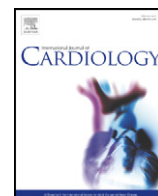




Contents lists available at ScienceDirect

International Journal of Cardiology

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

Review

Links between allergy and cardiovascular or hemostatic system

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ARTICLE INFO

Article history:

Received 5 February 2013
 Received in revised form 3 November 2013
 Accepted 17 November 2013
 Available online xxxx

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.

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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 et 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].

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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

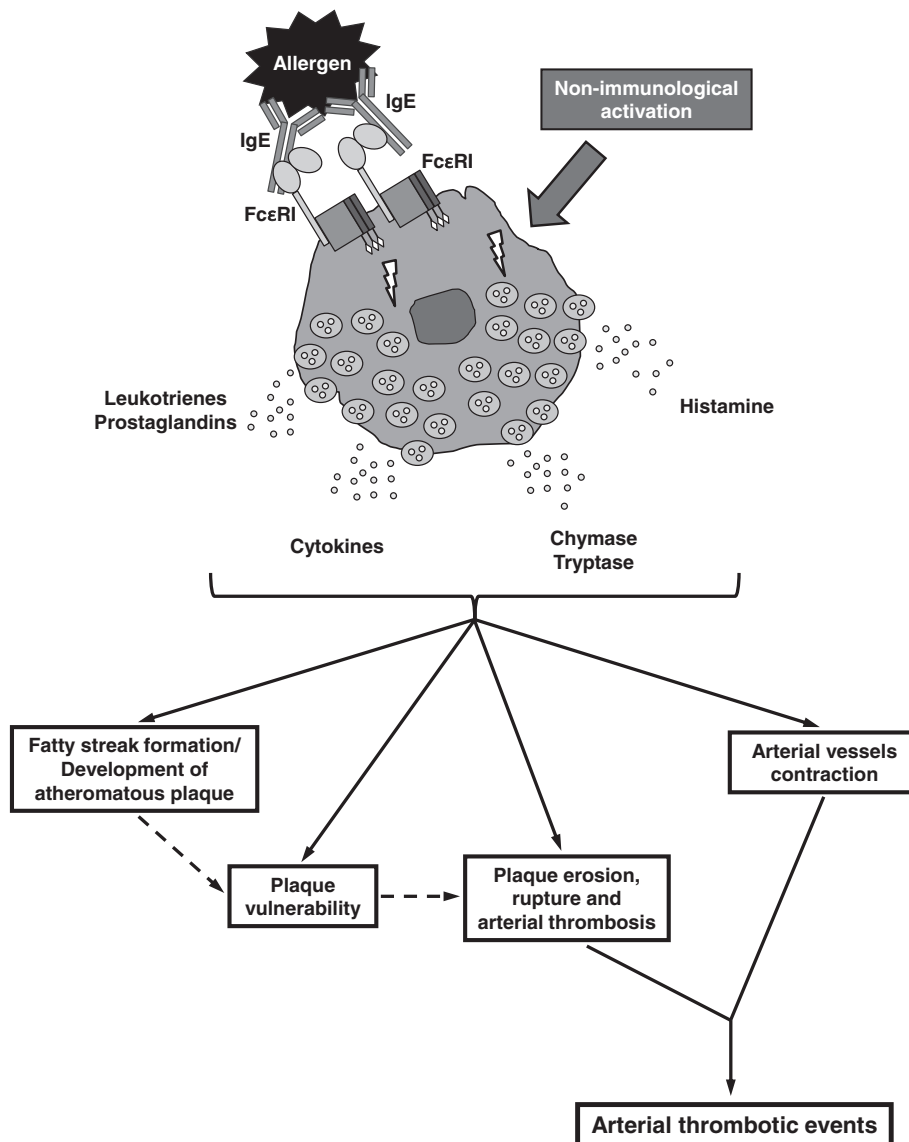


Fig. 1. Are mast cells the major allergy-related cells involved in the development of atherosclerosis and its resulting clinical events? Activated mast cells degranulate to secrete multiple biochemical factors contributing to atherosclerotic plaque formation, instability, erosion or rupture, and subsequent 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.

[39,40]. Interestingly, experiments in rats demonstrated that mast cells could affect the formation of foam cells from macrophages [41,42]. It was shown that granules exocytosed upon IgE-dependent activation of mast cells bind LDL particles and transport them to macrophages with resulting formation of foam cells [41,42]. Only very recently, a crucial role of the high-affinity IgE receptor in IgE-mediated activation of macrophages and thus the development of atherosclerotic lesions has been demonstrated [8,43]. Such activation of macrophages was found to require interaction between the high-affinity IgE receptor and toll-like receptor 4 [8,43]. Interestingly, the importance of the TLRs system in the pathogenesis of allergic disorders [44–47], especially in combination with the high-affinity IgE receptor has been demonstrated [48,49].

Further evidence for a link between allergy and atherosclerosis comes from epidemiologic studies. Already in 1980s, some relationships between IgE and cardiovascular diseases were noticed [50,51]. These initial observations have been very recently much expanded by a large study on the association between atopy measures and previous MI conducted in the United States [52]. Subjects with a history of MI were found to have lower specific IgE levels and were less likely to be atopic; from the other perspective, atopy or higher specific IgE concentrations were associated with a smaller chance of having MI in the past [52]. Most intriguing results come, however, from the large population-based genetic studies of the genome-wide association (GWA) type. A GWA study conducted by Benjamin et al. [53] in the Framingham Offspring sample was oriented on several selected biomarkers, including those related to the cardiovascular system. Interestingly, a single-nucleotide polymorphism (SNP) most strongly associated with monocyte chemoattractant protein-1 (MCP-1), rs2494250, was located just downstream of *FCER1A*, a gene encoding the α -subunit of the high-affinity IgE receptor that mediates IgE-dependent allergic reaction (Fig. 2) [53]. MCP-1 stimulates the recruitment of monocytes into the area where an atheromatous plaque is being formed, thus playing an important role in the development of atherosclerosis [54,55]. *FCER1A* and its encompassing chromosome 1q23 locus neighborhood have been (previously) associated with total serum IgE levels in genetic linkage [56–58], candidate gene [59–65] and GWA studies (Fig. 2)

[16,66–68]. The latter demonstrated *FCER1A* to be a major regulator of total serum IgE concentrations in the general population [16,66,68]. The association between 1q23 locus and MCP-1 levels has been subsequently replicated by two larger GWA studies on inflammatory markers [69,70]. Studies by Schnabel et al. [69] and Naitza et al. [70] demonstrated the highest association signal for MCP-1 levels to be located at SNP rs12075 within *DARC*, a gene located only about 80 kbp upstream of *FCER1A* (Fig. 2). Although it seems most probable that this association is functionally underlain by the effect of Duffy antigen/receptor for chemokines, a *DARC* expression protein product, on MCP-1 concentrations [69], a close proximity of *FCER1A* and location of the association signal downstream of *FCER1A* in the original study by Benjamin et al. [53] might also suggest that this gene could be partly functionally contributable. In addition, association signals from *DARC* have been also observed in one of the GWA studies on total serum IgE levels, which identified *FCER1A* to be their major susceptibility locus [68]. However, the association between *DARC* genetic variability and total serum IgE observed in this study was not resistant to adjustment for top IgE-associated *FCER1A* SNPs, suggesting it to result from high linkage disequilibrium between *DARC* and *FCER1A* genetic variants [68]. Interestingly, plasma concentrations of C-reactive protein (CRP), an inflammatory marker related to atherosclerosis and cardiovascular risk [71,72], have been shown to be associated with *FCER1A* transcript levels in a GWA expression study of monocytes [73]. In addition, an association signal for serum CRP concentrations has been found for a SNP rs3845624 located halfway between *DARC* and *FCER1A* (Fig. 2), which was independent of the major CRP susceptibility locus at *CRP*, a gene encoding CRP, located approximately 405 kbp downstream of *FCER1A* [70].

3. Blood lipids and allergy

FCER1A genetic variability or expression has not only been associated with inflammatory markers involved in the pathogenesis of cardiovascular disorders but their effects on the regulation of blood lipid metabolism have also been demonstrated [74,75]. A very interesting study by Inouye et al. [74] made simultaneous use of three kinds of

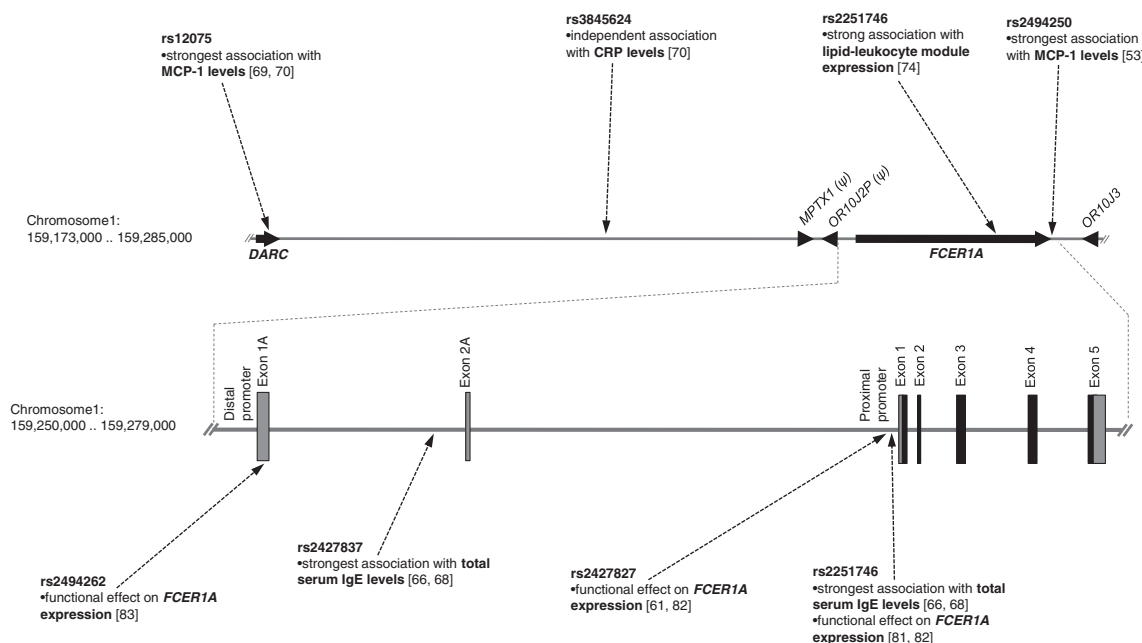


Fig. 2. Polymorphisms in *FCER1A*, a gene encoding for the α -chain of the high-affinity immunoglobulin E (IgE) receptor, and its neighborhood in chromosome 1q23 associated in genome-wide association studies (GWAS) with concentrations of blood cardiovascular markers or lipids (in the upper scheme, showing *FCER1A* and the surrounding region in general) and those associated in GWAS with total serum IgE levels or functionally affecting *FCER1A* expression (in the lower scheme, presenting *FCER1A* itself in more detail). References are given in square brackets. Base pair numbering corresponds to that in NCBI reference sequence of human chromosome 1 (GRCh37.p13 Primary Assembly, http://www.ncbi.nlm.nih.gov/nucleotide/NC_000001.10), while “rs numbers” of the polymorphism are in line with those currently (October 27, 2013) available at NCBI dbSNP database (<http://www.ncbi.nlm.nih.gov/snp/>). MCP-1 denotes monocyte chemoattractant protein-1; CRP, C-reactive protein; *DARC*, a gene encoding Duffy antigen/receptor for chemokines; ψ , pseudogene.

the data: blood lipid level measurements, genome-wide expression data of total blood extracts and genome-wide polymorphic variation profiles. Based on the correlations between blood lipids and genome-wide gene expression, they identified novel, previously uncharacterized, potentially tissue-specific gene network, a lipid–leukocyte (LL) module to be associated with blood lipid levels [74]. The LL module was found to harbor several genes crucial for inflammation and allergy, such as *FCER1A*, *MS4A2* (*FCER1B*, encoding β -chain of the high-affinity IgE receptor), *GATA2* (encoding transcription factor GATA2), *CPA3* (encoding mast cell carboxypeptidase A), *HDC* (encoding histidine decarboxylase, an important enzyme in the synthesis of histamine) and others, strongly suggesting the prominent role of basophils and mast cells in lipid metabolism [74]. Polymorphisms in *MS4A2* have been previously shown to be associated with serum IgE, atopy and allergic disorders [63,76–78], while *GATA2* belongs to a family of transcription factors of proven regulatory role in allergy-related cells [66,79,80]. Most interestingly however, *FCER1A* SNP rs2251746 belonging, together with rs2427837, to a tagging bin most strongly associated with total serum IgE levels in two population-based GWA studies [16,66,68], was strongly associated with the expression of the LL module (Fig. 2) [74]. SNP rs2251746, which has been also demonstrated to affect *FCER1A* proximal promoter activity by altering GATA1 transcription factor binding [81], is the first of the three functional *FCER1A* SNPs identified so far, including also rs2427827, another *FCER1A* proximal promoter SNP, and rs2494262 (Fig. 2) [16,61,63,81–84]. Additively with rs2427827, SNP rs2251746 influences expression of the high-affinity IgE receptor on human basophils [82]. Thus, the results by Inouye and colleagues [74] seem not only to demonstrate the potential influence of basophils and/or mast cells on blood lipid metabolism but also suggest that functional genetic variants regulating IgE levels, such as those in *FCER1A*, might have an effect on lipid turnover. Recent advances in genetic studies on serum IgE levels [16] and functional investigations of *FCER1A* polymorphisms are described elsewhere [16,63].

Another line of evidence for the relationship between blood lipids and atopy and/or allergic disorders also exists that derives from several recent epidemiological studies. One study conducted in United States analyzed the effect of serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and non-HDL-C (i.e. TC minus HDL-C) on asthma and atopy [85,86]. Serum TC and non-HDL-C were both found to be inversely correlated with asthma, although this association was mostly driven by a subgroup of Mexican Americans [85]. In the whole population, an increase in TC and non-HDL-C were associated with the elevated risk of atopic sensitization determined based on the specific serum IgE testing [86]. However, the associations observed for TC or non-HDL-C, and also for HDL-C, were opposite when a subgroup of non-Hispanic Blacks was analyzed separately [86]. In a Chinese study in turn, lower HDL-C and higher LDL cholesterol (LDL-C) were associated with an increased risk of atopic sensitization, especially in men [87]. In addition, a positive correlation of HDL-C with allergic rhinitis (AR) or atopic dermatitis (AD) was found in a German study [88]. Relationships between blood lipids (lipoproteins) or their protein components, apolipoproteins, have also been reported in pediatric populations [89,90]. Japanese children with higher TC or LDL-C had a greater chance of having allergic sensitization [89]. In German children, high apolipoprotein A-I, a major protein component of HDL, was associated with the manifestation of asthma and atopy [90]. It is generally difficult to speculate about the causality based on epidemiological studies of a cross-sectional [85–87,89,90] or nested case–control type [88], such as those described above. However, results from studies of the longitudinal design seem to suggest that it is lipid metabolism that affects the development of atopy and allergic disorders [91,92]. Lower serum TC in infancy and childhood was shown in a Finnish study to be associated with a higher chance of subsequent manifestations of allergy in childhood and adolescence, such as an occurrence of allergic symptoms, atopic sensitization and increased total serum IgE [91]. In turn, a study from Cyprus demonstrated that lower HDL-C in childhood was

associated with an increased risk of asthma in adolescence [92]. In summary, several independent groups demonstrated the relationship between serum lipids and atopic sensitization and/or allergic disorders, although the data were to some extent conflicting, also with regard to the direction of the effect. The mechanisms of interactions between blood lipid metabolism and atopic sensitization/allergic disorders, potentially underlying observed epidemiological associations, are under investigation also in mouse models [93–95].

4. Allergic diseases and venous thromboembolism

It has been suggested that some similarities in the pathogenesis may exist between venous thrombosis and arterial thrombosis or atherosclerosis, such as shared risk factors [96,97]. For example, inflammation that plays a crucial role in atherosclerosis [1–4,39] could be also an important factor in thrombotic disorders of the veins, i.e. venous thromboembolism (VTE), a clinical syndrome comprising deep-vein thrombosis (DVT) and/or pulmonary embolism (PE). Indeed, several studies have demonstrated elevated levels of inflammatory markers, such as IL-6 or CRP and others, to bring an increased risk of VTE, although it remained unclear, at least for some of those markers e.g. CRP, if they are only VTE predictors or they also functionally contribute to its development [98–101]. Considering the presence of the links between atherosclerosis and allergy described in the previous sections, it might thus be speculated that the relationship between allergic inflammation and VTE also exists. Epidemiologic and/or functional support for such hypothesis seems to be provided by the results of several studies briefly outlined below, although some of the data are conflicting.

The study by Nastalek et al. [102] comparatively analyzed fibrin clot properties in AD patients and healthy controls. Interestingly, it was demonstrated that AD is associated with reduced clot permeability, prolonged fibrinolysis time, faster fibrin polymerization, higher thrombotic mass and thicker fibers [102], i.e. features corresponding to a prothrombotic tendency [103,104]. Based on these findings, it might have been suggested that the presence of allergic inflammation could be a risk factor of arterial or venous thrombosis. This speculation was subjected to verification in a subsequent study, which analyzed in a case–control setting whether having allergic disorders is associated with an increased risk of VTE [105]. Indeed, atopic sensitization and allergic rhinitis were found to be more common among VTE subjects when compared to healthy controls [105]. Furthermore, VTE subjects with increased allergic burden, i.e. those having allergic rhinitis, atopic dermatitis or asthma, had more frequently a positive family history of VTE and a higher incidence of distal VTE when compared to the remainders [105]. Most of the distal DVT in subjects with allergic diseases occurred in the pollen spring–summer season and was accompanied by the presence of atopic sensitization to timothy grass [105]. Only proximal DVT was less common in subjects having allergic diseases [105]. The second part of that study sought to find a functional background for the observation of the increased VTE risk in subjects having allergic inflammation burden. Considering previous reports on the elevated levels of plasminogen activator inhibitor-1 (PAI-1) in allergic subjects and a positive correlation of PAI-1 with clot lysis time and VTE risk [106,107], it was speculated that the increased chance of having VTE observed in allergic subjects might have been, at least partly, underlain by PAI-1-mediated impairment of fibrinolysis. Indeed, this hypothesis seemed to be confirmed as VTE patients having allergic diseases were found to have higher PAI-1 levels and longer clot lysis time when compared to the rest of the subjects with VTE [105]. Interestingly, it has been reported that basophils and mast cells, crucial players in IgE-mediated allergy, synthesize PAI-1 [108]. In addition, a positive correlation between PAI-1 and serum total IgE levels was found [105], and a genome-wide linkage analysis had previously revealed the region of chromosome 7 containing the PAI-1 gene to be associated with total IgE levels [109]. Furthermore, genetic variability of PAI-1 itself had been

reported to be associated with (allergic) asthma and serum total IgE [106,110].

That asthma may increase the risk of VTE was first suggested in 1999 by Farmer et al. [111], based on their epidemiologic findings in primary care settings, although even authors themselves considered their original observations as “unexpected”. Since then, some more investigators have reported a similar effect, including Majoor and colleagues [112], who very recently presented the results on first asthma-focused study of VTE risk. In their study, Majoor et al. [112] sought to find if asthma and its sub-phenotypes determined with regard to disease severity might affect the risk of VTE and its components, DVT or PE. Having adjusted for most important confounders, in the final regression models, Majoor et al. [112] found that PE was independently predicted only by severe sub-phenotype of asthma and oral corticosteroid use (a clinical feature also related to asthma severity), whereas DVT incidence was not affected by asthma. The findings reported by Majoor et al. [112] seem to be in line with the results of the recent two studies conducted in primary care settings [113,114]. Huerta et al. [113] reported that asthma increased the risk of both, DVT and PE, although the effect observed for DVT was only marginally significant and weaker than in the case of PE. Also Cazzola and coworkers [114] found asthmatics to have a higher chance of PE, while the effect on DVT was not studied. The mechanisms underlying the intriguing association of asthma with VTE remain unclear, although some potential candidates can be suggested based on previous findings of several prothrombotic features reported in asthma, such as activation of coagulation, enhanced platelet activation, or impaired activities of protein C anticoagulant system and fibrinolysis, as described in more details elsewhere [115]. In addition, also chronic obstructive pulmonary disease is a moderate risk factor of VTE [116], which may suggest that not only allergic inflammation burden but also chronic lung inflammation itself might contribute to the development of VTE. Interestingly, *post hoc* analyses very recently conducted by Majoor and Bel in their cohort to check for a putative effect of atopic sensitization on VTE risk in subjects with asthma showed no difference in chance of DVT or PE between atopic and non-atopic asthmatics, suggesting that it is rather a (long-lasting) lung inflammatory process than atopic burden to be a major VTE susceptibility factor in chronic lower respiratory tract disease [117,118].

5. Platelet activation in allergic disorders

In addition to a well-established role of platelets in hemostasis, an increased activation level of circulating blood platelets in patients suffering from allergic disorders may play a role in the development and the course of allergic inflammation [119–121]. A number of potent mediators of vasodilatation and enhanced vascular permeability are secreted by blood platelets, which together with platelet-released substances chemoattracting the immune cells promote the development of allergic inflammation [119–121].

Increased platelet activation has been observed in AD [120–122] with elevated plasma levels of platelet activation blood markers in AD patients reported by several independent groups [123–128]. Kasperska-Zajac et al. [123] observed increased plasma β -thromboglobulin (β -TG) and platelet factor-4 (PF4) levels in AD patients when compared to healthy controls. This finding was subsequently corroborated by other studies, including those by Tamagawa-Mineoka et al. [124] and Koczy-Baron et al. [128], and finally confirmed in the study by Nastalek et al. [127], in which the analyses in multiple regression models covering for possible confounders were conducted in a relatively large number of subjects. Another study by Kasperska-Zajac et al. [125] reported plasma levels of β -TG and PF4 to be affected also by AD activity, being higher in AD patients in the active phase of the disease when compared to those in remission. In addition, elevated expression of PF4 has been observed also in a mouse model of AD [129]. In another work, Tamagawa-Mineoka and colleagues [126] found selectin P (P-sel) and platelet-derived microparticles (PDMs), further circulating blood markers of

platelet activation, to be elevated in patients with AD. The same study reported that 2–3 weeks of conventional AD therapy, including topical steroids and oral antihistaminics, decreases plasma levels of P-sel and PDMs [126]. Interestingly, in a mouse model, P-sel and platelets themselves were found to play an important role in a late phase of immediate hypersensitivity reaction in skin [130]. Finally, Nastalek et al. [127] observed that being an AD patient is also associated with the increase in plasma levels of further markers of platelet activation, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor. An independent study by Koczy-Baron et al. [128] also found VEGF to be elevated in plasma of AD patients, although no association with AD has been observed for soluble VEGF receptors. Increased production of VEGF was also noted in AD lesions when compared to that in healthy skin samples [131]. Conflicting data have been reported with regard to the relationship between AD severity and plasma platelet activation level. Tamagawa-Mineoka et al. [124,126] observed a correlation between the severity of AD as measured by SCORAD ranking system [132,133] and platelet activation expressed by β -TG, PF4, P-sel or PDMs. This was not, however, confirmed in the study by Nastalek et al. [127], in which β -TG, PF4, VEGF or PDGF, i.e. all four platelet activation markers under investigation, turned out not to be associated with dichotomized SCORAD. This discrepancy could be potentially attributed to the differences in the distribution of AD severity between the studies by Nastalek et al. [127] and Tamagawa-Mineoka [124,126]. Very recently, Koczy-Baron and colleagues [128] found no correlation between VEGF and EASI, another AD severity scoring system [133].

Another allergic disorder in the pathogenesis of which blood platelets have been implicated is asthma. Involvement of platelets in the local allergic inflammation of the lower airways has been demonstrated in mice [134–137]. Some studies in human suggested in turn that circulating platelets are systemically activated in asthmatic patients [137–139], although the data were conflicting [127,139,140]. Pitchford et al. [137] reported the presence of platelet-leukocyte aggregates in the circulating blood of several sensitized asthmatics during late phase of allergen-induced asthmatic response. Yamamoto and coworkers [138], who studied two platelet activation markers, β -TG and PF4, found their elevated concentrations in symptomatic asthmatics when compared to healthy controls; however, at the same time, they observed no differences in β -TG and PF4 levels when asymptomatic asthma patients were compared to normal controls. The study by Kowal et al. [139] analyzed platelet activation levels in asthmatics having atopic sensitization and healthy controls. While no baseline differences versus the controls were observed for β -TG, single (only early asthmatic) but not dual (early and late asthmatic) responders had elevated PF4 when compared to control subjects, and P-sel was higher than in controls only in dual but not single responders [139]. Furthermore, all three plasma markers were elevated at the time of early asthmatic response in single and dual responders, and at the time of late asthmatic response in dual responders only [139]. The results by Kowal et al. [139] are very interesting but it may be difficult to clearly determine whether asthma, atopic sensitization or both were contributable since all the cases in the study were asthmatics and atopics at the same time. In another work, Kasperska-Zajac and Rogala [140] observed no difference in β -TG or PF4 between persistent allergic rhinitis (AR) patients with and without asthma. Finally, in the study on AD patients, Nastalek et al. [127] found no effect of concomitant asthma on β -TG, PF4, VEGF or PDGF, four plasma platelet activation markers under investigation. The fact that no association between AD-accompanying asthma and platelet activation markers was observed in this study [127], even though such association had been found in symptomatic asthmatics by Yamamoto et al. [138], might be potentially explained by the fact that subjects with severe asthma were excluded from the study by Nastalek et al. [127]. In the same study however, AD-accompanying food allergy was found to be associated with increased levels of β -TG, VEGF and PDGF; furthermore, plasma β -TG, PF4, VEGF and PDGF concentrations were strongly elevated in AD

patients with concomitant AR when compared to the reminders [127]. This observation of an association between AR-accompanying AD and plasma platelet activation markers is intriguing because no effect of persistent or seasonal AR on β -TG and PF4 levels was reported by another two studies [140,141]. It could be thus speculated that AD-related allergic inflammation is potent enough to increase platelet activation in the upper respiratory tract in patients with accompanying AR, the effect observed in the study by Nastalek et al. [127]. Other views on the involvement of platelets in allergy and related disorders can be found elsewhere [119–122].

6. Protein C system and allergic disorders

Protein C (PC) system, comprising thrombomodulin, PC and protein S (PS), forms together with antithrombin and tissue factor pathway inhibitor a triad of the most important natural anticoagulants [142–144]. In addition to their central role as regulators of coagulation, components of the PC system seem to have important anti-inflammatory functions [144–146]. Several studies conducted in mouse models and in human demonstrated the involvement of the PC system in the pathophysiology of (allergic) inflammation of the airways and asthma.

Anti-inflammatory effects of early-administered recombinant human activated PC were demonstrated in a murine model of pneumococcal pneumonia [147]. In turn, in the mouse model of asthma a decreased activated PC:thrombin ratio in bronchoalveolar lavage fluid (BALF) was observed [148]. Furthermore, administration of inhaled activated PC [142,148] or transgenic overexpression of human activated PC [149] was shown to suppress allergic immune responses in mouse models of asthma.

Studies in human showed that being asthmatic is associated with lower activated PC:thrombin and activated PC:PC ratios [150] or lower PC activity [151] in induced sputum. In addition, activated PC levels in BALF obtained from asthmatic subjects were observed to decrease 4 h after local stimulation of the lung tissue with an allergen [152]. Surprisingly, AD-accompanying asthma was observed to be associated with increased plasma levels of PC and PS in the study by Undas et al. [153]. Considering the attenuating effect of externally administered or overexpressed activated PC on allergic inflammation of the lung tissue observed in murine models of asthma [142,148,149], and the fact that severe asthma cases had been excluded from the study by Undas et al. [153], it might be speculated that elevated plasma PC and PS found in mild-to-moderate asthma patients represented a long-term, compensatory mechanism reducing the intensity of allergic inflammation in lungs and thus preventing the progression to severe asthma [153]. The mechanism of the involvement of the PC system in the inflammation and allergic inflammation characteristic for asthma are described in more details elsewhere [115,142,144].

7. Conclusions and perspectives

In this review, the evidence for the presence of the links between allergy and atherosclerosis or thrombosis was described and discussed. Mechanisms of allergic inflammation can contribute to the development of atherosclerosis and the pathogenesis of its clinical manifestations. Allergy-related cells such as basophils and mast cells may play a role in the regulation of lipid metabolism; on the other hand, blood lipid levels can be the predictors of atopic status and allergic diseases. Asthma and other atopic disorders may increase the risk of venous thromboembolism. Platelet activation is observed in allergic diseases, especially in atopic dermatitis. The protein C system having anti-inflammatory properties may play a role in the pathogenesis of asthma.

Further studies should more deeply investigate the contribution of allergic inflammation mechanisms to the development of atherosclerosis, arterial or venous thrombosis, and lipid metabolism. The knowledge on the role of atopy and allergic disorders as predictors of cardiovascular

and thrombotic pathologies should be also expanded. On the other hand, the role of lipid turnover and hemostasis system components in the pathogenesis of allergic inflammation and atopic diseases should be more clearly elucidated.

Considering the effects of the major total serum IgE susceptibility locus 1q23/*FCER1A* on cardiovascular inflammatory markers and lipid levels in blood, well-designed candidate gene and functional studies should investigate the role of *FCER1A* variants in the pathogenesis of atherosclerosis and related diseases. In addition, pharmacogenetic trials should study the influence of functional *FCER1A* polymorphisms on the treatment with hypolipidemic drugs, such as statins or fibrates.

The author of this manuscript has certified that he complied with the Principles of Ethical Publishing in the International Journal of Cardiology.

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