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Review

Oxysterols and symptomatic versus asymptomatic human atherosclerotic plaque

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ABSTRACT

Atherosclerosis is the most common cause of mortality in the Western world, contributing to about 50% of all deaths. Atherosclerosis is characterized by deposition of lipids onto the coronary or carotid arterial wall and formation of an atherosclerotic plaque. Atherosclerotic plaques are categorized into two groups: symptomatic and asymptomatic. The symptomatic plaques tend to be unstable and prone to rupture, and are associated with an increase in ischemic events. Oxysterols, products of cholesterol oxidation, are cytotoxic materials. Their level and type may be associated with plaque formation, development and stability. Oxysterols stimulate the formation of foam cells, advance atherosclerotic plaque progression, and contribute to plaque vulnerability and instability due to their cytotoxicity and their ability to induce cell apoptosis. Studies indicate that plasma 7β-OH CH level can be used as a biomarker for detecting carotid and coronary artery disease. Further clinical studies are needed to evaluate the potential of oxysterols for use as biomarkers for plaque vulnerability and instability. The identification of biomarkers in the blood that can distinguish between symptomatic and asymptomatic plaques remains an unresolved issue.

Contents

1. Introduction

Atherosclerosis is a multifactorial disease and a major cause of morbidity and mortality in the Western world. It is a pathological process characterized by the deposition of lipids and compounds on the inner arterial wall, forming plaques [1–5]. Oxidative stress (OS) is believed to play a significant role in the initiation and progression of atherosclerosis [6]. It is postulated that this is primarily mediated through the oxidation of low-density lipoprotein (Ox-LDL) and other molecules, such as lipids, proteins, and DNA [5,7–9]. The human atherosclerotic plaque is characterized by increased levels of oxidized lipoproteins, such as LDL, HDL, phospholipids, triglycerides [10,11], oxidized cholesterol products (oxysterols) [12], free fatty acids, and fatty acid derivatives [13], as well as proteins such as fibrinogen, apolipoprotein A-I, clusterin, and paraoxonases (PONs) [14,15]. Atherosclerotic plaques can be categorized as stable (asymptomatic) or unstable (symptomatic, vulnerable), the latter being more prone to rupture, characterized by a large lipid core and a thin fibrous cap containing less collagen, and associated with an increase in ischemic events. Lipid-rich plaques are more often associated with symptomatic plaques (Scheme 1) [16,17]. Identifying biomarkers which can differentiate between asymptomatic and symptomatic patients is important for selecting the appropriate treatment.

Oxysterols are present in human and animal tissues, in the blood, and in coronary and carotid plaques [12,18]. They stimulate the formation of foam cells, advance atherosclerotic plaque formation, and contribute to plaque vulnerability [19,20]. Here we review recent findings related to the differences between symptomatic and asymptomatic plaques, the link between

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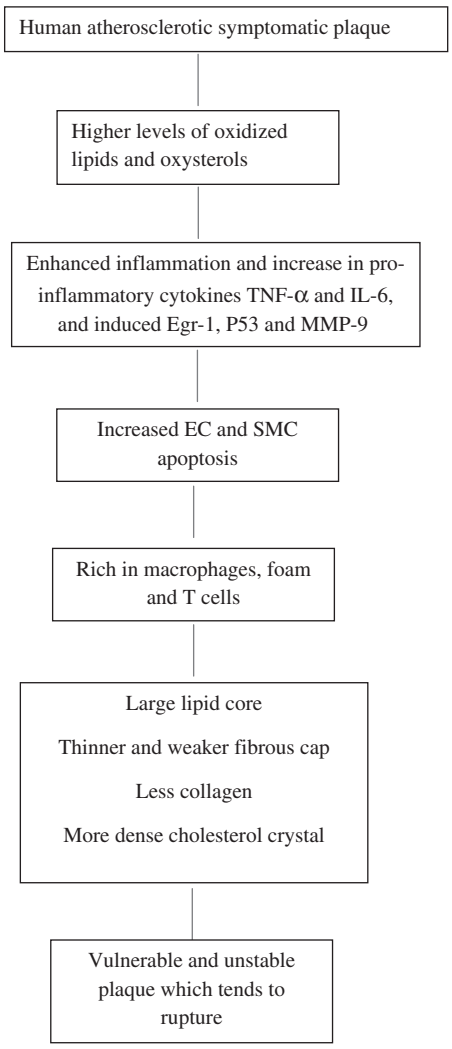

Scheme 1. Properties of atherosclerotic human symptomatic plaque.

oxysterols and plaque vulnerability and stability, and oxysterol content in symptomatic versus asymptomatic patients.

2. Symptomatic and asymptomatic plaques

Atherosclerotic plaques are categorized as either unstable—designated vulnerable to rupture, or stable. Golledge et al. suggested that stable carotid artery plaques are unlikely to produce symptomatic embolization, whereas unstable plaques are at high risk of producing symptomatic embolization and carotid occlusion [17]. Histological studies have shown that carotid plaques taken from symptomatic vs. asymptomatic patients are more inflamed, are rich in macrophages, foam and T cells, and have a thinner and weaker fibrous cap which tends to rupture [17,21]. Similar findings have been obtained in samples of coronary plaques taken postmortem and postatherectomy [22–24]. Noninvasive techniques, such as cardiovascular magnetic resonance (CMR) with 3 T scanners, have also been used to compare symptomatic and asymptomatic atherosclerotic carotid plaques. Grimm et al. found that symptomatic plaques have a higher prevalence of American Heart Association type 6 lesions (AHA-LT6) compared to asymptomatic plaques, in which AHA-LT3 and AHA-LT7 are more frequent. In the symptomatic group, a ruptured fibrous cap and necrotic core were found more frequently and the prevalence of hemorrhage (intraplaque hemorrhage and combined juxtaluminal hemorrhage/thrombus) was significantly higher than among the asymptomatic group [25]. Moreover, Mughal et al. reported that patients with more frequent neurological symptoms have more dense cholesterol-crystal formations within the necrotic core of the plaque. Cholesterol saturation has been shown to be a potentially major trigger for cholesterol crystallization, which can lead to volume expansion and plaque rupture [26].

Despite the differences between symptomatic and asymptomatic plaques, there is significant overlap among some of these plaques' features which limits the use of solely the CMR variable to completely separate between symptomatic and asymptomatic subjects. Identification of new reliable biomarkers in the blood which can provide information on plaque stability is important and could complement information collected from the various imaging techniques [27]. To date, there are no blood biomarkers available for clinical use to assess stability and status of carotid and coronary plaques.

Hermus et al. published a comprehensive review of serum biomarkers associated with plaque stability. Those shown to be highly associated with the presence of vulnerable carotid artery plaques are mainly markers of inflammation and proteolysis, such as the highly sensitive C-reactive protein, interleukin (IL) 6, matrix metalloproteinases (MMPs) 9 and 2, and tissue inhibitors of metalloproteinases (TIMPs) 1 and 2 [28]. This noninvasive method of identifying high-risk patients might serve as a promising tool in the future to select patients for carotid surgery but to date, none of these serum biomarkers have been designated for routine clinical use.

Serum markers of lipid metabolism and abnormal lipoprotein profiles are important predictors of atherosclerosis. For example, circulating levels of Ox-LDL have become a useful biochemical risk marker for coronary heart disease [29].

Tavori et al. extracted a lipid fraction of human carotid plaque which had the capacity to facilitate atherogenesis by enhancing LDL and macrophage oxidation and inhibiting HDL-mediated cholesterol efflux from macrophages, inducing macrophage foam-cell formation, and inhibiting the HDL-associated antioxidant enzyme PON1. Structural elucidation revealed the major atherogenic element in the plaque extract to be linoleic acid hydroperoxide (LA-OOH), which is derived from lipid peroxidation of linoleic acid [30]. Elad et al. showed significantly higher LA-OOH levels in plaques of symptomatic versus asymptomatic patients; in addition, LA-OOH level in the plaque was inversely correlated with HDL level in the circulation and HDL PON1 activity, and directly correlated to hemoglobin A1c level. Thus, based on HDL level and PON1 activity in the blood, it might be possible to predict the level of LA-OOH in the plaque and consequently, the plaque's status [31].

3. Oxysterols in symptomatic versus asymptomatic human plaques

Oxysterols are products of cholesterol oxidation that are present in human tissue and fluids, including plasma, lipoproteins and coronary and carotid plaques [12,18]. Oxysterols can be synthesized endogenously via enzymatic or radical-mediated oxidation, or they can be derived from food [19,32]. Enzymatic oxidation occurs mainly in the liver and steroidogenic tissues. 7α-Hydroxylated cholesterol (7α-OH CH), synthesized in the liver by the microsomal enzyme cholesterol 7α-hydroxylase, is traditionally considered the first and rate-limiting step in bile acid synthesis. 27-Hydroxylated cholesterol (27-OH CH) is synthesized by sterol 27-hydroxylase in the liver; in addition to its role in hepatic bile acid synthesis, sterol 27-hydroxylase is involved in the elimination of cholesterol from extrahepatic cells [19,33,34].