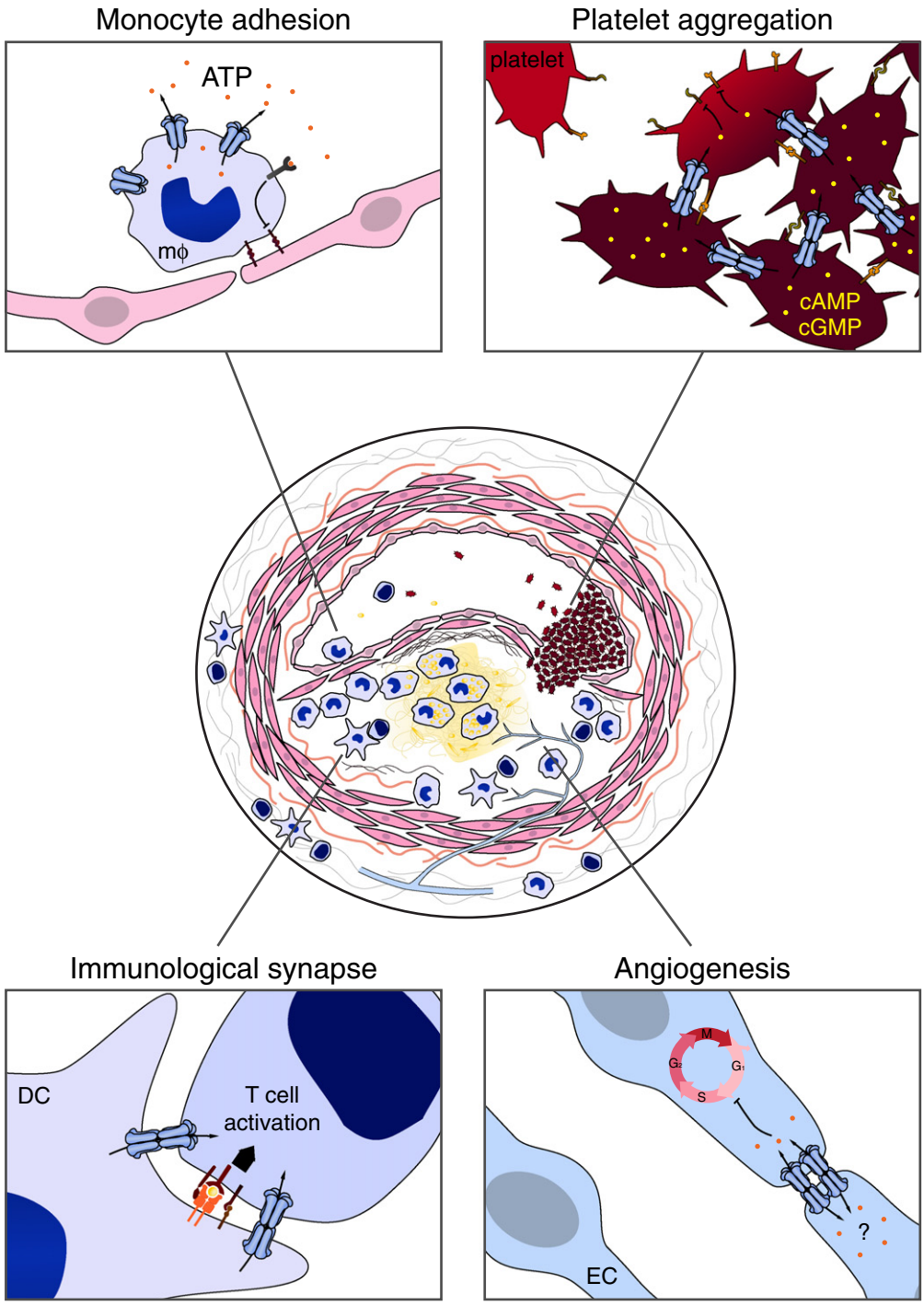

Fig. 1. Key aspects of the function of connexins in atherosclerosis development. *Top left*: Cx37 inhibits monocyte (mΦ) adhesion to the endothelium by the release of ATP through hemichannels. ATP then acts in an autocrine fashion by binding to its receptors, which ultimately leads to a reduced adhesiveness of the monocyte. *Bottom left*: Cx43 is involved in the immunological synapse. Cx43 is expressed by DCs and T lymphocytes and gap junctions are present at the outer aspect of the immunological synapse. Activation of T lymphocytes is favored by Cx43-dependent communication. *Top right*: Cx37 reduces platelet aggregation. Platelets form Cx37 gap junction channels. GJIC between platelets reduces aggregation, presumably through the diffusion of anti-aggregating metabolites (cAMP, cGMP) from the bulk of the thrombus to newly recruited platelets. *Bottom right*: Cx37 reduces angiogenesis. Cx37-deficient animals have increased angiogenesis and EC proliferation. The presence of Cx37 gap junction channels may reduce proliferation by blocking the transition from G1 to S phase of the cell cycle.