International Journal of Cardiology 170 (2014) 278–285

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Review

Links between allergy and cardiovascular or hemostatic system

Daniel P. Potaczek *

Institute of Laboratory Medicine, Philipps-Universität Marburg, Marburg, Germany
John Paul II Hospital, Krakow, Poland

ARTICLE INFO

Article history:
Received 5 February 2013
Received in revised form 3 November 2013
Accepted 17 November 2013
Available online 23 November 2013

Keywords:
Allergy
Atherosclerosis
Coagulation
Immunoglobulin E
FCER1A
Thrombosis

ABSTRACT

In addition to a well-known immunologic background of atherosclerosis and influences of inflammation on arterial and venous thrombosis, there is growing evidence for the presence of links between allergy and vascular or thrombotic disorders. In this interpretative review, five pretty well-documented areas of such overlap are described and discussed, including: (1) links between atherosclerosis and immunoglobulin E or atopy, (2) mutual effects of blood lipids and allergy, (3) influence of atopy and related disorders on venous thromboembolism, (4) the role of platelets in allergic diseases, and (5) the functions of protein C system in atopic disorders.

1. Introduction

The inflammatory background of atherosclerosis has been widely recognized. In addition to that, there is growing evidence that also an allergic type of inflammation plays a role in atherosclerosis-related diseases. Furthermore, clinical and functional links between allergy and hemostasis have been also identified recently. This interpretative review is focused on several quite well-documented areas of the suggested overlap between allergy and cardiovascular and/or hemostatic systems.

2. Allergy, immunoglobulin E and atherosclerosis

By the 90s of the 20th century, atherosclerosis had been considered to predominantly result from the accumulation of cholesterol in the atherosclerotic plaque with some additional influence of growth factors and smooth muscle proliferation. In the 1990s, based on laboratory and epidemiologic findings, the prominent role of inflammation in the pathogenesis of atherosclerosis became appreciated [1–4]. In addition to that, over the past decades some studies of varying types have suggested a possibility that links including those causal may exist also between a special kind of inflammatory process, an allergic inflammation, and atherosclerosis and related disorders.

In 1988, Szczeklik at al. [5] reported that 3–5 days after myocardial infarction (MI), there is a rise in the total levels of serum immunoglobulin E (IgE), an antibody mediating atopic reaction, with its peak concentrations reached on the 7th day of the follow-up. This original finding has been subsequently corroborated by Korkmaz et al. [6] and Erdogan et al. [7] who replicated this observation in MI and extended it to the patients with unstable angina pectoris. Finally, a recent paper by Wang et al. [8] described higher total serum IgE levels in subjects with coronary heart disease (CHD) when compared to unaffected subjects; the highest IgE levels were detected in MI subjects, followed by patients with unstable and then those with stable angina pectoris. In addition to that, an increase in total serum IgE levels has also been reported after coronary artery bypass grafting [9,10] or coronary artery stenting [11], further suggesting it to be a specific reaction to the damage of coronary arteries or myocardium. Although the increase in serum IgE levels seem not to be unique for the tissue damage related to MI, angina pectoris or surgery of coronary arteries [12], the elevation observed in case of coronary artery bypass grafting, complicated or not by perioperative MI, was reported to be higher when compared to that observed in case of other major injuries, such as thoracic or abdominal surgery [9,10], which suggests that this effect is at least partly heart-specific. A mechanism potentially underlying the observed associations might have been provided by a very interesting, although unfortunately rather unnoticed, paper by Marciniak-Sroka et al. [13]. In patients with CHD undergoing coronary artery bypass grafting, they observed a postoperative decrease in the proportion of the low-affinity IgE receptor (CD23)-positive B cells (i.e. those having a membrane form of CD23) and a simultaneous increase in plasma levels of soluble CD23 [13]. Both these changes preceded an elevation in plasma IgE levels [13]. These observations seem to perfectly fit to the mechanism by which a balance between membrane and soluble CD23 has been described to regulate serum IgE synthesis by B cells, with the negative effect of the former and a positive effect of the latter [14–16].

* Institute of Laboratory Medicine, Philipps-Universität Marburg, Hans-Meerwein-Straße 2, 35043 Marburg, Germany. Tel.: +49 6421 28 66085.
E-mail address: potaczek@staff.uni-marburg.de.

0167-5273/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2013.11.029

Another portion of evidence for the presence of links between allergy and atherosclerosis comes from the literature on the so-called "Kounis syndrome" [17–20]. Kounis syndrome can be defined by the concurrence of allergic reaction, induced by a variety of drugs and environmental exposures, such as urticaria, asthma, food allergy, mastocytosis and others, with coronary syndrome ("allergic angina"), which can further progress to MI ("allergic MI") [21–24]. The central role in the mechanism underlying the Kounis syndrome is played by mast cells, degranulation of which leads to the release of mediators of allergic inflammation, including histamine, proteases (tryptase and chymase), leukotrienes, tromboxanes or platelet activation factor. These mediators are capable of inducing coronary artery spasm, plaque rupture and/or thrombosis, leading to a clinical picture of the Kounis syndrome (Fig. 1) [17,18,25,26]. It has been proposed that the Kounis syndrome may represent a final mast cell-related trigger pathway, which could be shared between allergic and non-allergic coronary syndromes [17,18,26]. This seems to be supported by several lines of evidence. First, elevated levels of the mast cell-released inflammatory mediators such as tromboxanes, leukotrienes [27], histamine [28] or tryptase [29] have been detected in the blood of patients with non-allergic acute coronary syndromes. Second, an excess of (degranulated) mast cells has been found in coronary arteries, atheromas or atherosclerotic plaque rupture areas of patients after acute coronary syndrome or MI [30–34]. Third, experiments conducted in hamsters demonstrated that pharmacologic mast cell stabilization in lungs is capable of preventing inflammation-induced thrombosis in the systemic circulation [35]. The role of mast cells is not only limited to triggering atherothrombotic syndromes, also under the paradigm of Kounis syndrome, but they actively contribute to the preceding development of atherosclerotic plaque, the process of its destabilization and subsequent erosion or rupture as well (Fig. 1) [34,36–38].

In addition to mast cells, a contribution to the pathogenesis of atherosclerosis by (an interaction with) allergy-related mechanisms has been shown also for other types of immune cells, such as monocytes and their derivatives, macrophages. Through accumulation of oxidized or otherwise modified low-density lipoproteins (LDLs) macrophages give rise to so-called foam cells, which initiates the formation of fatty streaks, a crucial step in the development of atheromatous plaques

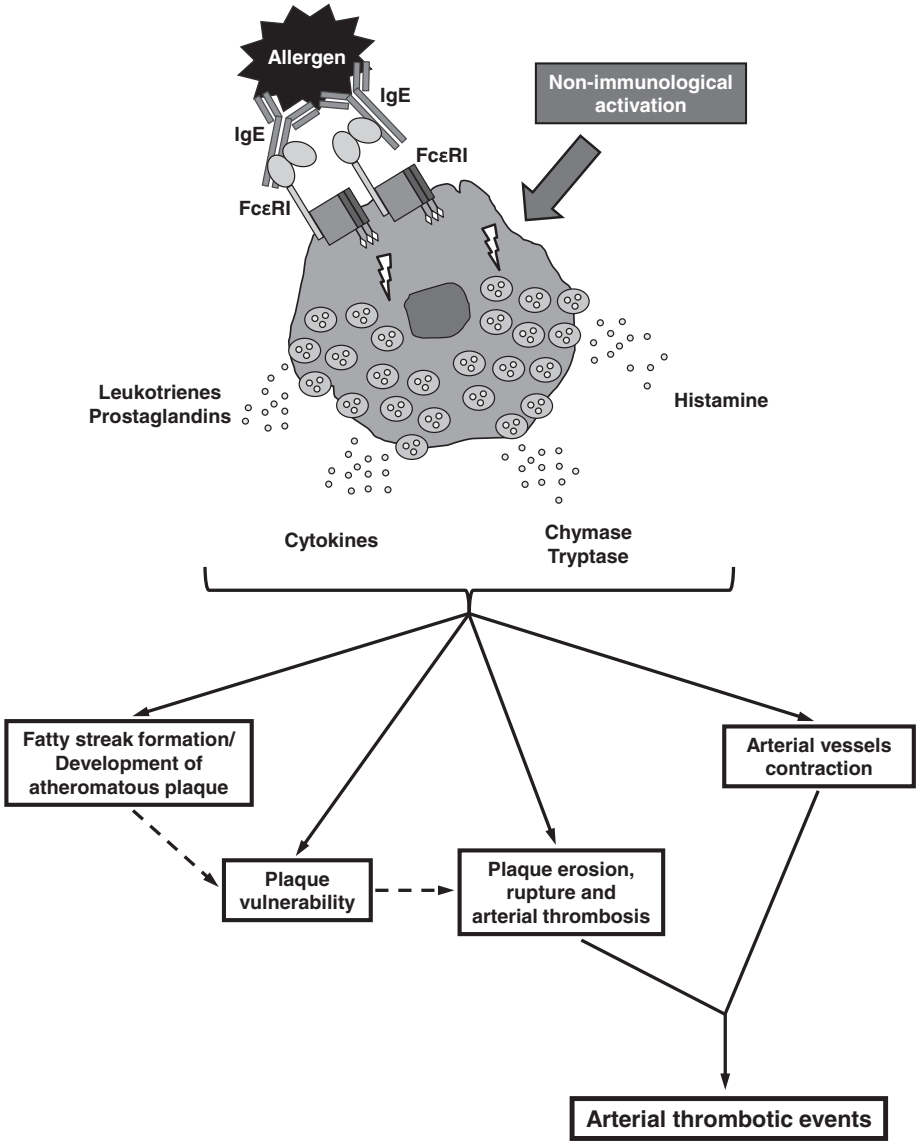

Fig. 1. Are mast cells the major allergy-related cells involved in the development of atherosclerosis and its resulting clinical events? Activated mast cells degranulate to secrete multiple biochemical factors contributing to atherosclerotic plaque formation, instability, erosion or rupture, and subsequent thrombosis, which is reflected by a clinical picture of arterial thrombotic events, e.g. acute coronary syndrome/myocardial infarction, also under the paradigm of Kounis syndrome. IgE denotes immunoglobulin E; FcεRI, the high-affinity IgE receptor.