Phytomedicine 23 (2016) 1068–1081

Contents lists available at ScienceDirect

Phytomedicine

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

Anti-atherosclerotic plants which modulate the phenotype of vascular smooth muscle cells

Tuqa Saleh Al-Shehabi[a], Rabah Iratni[b,**], Ali H. Eid[c,d,*]

[a] Department of Health Sciences, College of Arts and Sciences, Qatar University, Doha, Qatar
[b] Department of Biology, College of Science, United Arab Emirates University, PO Box 15551, Al Ain, United Arab Emirates
[c] Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut, PO Box 11-0236, Beirut, Lebanon
[d] Department of Biological and Environmental Sciences, College of Arts and Sciences, Qatar University, Doha, Qatar

ARTICLE INFO

Article history:
Received 10 September 2015
Revised 27 October 2015
Accepted 30 October 2015

Keywords:
Cardiovascular disease
Atherosclerosis
Vascular smooth muscle cells
Phenotypic switch
Herbal medicine

ABSTRACT

Background: Cardiovascular disease (CVD) remains the leading cause of global death, with atherosclerosis being a major contributor to this mortality. Several mechanisms are implicated in the pathogenesis of this disease. A key element in the development and progression of atherosclerotic lesions is the phenotype of vascular smooth muscle cells. Under pathophysiologic conditions such as injury, these cells switch from a contractile to a synthetic phenotype that often possesses high proliferative and migratory capacities.

Purpose: Despite major advances made in the management and treatment of atherosclerosis, mortality associated with this disease remains high. This mandates that other approaches be sought. Herbal medicine, especially for the treatment of CVD, has been gaining more attention in recent years. This is in no small part due to the evidence-based values associated with the consumption of many plants as well as the relatively cheaper prices, easier access and conventional folk medicine "inherited" over generations.

Sections: In this review, we provide a brief introduction about the pathogenesis of atherosclerosis then we highlight the role of vascular smooth muscle cells in this disease, especially when a phenotypic switch of these cells arises. We then thoroughly discuss the various plants that show potentially beneficial effects as anti-atherosclerotic, with prime attention given to herbs and plants that inhibit the phenotypic switch of vascular smooth muscle cells.

Conclusion: Accumulating evidence provides the justification for the use of botanicals in the treatment or prevention of atherosclerosis. However, further studies, especially clinical ones, are warranted to better define several pharmacological parameters of these herbs, such as toxicity, tolerability, and efficacy.

Introduction

Cardiovascular disease (CVD) continues to be the leading cause of worldwide morbidity and mortality (WHO 2013). Globally, about one third of total deaths in 2012 were due to CVD (WHO 2014). In Europe alone, CVD accounts for approximately half of all deaths killing more than 4 million people per year (Nichols et al. 2014). In the United States, CVD kills more than 787,000 people annually, and consumes about 30% of the total medical expenditure (Mozaffarian et al. 2015b; Trogdon et al. 2007). CVD-related deaths are expected to rise, reaching 23 million deaths by 2030 (WHO 2013). In spite of the many key advances in its management and treatment, CVD claims more lives than all forms of cancer combined (Mozaffarian et al. 2015a).

There are several risk factors that contribute to the CVD-associated mortality. These include high cholesterol levels, smoking, sedentary lifestyle, diet, hypertension and atherosclerosis (Falk 2006). Atherosclerosis, in particular, is responsible for nearly 50% of all deaths in developed countries (Tedgui and Mallat 2006b). The underlying pathological basis for atherosclerosis lies in the prolonged inflammation of the arterial wall and the accompanying endothelial dysfunction.

Endothelium dysfunction allows lipoproteins to leak into the sub-endothelial cell layer (intima) and accumulate there (Wang et al. 2012a). After getting oxidized, these trapped low density lipoproteins (LDL) then recruit monocytes into the intima (Fig. 1).

Abbreviations: CVD, cardiovascular disease; VSMC, vascular smooth muscle cell; NO, nitric oxide; CAM, complementary and alternative medicine; V-CAM-1, vascular cell adhesion molecule-1; I-CAM, intercellular adhesion molecule; ECM, extracellular matrix; MMP, matrix metalloproteinase; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase.

* Corresponding author at: Department of Pharmacology and Toxicology, Faculty of Medicine, American University of Beirut, PO Box 11-0236, Beirut, Lebanon. Tel.:+961 350000x4891; fax: +961 343450.

** Corresponding author. Tel.:+971 37136526; fax: 971 37134927.

E-mail addresses: ts1004660@qu.edu.qa (T. Saleh Al-Shehabi), R_iratni@uaeu.ac.ae (R. Iratni), ae81@aub.edu.lb, ali.eid@qu.edu.qa (A.H. Eid).

http://dx.doi.org/10.1016/j.phymed.2015.10.016
0944-7113/

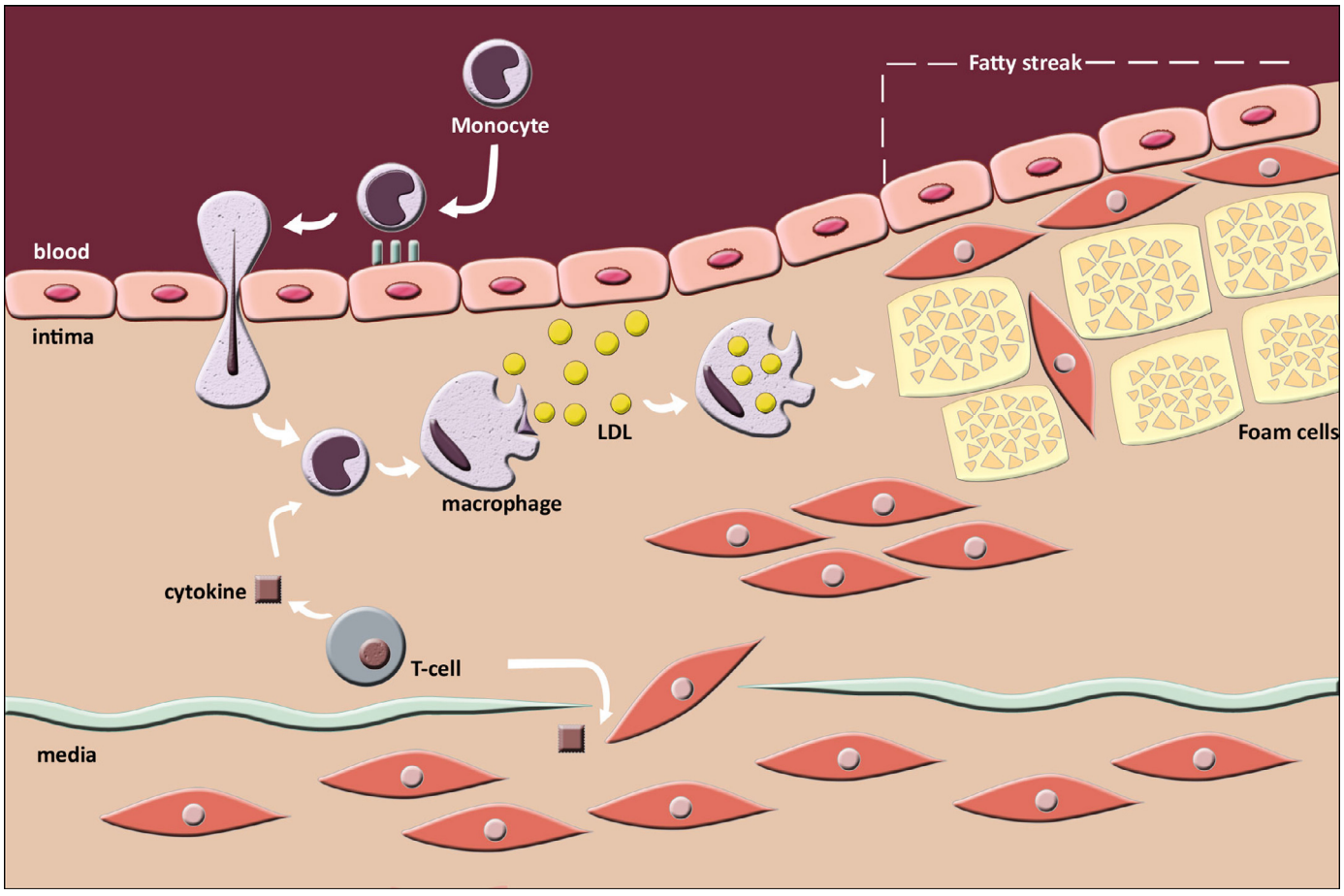

Fig. 1. The interplay between cells and other cues in the onset of atherosclerosis. Monocyte adhesion to the intima is mediated by increased expression of endothelial adhesion molecules. These monocytes then differentiate to macrophages that phagocytose LDL and become "foamy". The different signaling molecules released in the proximity of the intima (e.g. cytokines) act as chemoattractant for tunica media's VSMCs. Upon stimulation, these cells then dedifferentiate and migrate to the intima where they form a lesion that may eventually rupture.

Once monocytes reach the lesion, they proliferate and differentiate into macrophages which then give rise to foam cells after attempting to take up oxidized LDL (Douglas and Channon 2010). The repeated incidence of the production and death of foam cells ends up with the development of a necrotic lipid core within the intima (Douglas and Channon 2010). Adhesion of leukocytes and platelets is then potentiated as a result of the upregulated expression of cell adhesion molecules. As platelets aggregate, they start to release platelet – derived growth factor (PDGF) and transforming growth factor β (TGF-β). Both PDGF and TGF-β, among many other physical and biochemical cues, induce a phenotypic switch in VSMCs, which often results in increased proliferative, migratory and invasive capacities of these cells. Eventually, the behavior of these "now-synthetic" cells leads to narrowing of the arterial lumen and dysregulation of vasotone (Douglas and Channon 2010).

There is an intricate relationship between vasotone and atherosclerosis. For example, under normal physiological conditions, nitric oxide (NO), which is a potent vasodilator, plays a major role in regulating vascular tone. Interestingly, NO also inhibits vascular smooth muscle cell (VSMC) proliferation and migration, decreases platelet adhesion and aggregation, as well as represses inflammation (Doughlas and Channon 2010). All these NO-modulated parameters are key elements in the pathogenesis of atherosclerosis. Indeed, atherosclerotic lesions could more readily develop when endothelial cells lose the ability to produce NO (Doughlas and Channon 2010). This would not be surprising given that atherosclerosis is an inflammatory disease and that NO possesses a potent anti-inflammatory capacity. If left unchecked, increased inflammation can then modulate the behavior of VSMCs by inducing their dedifferentiation. It is worth mentioning that development of atherosclerosis involves many cell types including endothelial cells, neutrophils, lymphocytes, VSMCs and macrophages (Fig. 1) (Chistiakov et al. 2015; Orekhov et al. 2015). However, in the following sections, we will focus our attention on VSMCs and their phenotypic modulation by plants.

Differentiation of VSMCs

VSMCs originate from at least 5 different progenitors during embryonic development. They are responsible for controlling vessel tone and diameter, both of which are key players in the regulation of blood pressure and flow. Differentiated VSMCs proliferate at a very low rate, display a reduced synthetic activity as well as express a distinctive group of contractile proteins, ion channels, and signaling molecules that are essential for cellular function. However, unlike skeletal or cardiac muscle cells, VSMCs maintain a remarkable plasticity that allows them to undergo a phenotypic switch from the differentiated, quiescent and "contractile" phenotype to the proliferative, less differentiated and synthetic state, especially in response to pathological stimuli (Owens 1995; Wang et al. 2012a) (Fig. 2).

Differentiated or contractile VSMCs express unique markers, such as smooth muscle myosin heavy chain (SM-MHC), smooth muscle α-actin, transgelin, high molecular weight caldesmon (h—caldesmon) and calponin, all of which are crucial for vasoregulation. During development, smooth muscle α-actin is the earliest marker expressed by differentiating cells. About 40% of total cell protein is made up