Predicting probability of tolerating discrete amounts of peanut protein in allergic children using epitope-specific IgE antibody profiling

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ARTICLE SUMMARY

- Existing diagnostic testing is not predictive of severity or the threshold dose of clinical reactivity, and many patients still require an Oral Food Challenge (OFC). While OFCs are very useful for making an allergy diagnosis and determining clinical reactivity, they often cause anaphylaxis, which can increase patient anxiety. and are time and resource intensive.[1]
- An extensive validation was performed across 5 cohorts (all with confirmed oral food challenge results) across six different countries. Cohorts used: BOPI, OPIA, CAFETERIA, CoFAR6, and PEPITES with specimens from Australia, UK, US, Ireland, and Germany.
- This paper reports the first validated algorithm using two key peanut specific IgE epitopes to predict probabilities of reaction to different amounts of peanut in allergic subjects and may provide a useful clinical substitute for peanut oral food challenges.
- Using the algorithm, subjects were assigned into "high", "moderate", or "low" dose reactivity groups. On average, subjects in the "high" group were 4 times more likely to tolerate a specific dose, compared to the "low" group.[1] For example, 88% of patients in the high dose reactivity group were able to tolerate ≥ 144 mg of peanut protein whereas only 29% were able to tolerate the same amount in the low dose reactivity group.[1-2]

CLINICAL CONSIDERATIONS

- The new epitope test offers more granular information to help clinicians stratify treatment and peanut avoidance plans for their patients.
- See below for summary of clinical considerations based on threshold reactivity level.[1]

allergenis peanut diagnostic result	clinical considerations[1]
likely allergic – low dose reactor	• inform or avoid oral food challenge to reduce risk of anaphlyaxis • confirm strict avoidance of peanut • consider immunotherapy to reduce risk of reaction
likely allergic – moderate dose reactor	• consider a single oral food challenge (30 to 100 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider immunotherapy to reduce risk of reaction
likely allergic – high dose reactor	• consider a single oral food challenge (100 to 300 mg) to reduce anxiety and improve quality of life • less stringent avoidance of peanut regime • consider inclusions of precautionary labeled foods such as 'May contain peanut' • consider starting immunotherapy at higher doses to shorten time to maintenance dose
unlikely allergic	• oral food challenge to rule out the diagnosis of peanut allergy

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REVIEW ARTICLE

The impact of type 2 immunity and allergic diseases in atherosclerosis

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Abbreviations: AD, atopic dermatitis; AH, acetylhydrolase; Apo, apolipoprotein; AR, allergic rhinitis; ARMY, Atherosclerosis Risk Factors in Male Youngsters study; Blimp-1, B lymphocyte-induced maturation protein-1; C, complement component; CCL, C-C motif chemokine ligand; CRTH2, prostaglandin D2 receptor 2; CVD, cardiovascular disease; CysLT, cysteinyl leukotrienes; ECP, eosinophil cationic protein; F, coagulation factor; FcγR, Fcγ receptors; FcεRI, Fcε receptor I; HFD, high cholesterol/fat diet; HPGDS, hematopoietic prostaglandin D synthase; HR, hazard ratio; ILC2, innate-like lymphoid cells type 2; LDLr, low-density lipoprotein receptor; MC, mast cell; MI, myocardial infarction; OR, odds ratio; OVA, ovalbumin; oxLDL, oxidized LDL; RR, risk ratio; SCF, stem cell factor; SMC, smooth muscle cell; Th, T-helper cell; T-reg, CD4 T-regulatory cell; TSLP, thymic stromal lymphopoietin; VWF, von Willebrand factor; α-gal, galactose-α-1,3-galactose.

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Abstract

Allergic diseases are allergen-induced immunological disorders characterized by the development of type 2 immunity and IgE responses. The prevalence of allergic diseases has been on the rise alike cardiovascular disease (CVD), which affects arteries of different organs such as the heart, the kidney and the brain. The underlying cause of CVD is often atherosclerosis, a disease distinguished by endothelial dysfunction, fibrofatty material accumulation in the intima of the artery wall, smooth muscle cell proliferation, and Th1 inflammation. The opposed T-cell identity of allergy and atherosclerosis implies an atheroprotective role for Th2 cells by counteracting Th1 responses. Yet, the clinical association between allergic disease and CVD argues against it. Within, we review different phases of allergic pathology, basic immunological mechanisms of atherosclerosis and the clinical association between allergic diseases (particularly asthma, atopic dermatitis, allergic rhinitis and food allergy) and CVD. Then, we discuss putative atherogenic mechanisms of type 2 immunity and allergic inflammation including acute allergic reactions (IgE, IgG1, mast cells, macrophages and allergic mediators such as vasoactive components, growth factors and those derived from the complement, contact and coagulation systems) and late phase inflammation (Th2 cells, eosinophils, type 2 innate-like lymphoid cells, alarmins, IL-4, IL-5, IL-9, IL-13 and IL-17).

KEYWORDS
allergic inflammation, atherogenesis, atherosclerosis, cardiovascular disease, type 2 immunity

1 | ALLERGIC AND CARDIOVASCULAR DISEASE (CVD): A GROWING ISSUE

Allergic diseases are a heterogeneous group of allergen-induced immunological disorders including allergy to foods, drugs and insects, allergic asthma, allergic rhinitis (AR), atopic dermatitis (AD) and eosinophilic esophagitis. The clinical manifestations of allergic reactions range in severity from mild symptoms to life-threatening anaphylaxis. Around 1.5 billion people have an allergic disease and their overall prevalence has been increasing in the last few decades.[1,2] Allergic diseases are often chronic and there is a need for effective, curative treatments. Furthermore, there is increasing awareness of the negative impact on the quality of life of allergic patients and their relatives, notably in asthma[3] and food allergy.[4] In addition to being a health and social concern, allergic diseases entail a tremendous economic burden.[5,6]

The rise in allergy is paralleled by the increasing CVD prevalence, which affects arteries of different organs such as the heart, the kidney and the brain. CVD can remain asymptomatic for decades and manifest as a stroke or heart attack, causing sudden death in the most severe cases.[7] Approximately 523 million people suffer from CVD, the leading cause of mortality worldwide with 18.6 million deaths per year (>31% of total deaths).[8] Furthermore, the prevalence of risk factors of CVD is increasing in younger adults.[9] As this younger population ages, there is a growing CVD burden at the health, social and economic level.[10] Noteworthy, atherosclerosis often underlies CVD, particularly in ischemic heart disease and stroke, which are major causes of morbidity and mortality globally accounting for 50% and 35% of CVD deaths, respectively.[11,12]

2 | ATHEROSCLEROSIS

Atherosclerosis is a chronic disease characterized by endothelial dysfunction, accumulation of fibrofatty material in the intima of the artery wall, smooth muscle cell (SMC) proliferation, and local and systemic inflammation (Figure 1).[13,14] The atherosclerotic plaque can become more fibrous and accumulate calcium with time. When advanced plaques progress, they can remodel the arterial wall invading the arterial lumen, obstructing blood flow and provoking myocardial

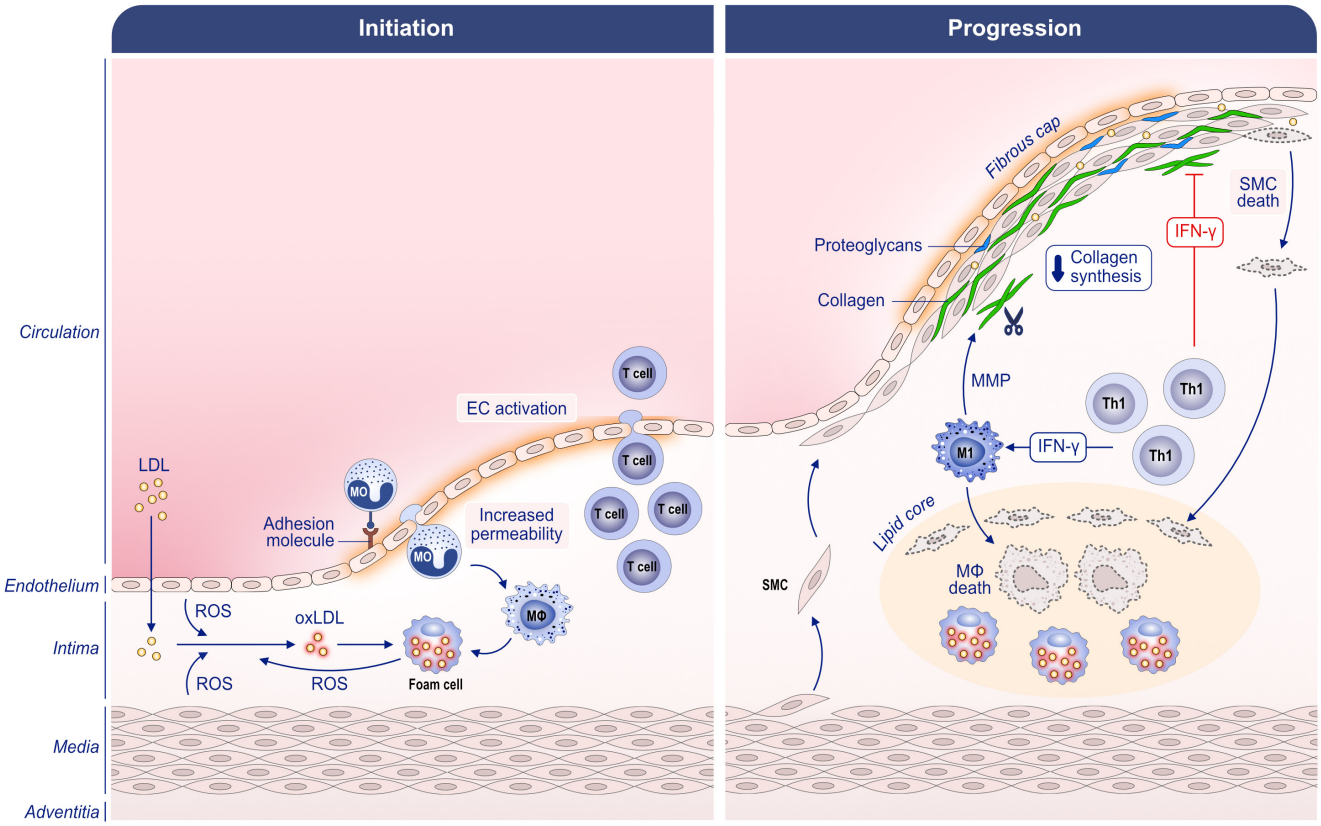

FIGURE 1 Initiation and progression of an atherosclerotic lesion. Left panel: subendothelial accumulation of LDL initiates an atherosclerotic lesion. Reactive oxygen species (ROS) production in the intima layer causes LDL oxidation (oxLDL), inducing the activation of endothelial cells (EC). Increased permeability and the upregulation of adhesion molecules of activated endothelial cells facilitate recruitment of leukocytes such as T cells and monocytes (MO). Lesional monocytes differentiate into macrophages (MΦ) that internalize and retain oxLDL. Activated macrophages contribute to ROS generation and, thus, LDL modification, which leads to cholesterol-rich macrophage foam cells formation. Right panel: when an atherosclerotic lesion progresses, foam cell accumulation contributes to lipid storage and plaque growth. Smooth muscle cells (SMC) migrate from the media layer to the subendothelial space in response to proinflammatory mediators. SMC produce extracellular matrix molecules (collagen, proteoglycans, etc.) promoting intima layer thickening and developing a fibrous cap that confers plaque stability. In contrast, IFN-γ and other inflammatory mediators produced by Th1 cells inhibit SMC proliferation and collagen expression; they also induce matrix metalloproteinases (MMPs) production by M1 macrophages, which weakens the fibrous cap and increases plaque vulnerability. Cell death of foam cells and SMC overloaded with cholesterol result in extracellular cholesterol deposition and formation of a lipid necrotic core

ischemia. Acute myocardial events also occur due to an impaired blood flow caused by intra-arterial thrombosis induced by coronary plaques ulceration.[15,16] This acute lack of irrigation can affect myocardial perfusion itself resulting eventually in acute myocardial infarction (MI), or as a chronic condition causing symptoms related to stable coronary artery disease in a chronic coronary syndrome.[17] In addition, a lack of blood supply to the cerebral arteries triggers ischemic strokes. In the case of ischemia in peripheral arteries, intermittent claudication, ulceration and gangrene may occur.[18]

Low-density lipoproteins (LDLs) are involved in the initiation and progression of atherosclerosis. Due to interactions with extracellular structures, such as arterial wall proteoglycans, LDLs are retained in the subendothelial space, where they can oxidize (oxLDL) or suffer other modifications.[19] This process appears to be eased by inflammatory insults that increase endothelial permeability.[10] Moreover, lesional macrophages internalize oxLDL yielding foam cells, which contribute to lipid storage and plaque growth.[20] In addition, oxLDL promotes the release of cytokines by macrophages, which favours cell recruitment (monocytes, T cells, eosinophils, mast cells [MCs], etc.). Lipoprotein lipase and phospholipase-A2 secreted by macrophages induce LDL-binding proteoglycan formation, enhancing atherosclerosis progression. Furthermore, through platelet-derived growth factor secretion, macrophages promote SMC migration from the tunica media to the intima.[21] IFN-γ-producing-Th1 cells also enter the intima and respond to oxLDL in an antigen-specific manner regulating some functions of innate cells, the endothelium and SMCs. For example, IFN-γ promotes M1 macrophage polarization and metalloproteinase production, and decreases collagen synthesis by SMCs, which contribute to plaque vulnerability.[10] T-regulatory cells (T-reg) recognize modified apolipoprotein (Apo) B[22] epitopes and respond to oxLDL via CD69 inducing the expression of anti-inflammatory factors.[23] Regarding Th2 (the hallmark allergic cells) and Th17 cells (present in some allergic phenotypes), there are conflicting data that are discussed in Section 4.

3 | ALLERGIC PATHOLOGY

Allergic sensitization, understood as the development of type 2 immunity and IgE responses against allergens, usually occurs early in life and can become chronic. It is the outcome of an interplay between the allergen and the dendritic cell influenced by the allergen innate immunostimulatory properties, individual genetic predisposition to atopy, and the level of tissue damage.[24] Indeed, a compromised epithelial barrier is the current paradigm on the global rise in allergy.[25] Once someone becomes allergic there are, by and large, three clinical scenarios determined by allergen exposure (Figure 2).

The first scenario refers to allergic individuals that are unexposed to the allergen. While allergen avoidance protects them from undergoing allergic reactions, strict avoidance is an unsurmountable challenge when dealing with ubiquitous allergens such as those from pollen, dust mites, pets or certain foods.[26,27]

Allergen exposure triggers acute allergic reactions. These are largely mediated by the so-called "classical pathway" dependent on IgE and Fcε receptor I (FcεRI) signaling in MCs and basophils.[28] In addition, alternative pathways of acute reactions involve the activation of monocytes/macrophages or neutrophils via IgG and Fcγ receptors (FcγR).[29,30] Both pathways converge on the rapid release of proinflammatory and vasoactive mediators, which can be preformed (histamine, tryptase, chymase, etc.), or synthesized de novo (prostaglandins, leukotrienes, PAF, etc.).[31] Whether via IgE and/or IgG1 signalling, the released allergic mediators disrupt endothelial barrier function[32-34] and impact the cardiovascular system by mechanisms reviewed recently.[31,35]

Late phase allergic reactions occur within hours, or days, following allergen encounter. These reactions involve inflammatory mediators released in the early-phase reaction by MCs and basophils, and allergen-specific Th2 lymphocytes.[36] Activated memory Th2 cells proliferate and produce cytokines (IL-4, IL-5, IL-9, IL-13, and IL-31). Th2 cells act synergistically with type 2 innate-like lymphoid cells (ILC2) activated during the acute phase. They recruit effector cells such as eosinophils, basophils, as well as other lymphocytes, to the site of allergen exposure.[37-39] The Th2-IL-5-eosinophil axis enables or exacerbates other pathways that positively feedback into late phase inflammation. As such, IL-4, IL-5, and IL-13 drive Th2 cells towards

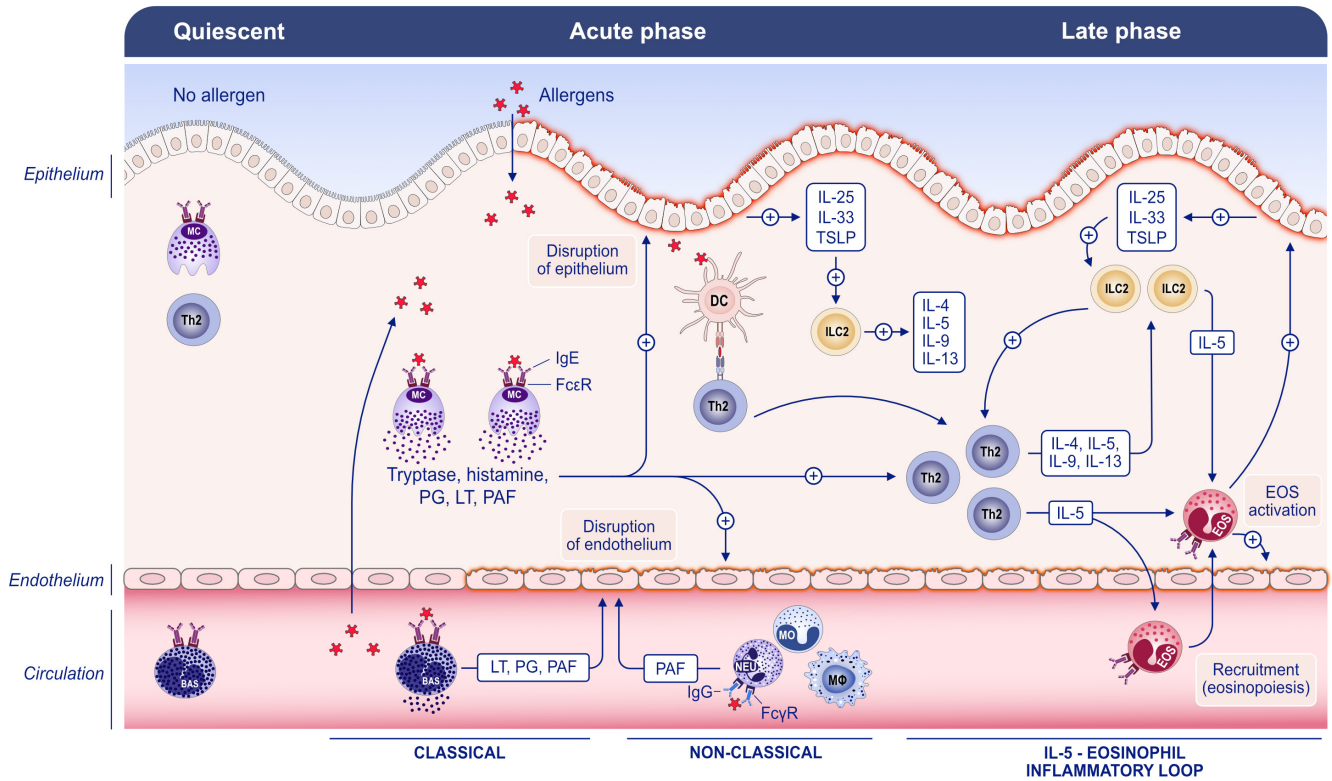

FIGURE 2 Overview of clinical scenarios in allergic pathology determined by allergen exposure. In the absence of allergen re-exposure, the cellular machinery that mediates allergic reactions remains quiescent (left panel). Upon allergen re-encounter, whether systemically and/or through the epithelium, two reactions take place in a time-dependent manner. There is an immediate reaction that develops within seconds, or minutes, and that is dependent on IgE/IgG; the activation of the classical pathway (IgE) leads to the degranulation of mast cells (MCs) and basophils (BAS) while the alternative (IgG) can operate on monocytes (MO), macrophages (MΦ) and neutrophils (NEU). Both pathways concur in the release of inflammatory mediators such as PAF, histamine, prostaglandins (PGs), leukotrienes (LTs), etc., which damage and increase the permeability of the epithelium/vasculature leading to clinical manifestations (middle panel) and contributing to the late phase reaction. The latter occurs within hours, or days, following allergen exposure via antigen-presenting cells such as dendritic cells (DC); it is orchestrated by Th2 cells and related cytokines (IL-4, IL-5, IL-9, IL-13). The Th2-IL-5 axis induces eosinophil (EOS) recruitment to the sites of allergen exposure. Eosinophils contribute to the inflammatory ambient that can be exacerbated with the presence of type 2 innate lymphoid cells (ILC2) and epithelial-cell derived alarmins (IL-33, TSLP, IL-25) (right panel)

a specialized Th2A phenotype ($CRTH2^+CD49d^+CD161^+$) associated with persistent allergy and high *IL5*, *IL9*, and *HPGDS* expression.[40,41] Moreover, degranulating eosinophils, together with early-phase mediators, cause the release of epithelial-derived alarmins (IL-33, TSLP, IL-25, etc.), promote ILC2 differentiation, and foster a pernicious cycle of (chronic) inflammation.[37,42,43] Ultimately, allergic inflammation impairs tissue functionality, rather than restoring homeostasis.[44]

4 | THE CLINICAL ASSOCIATION BETWEEN ALLERGY AND ATHEROSCLEROSIS

The association of serum IgE levels and CVD has been assessed with inconclusive results.[45] This may insinuate that IgE plays different roles under homeostatic vs inflammatory conditions. When focusing specifically on IgE in atopy or allergy, several observational studies have analyzed the association between allergic disease and CVD risk (Table 1).

A prospective study with two matched cohorts of asthmatic and non-asthmatic patients (>200,000 patients per cohort) followed from 1996 to 2008 in the USA and showed a significant CVD risk increase in asthmatic patients as compared to controls.[46] Although the asthma patient cohort was not stratified (allergic vs non-allergic asthma), there was a significant effect of allergic disease, without asthma, on the risk of coronary heart disease (hazard ratio, [HR] 1.31), cerebrovascular disease (HR 1.22), and heart failure (HR 1.11).[46]

Regarding AD, a meta-analysis of 17 population-based studies reported that increasing severity was associated with higher risk of major cardiovascular outcomes (angina, MI, coronary revascularization, heart failure, cardiac arrhythmias, stroke, and cardiovascular death); AD was also associated with increased risk of MI (risk ratio [RR] 1.12), stroke (RR 1.10), ischemic stroke (RR 1.17), angina (RR 1.18), and heart failure (RR 1.26).[47] Similarly, a recent meta-analysis of 37 studies from Europe, Asia and North America, showed significantly higher overall odds ratio (OR) of CVD (1.08) in AD patients.[48] In addition, a Swedish nationwide, register-based, case–control study analyzed data from >100,000 AD patients and >1,000,000 controls from 1968 to 2016.[49] This study found that AD was associated with angina pectoris (OR 1.13) and MI (OR 1.07), and severe AD with ischaemic stroke (OR 1.19).[49] Furthermore, hypertension and hyperlipidemia -known CVD risk factors- were more prevalent in AD patients, as compared to controls.[49] It is pertinent to remark that ~20% of AD patients do not show elevated serum IgE levels or allergen-specific sensitization. This AD phenotype, known as intrinsic, usually starts in adulthood. Intriguingly, both intrinsic and extrinsic AD patients show a Th2-biased gene expression in lesional skin, although the former seems to present with a more robust Th17 and Th22 response.[50] Hence, evaluating CVD risk of these two AD phenotypes would be informative.

The impact of AR on CVD risk is controversial. For instance, one study analyzed data of 110,207 AR patients in a matched cohort from 1999 to 2012 in South Carolina (USA).[51] It showed a lower risk for MI (HR 0.63), coronary heart disease (HR 0.81) and CVD (HR 0.67) in AR patients.[51] In contrast, a large-scale cohort study of ~9.5 million individuals followed from 2010 to 2018 through the Korean National Health Insurance Service[52] found an increased MI risk in AR patients (HR 1.11). This study also reported an increased MI risk in AD (HR 1.14) and asthmatic patients (not stratified based on asthma type; HR 1.37). Interestingly, the combined risk of MI in patients with AD and asthma (HR, 1.81) was higher than in patients with AD, asthma and AR (HR, 1.71).[52] The allergic group presented more CVD risk factors such as hypertension or dyslipidemia than controls, although it was partly attributed to the significant differences in age. Nevertheless, a recent cross-sectional study in Egypt with 150 AR patients followed for 2 months reported dyslipidemia in 56% of them.[53] Moreover, serum levels of IgE and IL-17A, as well as house-dust-mite-sensitization, were identified as independent risk factors that significantly increased dyslipidemia risk.[53] In agreement, a multicenter prospective study conducted in Italy in 160 adult AR patients and matched controls reported a significantly higher dyslipidemia risk in AR patients.[54]

The relationship between food allergy and CVD has been less investigated. A study in the USA included 118 subjects that underwent cardiac catheterization and intravascular ultrasound to investigate galactose-α-1,3-galactose (α-gal)-specific IgE levels in atherosclerosis.[55] It reported that 26.3% of them had α-gal-specific-IgE and found a strong association between α-gal-specific-IgE and atheroma burden. Unstable plaques with more fibrofatty, necrotic and calcified content, and less fibrous, were associated with α-gal-specific IgE serum levels.[55] Interestingly, IgE-specific levels to common aeroallergens and to peanut, did not significantly correlate with atheroma burden and volume, nor with maximal stenosis.[55] Sensitization to α-gal is often attributed to tick bites. However, α-gal is present in non-primate mammals and can be found in many dietary sources and in carrageenan (E407).[56,57] Therefore, the continuum environmental exposure to α-gal presumably sustains a level of chronic inflammation. The fact that α-gal is involved in delayed rather than acute reactions may favour recurrent exposures because these reactions are often misdiagnosed; not to mention that patients with a low degree of α-gal sensitization likely remain asymptomatic.[56]

Altogether, different lines of evidence indicate that allergic diseases increase CVD risk, which is often driven by atherosclerosis. Some clinical studies, such as the Bruneck and the ARMY (Atherosclerosis Risk Factors in Male Youngsters study), have found a significant association between allergic diseases and subclinical atherosclerosis.[58] The Bruneck study, conducted in Italy in a cohort of 826 individuals (40–70 year olds) reported that allergic patients were at a higher risk of atherosclerosis development and progression (OR 3.9 for asthma [not stratified based on type], AR or both; OR 1.7 for IgE). Similarly, the ARMY study, performed in Austria in a cohort of 141 men (17–18 year olds) concluded that young allergic individuals were at a significantly increased risk for high intima media thickness (OR 3.0 for asthma [not stratified based on type], AR or both).[58] Yet, these findings are observational and usually lack of patient stratification according to allergic disease severity or phenotype. Scientific evidence demonstrating the causal relationship between

TABLE 1 Summary of observational studies regarding the association between allergic disease and CVD. The Table references are included as Data S1, supplementary references

Study	Study design	Patients	Follow up	Conclusions
Iribarren et al. (2012)[1] Country: USA	Retrospective	407,190 AS patients and controls [♀ = 66%]	9 years (1999–2008)	• AS: ↑ risk of CVD • Allergic co-morbidities: ↑ risk of CVD • AS medication: ↑ risk of CVD and all-cause mortality • Allergic disease: ↑ risk of coronary heart disease, cerebrovascular disease and heart failure
Asscott et al. (2018)[2] Country: USA	Population-based meta-analysis	AD patients		• AD: ↑ risk of CVD. No evidence with stroke or ischemic stroke
Andersen et al. (2016)[3] Country: Denmark	Cohort	174,797 patients and controls [♀ = 54%]	15 years (1997–2012)	• Severe AD: ↑ burden of comorbidities and detrimental lifestyle; ↑ risk of CVD
Drucker et al. (2016)[4] Country: USA	Cross-sectional	78,702 patients and controls [♀ = 100%]	20 years (1989–2009)	• AD: ↑ risk of stroke but no MI
Drucker et al. (2017)[5] Country: Canada	Cross-sectional	259,119 patients and controls [♀ = 61.4%]	2009 onwards	• AD: ↓ risk of HT, MI and stroke
Egeberg et al. (2016)[6] Country: Denmark	Cross-sectional	111,812 AD and psoriasis patients, and controls [♀ = 61.4%]	17 years (1995–2012)	• AD: ↑ risk factors and comorbidities for CVD • Psoriasis risk > AD risk for CVD
Kwa et al. (2017)[7] Country: USA	Cross-sectional	72,651,487 inflammatory skin disease patients	10 years (2002–2012)	• Skin diseases: ↑ risk of CVD
Marshall et al. (2013)[8] Country: USA	Restricted cohort study, analyzed as case–control	8526 inflammatory skin disease patients and controls [♀ = 67%]	3 years (2005–2007)	• AD: no independent 1-year risk of CVD
Radtke et al. (2017)[9] Country: Germany	Cross-sectional	1,349,671 inflammatory skin disease patients	1 year (2009)	• Psoriasis risk > AD risk for CVD
Riis et al. (2016)[10] Country: Denmark	Cohort	53,210 AD patients and controls [♀ = 55%]	33 years (1977–2013)	• AD: ↑ risk of MI
Silverberg. (2015)[11] Country: USA	Cross-sectional	66,652 AD patients and controls	2 years (2005–2006) 1 year (2010) 1 year (2012)	• AD: ↑ risk of CVD and stroke
Silverwood, Forbes, et al. (2018)[12] Country: UK	Cohort	1,915,916 AD patients and controls [♀ = 66%]	18 years (1998–2015)	• AD: moderate ↑ risk of non-fatal CVD
Standl et al. (2016)[13] Country: Germany	Cohort			• No association between AD and CVD risk factors
		AOKPLUS cohort 1,214,133 patients 1,180,678 patients	10 years (2005–2014) 2 years (2012–2014)	
		KORAF4 cohort 2990 AD patients and controls [♀ = 51.5%]	7 years	
		GINIplus & LISAplus 2286 AD patients and controls [♀ = 51%]	15 years	

TABLE 1 (Continued)

Study	Study design	Patients	Follow up	Conclusions
Su et al. (2014)[14] Country: Taiwan	Cohort	40,646 AD patients and controls [♀ = 61.9%]	5 years (2005–2008)	• AD: ↑ risk of ischemic stroke
Sung et al. (2017)[15] Country: Taiwan	Cohort	75,515 AD patients and controls [♀ = 54.2%]	11 years (2000–2010)	• AD severity correlates with risk of ischemic stroke
Treudler et al. (2017)[16] Country: Germany	Cross-sectional	9481 AD patients and controls [♀ = 57%]	4 years (2011–2014)	• No correlation of AD with CVD
Tsai et al. (2016)[17] Country: Taiwan	Cohort	470,440 AD patients and controls [♀ = 58.13%]	12 years (2000–2011)	• Corticosteroid treatment in AD patients is a risk factor for stroke
Varbo et al. (2017)[18] Country: Denmark	Cohort	84,601 *FLG-mut*[*] patients and controls [♀ = 56.3%]	13 years (2001–2014)	• *FLG-mut*: ↑ risk of ischemic stroke
Chester et al. (2021)[19] Country: Italy	Random-effect model meta-analysis	237,226,993 AD patients	30 years (1990–2020)	• AD: ↑ risk of CVD
Ivert et al. (2019)[20] Country: Sweden	Case–control	1,127,267 AD patients and controls [♀ = 66.1%]	48 years (1968–2016)	• AD associates with CVD
Crans Yoon et al. (2016)[21] Country: USA	Retrospective population-based matched cohort	220,414 AR patients and controls [♀ = 65.8%]	13 years (1999–2012)	• AR: ↓ risk of CVD and all-cause mortality • IgE +: ↓ risk of CVD
Rhee et al. (2020)[23] Country: Korea	Prospective	9,548,939 patients with allergic diseases [♀ = 45%]	8 years (2009–2018)	• Allergic diseases (AS, AR and AD): ↑ risk of CVD • AD + AR: ↑↑ risk of MI and all-cause mortality
Sheha et al. (2021)[24] Country: Egypt	Comparative cross-sectional	150 AR patients with DL and DL-free [♀ = 41.3%]	2 months	• AR: ↑ prevalence of DL
La Mantia et al. (2017)[25] Country: Italy	Prospective	160 AR patients [♀ = 47.5%]	7 months	• AR: ↑ correlation with DL
Wilson et al. (2018)[26] Country: USA	Retrospective	118 catheterization patients [♀ = 50%]		• α-gal-IgE: ↑ atheroma volume and unstable plaques
Knoflach et al. (2005)[27]	Prospective population-based survey			• AS and AR: ↑ association with Ath
Country: Austria		Bruneck study 1872 Ath patients and controls [♀ = 51%]	5 years (1990–1995)	
Country: Italy		ARMY 141 subjects with low vs. high intima media thickness [♀ = 0%]	5 months	

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; ARMY, Atherosclerosis Risk Factors in Male Youngsters; AS, asthma; Ath, atherosclerosis; CVD, cardiovascular disease; DL, dyslipidemia; FLG, filaggrin; HT, hypertension; MI, myocardial infraction; α-gal, galactose-α-1,3-galactose.

*FLG mutations cause AD, previously found to be associated with ischemic stroke.

allergic diseases and atherosclerosis is scarce. Indeed, intervention studies demonstrating that allergy treatment reduces atherosclerosis, or related events, are lacking, and the mechanisms by which allergic diseases promote atherosclerosis remain largely unexplored.

5 | PUTATIVE ATHEROSCLEROTIC MECHANISMS OF ALLERGIC DISEASE

Experimental CVD models have been useful to investigate atherosclerosis. ApoE$^{-/-}$ and LDL receptor (LDLr)$^{-/-}$ mice are genetically predisposed to develop atherosclerosis, particularly when fed a high cholesterol/fat diet (HFD; otherwise indicated in the text).[59-61] These models have proven useful to investigate the relationship between allergy and CVD as they mimic the clinical association observed in humans.[62,63] However, in most cases, they have been applied to investigate the contribution of canonical type 2 immunity players to CVD under homeostatic conditions. In other words, how basal IgE[64] or MCs,[65] without established allergy, influence atherosclerosis.

5.1 | Atherosclerotic potential of acute allergic reactions

The key effector molecules of immune-mediated, acute allergic reactions are IgE and IgG,[28] and both have been associated with

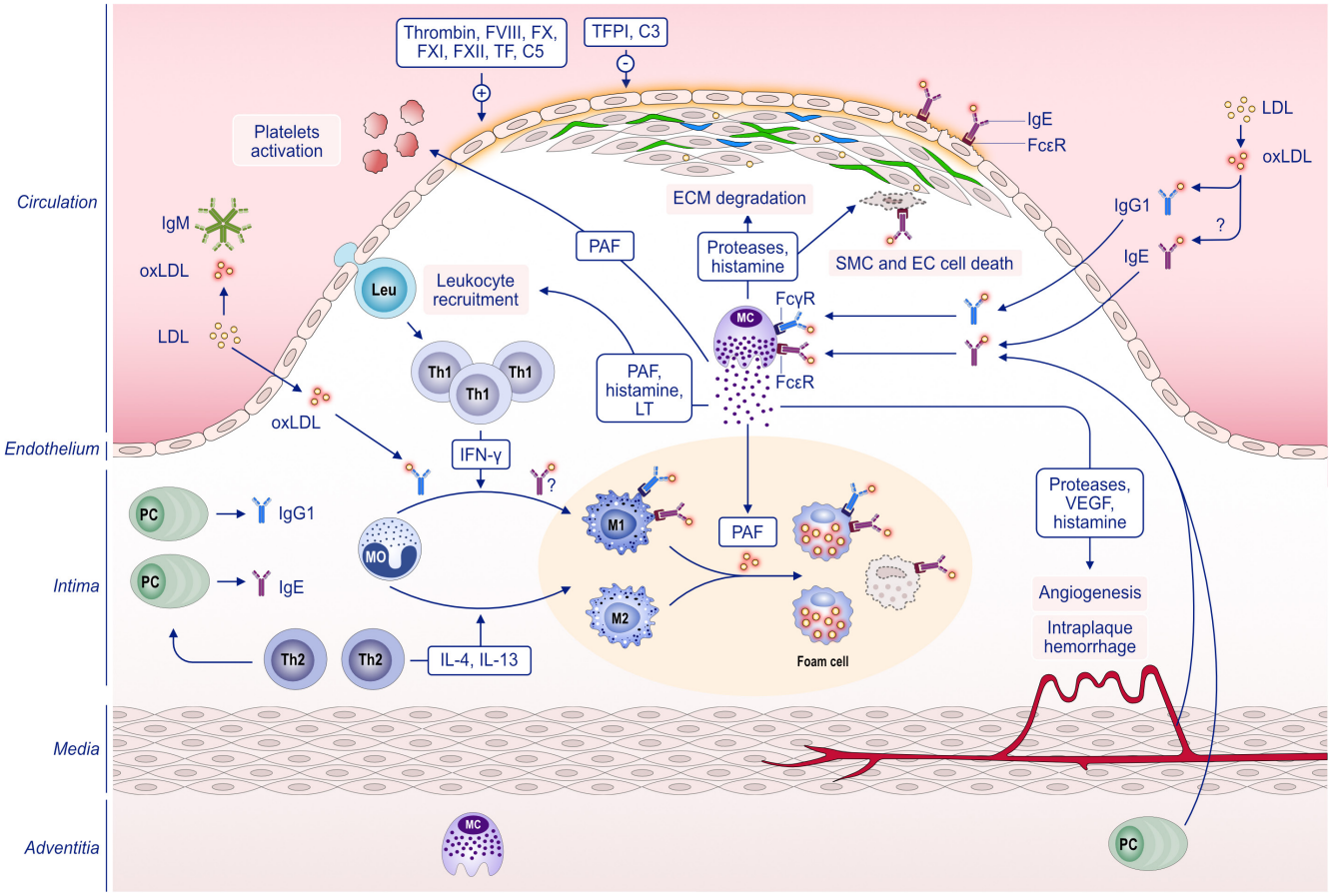

FIGURE 3 Potential atherosclerotic mechanisms of acute allergic reactions. Mast cells (MC) are found in lesions in a greater number than in healthy arterial intima, although they are much fewer than macrophages (MΦ). Activated MC release inflammatory mediators that contribute to atherosclerosis progression and plaque destabilization. PAF and histamine activate endothelial cells (EC) and increase adhesion molecules expression and vascular permeability, facilitating the entry of LDL, other mediators, or leukocytes (Leu). Furthermore, PAF enhances foam cell formation by oxidized LDL (oxLDL) uptake and thrombus by platelet activation. Proteases such as tryptase and chymase damage extracellular matrix (ECM), EC and smooth muscle cells (SMC), thus facilitating fibrous cap erosion and intraplaque hemorrhage. Along with the release of angiogenic growth factors such as VEGF, MC induce local microvessel growth. MC can be activated by antigen-IgE-FcεR, via oxLDL-IgG1-FcγR or other signals like C5a-C5aR. Plaque Ig can originate from B cells in adventitia or intima, circulating Ig that enters through the dysfunctional endothelium, or even microvessels in neovascularized areas of plaques, or intraplaque hemorrhages. IgE signalling in plaque macrophages favours M1 macrophage polarization and foam cell formation. IgE stimulation is also associated to SMC, EC and macrophage apoptosis. IgE-binding to atherosclerosis antigens like oxLDL remains unknown. Serum IgM and IgG1 form oxLDL immune complexes playing an atheroprotective role. Intraplaque oxLDL-specific IgG1 may also exhibit a protective neutralizing effect, although it may induce MC and macrophage activation via FcγR engagement. PC, plasma cell; LT, leukotriens; MO, monocyte; M2, M2 macrophage; F, factor; TFPI, tissue factor pathway inhibitor

atherosclerosis (Figure 3). IgE contributes to plaque progression through several mechanisms including M1 macrophage polarization, foam cell formation, and vascular cell apoptosis.[64,66,67] In addition, anti-IgE has been postulated as an atheroprotective intervention in autoimmune diseases.[68,69] On the other hand, the number of IgG subtypes and diverse functionality of Fcγ receptors (activating vs inhibitory) have made it challenging to ascertain its role, which is also influenced by its specificity toward atherosclerosis-derived-antigens.[70-72] As it pertains to IgG1, high serum concentrations have been observed in ApoE$^{-/-}$ mice[73] and atherosclerotic mechanisms have been reported involving Fcγ receptors and macrophages.[74] Noteworthy, oxLDL-specific IgG has been detected in human plaques,[70] and different experimental strategies support the therapeutic role of oxLDL- (or atherosclerosis-derived-antigen)-specific IgG1 for plaque progression or stabilization.[75-77] Therefore, an increased serum level of oxLDL-specific IgG1, while indicative of atherosclerosis, may be atheroprotective.

MCs play a pivotal role in acute allergic reactions and in atherosclerosis.[78-80] Activated MCs contribute to plaque growth and instability including intraplaque hemorrhage, increased lipid uptake, leukocyte influx, endothelial and SMC apoptosis, and matrix degradation.[81] Increased lesion size in the brachiocephalic artery and an enhanced incidence of intraplaque hemorrhage in carotid artery lesions has been observed in a dinitrophenyl-IgE-mediated anaphylaxis model in ApoE$^{-/-}$ mice.[82] Moreover, MC–deficiency was shown to inhibit plaque development in LDLr$^{-/-}$ mice, which was attributed to decreased levels of IL-6, IFN-γ, cholesterol and triglycerides.[65,83]

5.1.1 | Mediators of acute allergic reactions

Mediators released during acute allergic reactions contribute to atherosclerosis, notably via plaque destabilization as observed in some Kounis syndrome variants.[84] Serum tryptase, a common anaphylaxis biomarker, has been positively correlated with lesion size,[85] increased intraplaque hemorrhage[86] and cardiovascular events. Chymase has also been associated with plaque destabilization via matrix degradation with the consequent apoptosis of vascular SMCs and endothelial cells, and plaque erosion.[82,87] In addition, chymase has been reported to reduce macrophage cholesterol efflux via proteolytic HDL inactivation.[88] In agreement, chymase inhibition reduced intraplaque hemorrhage in carotid artery atherosclerosis in ApoE$^{-/-}$ mice[89] and impaired atherosclerosis in hamsters.[90]

Growth factors and vasoactive agents are detrimental in atherosclerosis. For example, it has been reported that VEGF decreases vessel tone and destabilizes the endothelium[91]; GM-CSF accelerates plaque progression in LDLr$^{-/-}$ mice by increasing macrophage apoptosis[92]; and low stem cell factor (SCF) levels are associated with increased incidence of coronary events.[93] In addition, histamine contributes to plaque destabilization and intraplaque hemorrhage by enhancing vascular permeability and inflammation[81]; and histamine deficiency has been shown to decrease the expression of adhesion molecules and metalloproteinases.[94] However, studies addressed in ApoE$^{-/-}$ mice have demonstrated the antagonistic role of histamine receptors, which exert atherogenic (receptor 1) and atheroprotective (receptor 2) functions.[95]

PAF participates in endothelial dysfunction, platelet reactivity, and foam macrophage differentiation.[96,97] It induces the expression of adhesion molecules, which likely favour atherosclerosis through leukocyte recruitment and tissue extravasation.[98] In addition, during plaque growth and expansion, PAF and its receptor have been linked to macrophage activation by oxidative stress and oxLDL uptake.[99] The activity of PAF is regulated by PAF acetylhydrolase (PAF-AH),[100] whose reduction in circulation has been identified as a biomarker of severe anaphylaxis.[101] PAF-AH circulates forming a complex with LDL and HDL,[102,103] and prevents their oxidation.[104] Consequently, allergic reactions may impair the atheroprotective role of PAF-AH. Lastly, other arachidonic-acid-derived allergic mediators, especially cysteinyl leukotrienes (CysLT), have been shown to be determinant in MI, brain ischemia, aortic aneurysms and intimal hyperplasia.[105,106] Indeed, CysLT participate in plaque progression and the use of CysLT receptor antagonists reduces CVD risk.[107,108]

5.1.2 | Coagulation, contact and complement systems

The activation of the coagulation, contact and complement systems concurs in acute allergic reactions and atherosclerosis. The relationship between coagulation and atherosclerosis has been reported in different models and clinical studies, supporting the use of anticoagulants in atherothrombotic events.[109] The importance of thrombin, and consequently of coagulation in atherosclerosis, has been conclusively demonstrated using both ApoE$^{-/-}$ mice and pharmacological tools.[110,111] Other relevant components such as tissue factor pathway inhibitor,[112] coagulation factor (F) VIII,[113] and activated FX[114] have been implicated in murine plaque development. Furthermore, the genetic ablation of FXII decreased lesion formation by reducing the expression of pro-inflammatory cytokines in antigen-presenting cells.[115] In addition, FXI genetic deficiency or pharmacological inhibition in ApoE$^{-/-}$ and LDLr$^{-/-}$ mice slowed down atherogenesis.[116,117] Regarding kininogen, its genetic deficiency promotes aneurysm formation but not atherosclerosis.[118]

C3a, C4a, and C5a peptides, which derive from C3, C4 and C5 proteolysis, have been considered, along with IgG, to be the main non-IgE elicitors in acute allergic reactions.[119] In the vascular setting, high C3/C4 plasma levels have been observed in primary hypercholesterolemic patients, and C5 has been suggested as a subclinical atherosclerosis biomarker.[120,121] The effect of complement activation in vascular wall remodeling is similar to that observed in coagulation.[122] Aortic tissue from mice or human atherosclerotic lesions upregulates mRNA of anaphylatoxin receptors C3a and C5a. C3 deficiency aggravated atherosclerosis by increasing the frequency of macrophages and decreasing vascular SMC content, yielding prone-to-rupture-plaques in LDLr$^{-/-}$ or ApoE/LDLr$^{-/-}$ mice.[123,124] In

contrast, inhibition of C5 or CD88 (C5a receptor) in ApoE$^{-/-}$ mice diminished plaques by attenuating inflammation.[125-128]

5.2 | Atherosclerotic potential of late phase inflammation

Th2 cells are at the heart of late-phase allergic inflammation, which contrasts with the atherosclerotic ambient governed by M1 macrophages and IFN-γ-producing Th1 cells.[59,129,130] The mutually-suppressive Th1/Th2 equilibrium implied an atheroprotective role for Th2 cells by counteracting Th1 responses.[131] In fact, Th2-biased mouse strains (BALB/c) are resistant to atherogenesis, while Th1-prone (C57BL/6) develop fatty streaks when HFD-fed.[132-134] Also, some clinical studies have found that a high Th2 cell frequency in circulation is associated with a lower carotid intima-media thickness.[135,136] On the other hand, the positive clinical association between allergic disease and CVD (Table 1), together with the few experimental studies in allergic inflammation, argues against the atheroprotective function of Th2 responses. This conundrum might be the result of a divergent role of homeostatic vs induced type 2 immunity in CVD (Figure 4).

The impact of allergic inflammation in atherosclerosis has been studied in ovalbumin(OVA)-sensitized ApoE$^{-/-}$ mice on a chow diet and challenged with aerosolized OVA thrice per week during 8 and 16 weeks.[63] The allergic mice exhibited larger and more vulnerable lesions with increased macrophage and SMC infiltration, and less collagen content as compared to control mice.[63] Remarkably, anti-IL-4 or anti-IL-17A administration reduced lesion size, with a greater effect when combined.[63] Another group applied an allergic asthma model in ApoE$^{-/-}$ mice for 12 weeks; the HFD started before, after, or at the same time of sensitization.[62] Allergic mice had lesions with more pathogenic features (lesion cell proliferation, collagen and elastin degradation, SMC loss, apoptosis and angiogenesis) than control mice. However, mice only had larger lesion size when allergy was induced concomitantly with the introduction of a HFD.[62] Also, daily treatment with nebulized ketotifen (MC inhibitor), or budesonide (corticosteroid) alleviated lesion pathology, but did not reduce lesion size.[62] These studies demonstrate that exacerbated atherosclerosis in allergic asthma is partly mediated by IL-4 and IL-17, and the involvement of a MC-independent mechanism driven by allergic inflammation. Notwithstanding, the association between allergic disease and atherosclerosis is blurred when type 2 immunity players are studied individually outside of allergic pathology.[129,130]

5.2.1 | IL-4 and IL-13

The role of IL-4 in atherosclerosis is unclear. Some gain- and loss-of-function experiments (IL-4 administration, IL-4 deficiency) in ApoE$^{-/-}$ or LDLr$^{-/-}$ mice showed that IL-4 did not affect lesion size or composition.[137,138] Yet, another group reported that IL-4 administration decreased lesion size by impairing Th1-cell expression in C57BL/6 mice.[133] Moreover, a novel study using IL-4/IL13-deficient mice and several atherosclerosis models discovered that the Wnt signaling pathway favoured IL-4 responsiveness in macrophages and enhanced atherosclerosis resolution.[139] In contrast, others suggest a proatherogenic effect for IL-4 based on the reduced plaque size observed in IL-4-deficient mice on an ApoE$^{-/-}$ or LDLr$^{-/-}$ background with atherosclerosis induced by a HFD or inflammatory stimulus.[140-142]

While IL-4 data on atherosclerosis are inconclusive, potentially due, in part, to the heterogeneity of mouse strains and models applied, IL-13 has been reported atheroprotective. IL-13$^{-/-}$ bone marrow chimeric LDLr$^{-/-}$ mice exhibited suppressed M2 macrophage activation that accelerated atherosclerosis. Additionally, IL-13 administration induced a more stable plaque composition (increased collagen content and M2 macrophage polarization, and reduced macrophage accumulation).[143] Also, IL-13-deficient mice exhibited increased weight gain, hyperglycemia, and hepatic insulin resistance.[144] In vitro and in vivo data support that activated T-regulatory (Treg)-cell-derived IL-13 induces IL-10 secretion and efferocytosis by macrophages, which controls atherosclerosis.[145] Moreover, it has been reported that oxLDL treatment downregulates IL-13 expression in eosinophils and promotes M1 macrophages.[146]

IL-4 and IL-13 share a common receptor-signaling pathway, which can be inhibited with IL-4Rα-specific antibodies (e.g., dupilumab). Recently, a significant correlation was reported between vascular inflammation and Th2-related products in the skin and blood of young moderate-to-severe AD patients as compared to controls.[147] Interestingly, dupilumab treatment for 16 weeks significantly modulated the expression of 23/63 atherosclerosis-related genes in AD patients.[147]

5.2.2 | IL-5 and eosinophils

Experimental studies have attributed an indirect atheroprotective effect to IL-5. It has been shown that IL-5 induces B1 cell expansion and natural IgM production, some of which blocks oxLDL.[148-151] Although human plasma IL-5 levels do not predict CVD risk, high IL-5 levels have been associated with lower carotid intima-media thickness and increased oxLDL-specific antibody production.[149,152] Eosinophils also appear to participate in atherosclerosis[153,154] as they were absent within stable human plaques but were detected in the ruptured ones.[155] A recent study using eosinophil-deficient ApoE$^{-/-}$ mice delineated a self-reinforcing interplay between eosinophils and platelets in atherosclerosis. CCL5 and particularly CCL11 were increased in atherosclerotic plaques.[156] This was associated with endothelial activation and exposure of von Willebrand factor (VWF), which induced platelet adhesion to the vessel wall and empowered eosinophil recruitment. Platelet-eosinophil interactions contributed to reciprocal activation and fostered plaque formation[156]; activated eosinophils release granules or extracellular traps that contain components, such as eosinophil cationic protein (ECP), and participate in atherosclerosis.[154,157,158] ECP induces CD54 (ICAM-1) expression on endothelial cells, leading to monocyte adhesion, and regulates

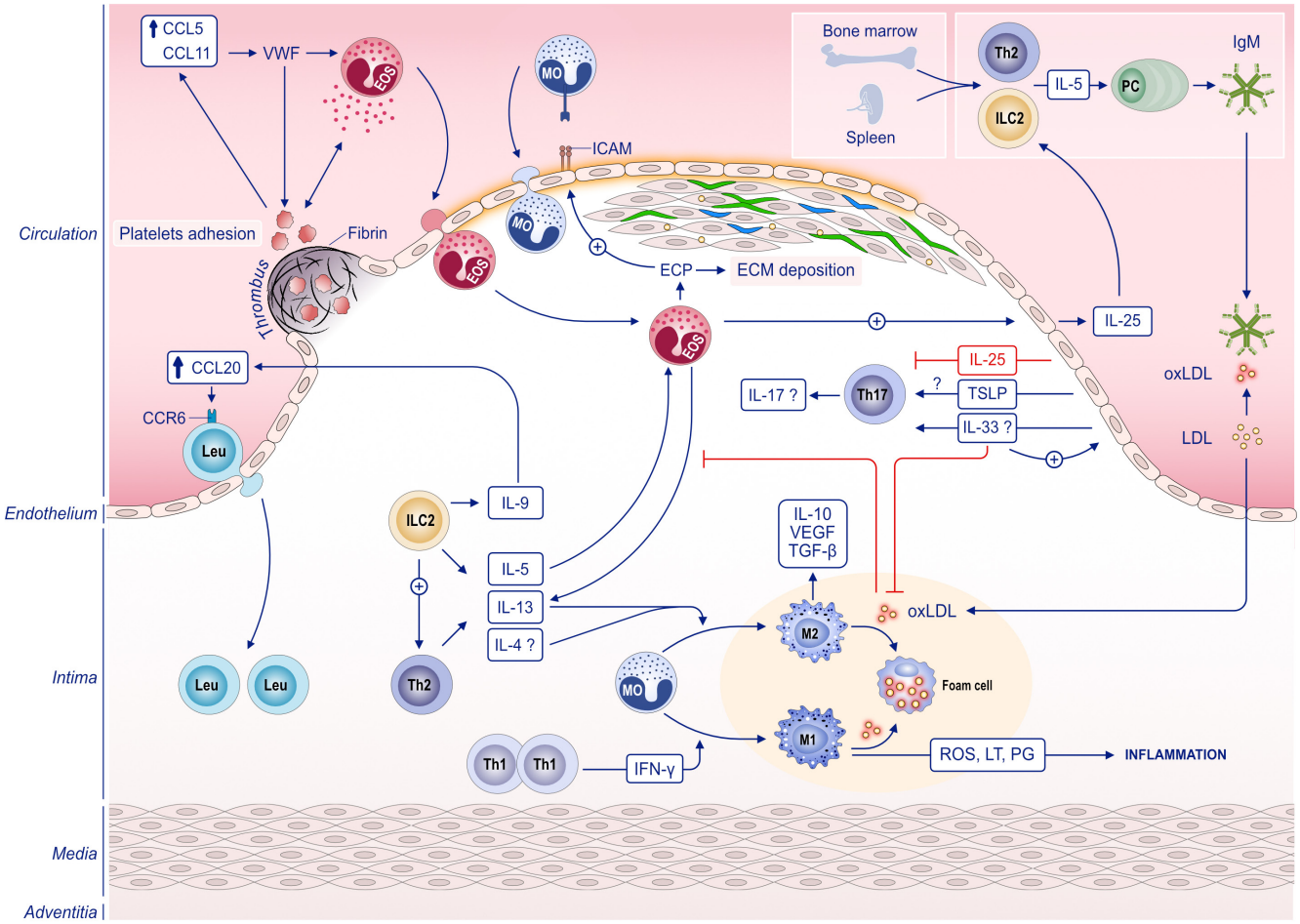

FIGURE 4 Putative atherosclerotic mechanisms of late phase allergic inflammation. The atherosclerotic plaque usually contains macrophages and Th1 lymphocytes, with only a few cells producing Th2-type or Th17-type cytokines. Th2 responses are promoted by type 2 innate lymphocytes (ILC2) which generate Th2-related cytokines (IL-4, IL-5, IL-9, IL-13). The role of IL-4 in atherosclerosis is incompletely understood. Both IL-13 and IL-4 promote protective M2-macrophage polarization and IL-10, VEGF and TGF-β secretion. In contrast, Th1 cell-derived IFN-γ induces proinflammatory M1-macrophage polarization and reactive oxygen species (ROS), prostaglandins (PG) and leukotrienes (LT) production. IL-9 induces CCL20 expression that binds to CCR6 promoting cell recruitment into the plaque. IL-5 has been attributed to an indirect atheroprotective effect by inducing IgM-secreting B1 cells, which can recognize oxLDL. In contrast, IL-5 exacerbates eosinophilic inflammation; eosinophils (EOS) can be recruited into the plaque through the CCL5/CCL11-von Willebrand factor (VWF) axis. In turn, VWF promotes platelet adhesion that increases CCL5 levels. These events together with the eosinophil-platelet interaction favour thrombus formation. Activated eosinophils release eosinophil cationic protein (ECP) which induces extracellular matrix (ECM) deposition and adhesion molecules expression (ICAM-1) facilitating monocyte (MO) extravasation. The cytotoxic activity of eosinophils damages endothelial cells that release alarmins (IL-25, IL-33 and TSLP). IL-25 decreases plaque Th17 responses and IL-17 levels, which have a controversial role. Circulating IL-25 stimulates bone marrow and splenic Th2 and ILC2 cells to produce atheroprotective IL-5. IL-33 activates the endothelium, but it can inhibit macrophage oxLDL uptake. The effect of TSLP in Th17 responses remains unclear. Leu, leukocytes; PC, plasma cell

fibroblast activity promoting proteoglycan and extracellular matrix deposition. Indeed, it has been described that serum ECP levels are increased in patients with allergy and coronary atherosclerosis.[153,159] Additional clinical studies have shown a positive correlation between eosinophil counts and coronary artery calcification.[160]

5.2.3 | The alarmin-ILC2 axis

Alarmins such as IL-33, TLSP and IL-25 are involved in both allergic sensitization and inflammation.[161,162] The role of IL-33 in CVD is controversial. Its administration in ApoE$^{-/-}$ mice reduced plaque size via IL-5 and oxLDL-specific antibodies.[163] The co-administration of IL-33 with anti-IL-5 prevented plaque size reduction, but not the decreased macrophage infiltration, thus revealing an IL-5-independent atheroprotective mechanism for IL-33.[163] Moreover, IL-33 administration impaired foam macrophage formation in vitro and in ApoE$^{-/-}$ mice by reducing oxLDL uptake, intracellular cholesterol content, and enhancing cholesterol efflux.[164] A few reports have further explored the atheroprotective effect of IL-33 at the genetic level in macrophages.[165-167] Nevertheless, others have shown contradictory results, where IL-33 promoted endothelial activation.[168] Of note,

IL-33 deficiency in ApoE$^{-/-}$ altered neither atherosclerotic lesion nor the Th1/Th2 cytokine profile in supernatants of stimulated lymph node cells, which questions the role of endogenous IL-33.[169]

Genetic or antibody inhibition of IL-25 during plaque formation in ApoE$^{-/-}$ mice promoted Th1/Th17-related immune responses that induced larger lesions in the aortic arch.[170] Accordingly, IL-25 treatment of ApoE$^{-/-}$ mice reduced atherosclerosis via IL-5-producing-ILC2 expansion.[171] In human PBMCs, IL-25 has been reported to decrease Th1 and Th17 responses.[172]

TSLP and its receptor have been detected in human plaques.[173-175] Angiotensin II-induced TSLP promotes atherogenic Th17 responses.[173,174] It has been reported to induce a Th17/Treg imbalance in ApoE$^{-/-}$ mice.[175] In contrast, TSLP was shown to inhibit plaque formation in ApoE$^{-/-}$ mice by inducing tolerogenic dendritic cells and Tregs; this caused a phenotypic switch from an inflammatory Th1 toward a non-inflammatory Th2 phenotype, and oxLDL-specific antibody production.[176]

ILC2 can secrete large quantities of IL-5, IL-13 and IL-9,[162,177] and have been identified in cardiovascular tissues.[178,179] Bone marrow chimera experiments showed that genetic deletion of ILC2 in LDLr$^{-/-}$ mice aggravates atherosclerosis; the reconstitution with ILC2 was protective but not when IL-5- or IL-13-deficient ILC2 were used.[178] ApoE$^{-/-}$ mice transferred with ILC2 exhibited decreased lipid content and increased peritoneal B1 cells.[180] Moreover, it has been reported that IL-25-driven ILC2 expansion reduced plaque development through the IL-5-B1-IgM axis in ApoE$^{-/-}$ mice.[171] In vitro and in vivo experiments revealed an atheroprotective role for Treg cells by expanding ILC2 and increasing IL-13 secretion.[181]

5.2.4 | Other players of allergic inflammation

IL-9 participates in several pathologies including allergic inflammation.[182,183] IL-9 blockade in ApoE$^{-/-}$ mice decreased macrophage and T-cell infiltration in lesions, which reduced atherosclerosis, and exogenous IL-9 administration had the opposite effect.[184] Moreover, Blimp-1-mediated inhibition of Th9 cell differentiation was protective in a diabetic coronary heart disease rat model.[185] In line, acute coronary syndrome patients showed a greater number of peripheral CD4^{+}IL-9^{+} T cells and IL-9 levels[184,186]; and patients with carotid atherosclerosis had increased IL-9 levels too.[187] In allergic disease, Th9 cells induce CCL17 and CCL22 expression,[188] which facilitate atherosclerosis.[189,190] Additional studies in ApoE$^{-/-}$ mice revealed that CCR6 and CCL20, which are induced by IL-9, are proatherogenic.[191,192]

The role of IL-17A in atherosclerosis is controversial.[193-195] For instance, IL17A-deficient ApoE$^{-/-}$ mice had smaller plaques in the aortic arch and roots than controls, but with a similar plaque burden in the thoracoabdominal aorta.[196] In stark contrast, in vivo administration of IL-17A reduced plaque burden in aortic roots of LDLr$^{-/-}$ mice,[197] and may promote plaque stability by increasing vascular SMC collagen production.[198] Accumulating evidence suggests the participation of Th17 cells in allergic asthma and even the presence of a subgroup of dual positive Th2/Th17 cells in bronchoalveolar lavage fluid from asthmatic patients.[199-201] As abovementioned, data from experimental systems support a proatherogenic role for IL-17A in allergic asthma.[63]

6 | CONCLUDING REMARKS & PROSPECTS

Allergy and atherosclerosis are immune-mediated diseases with an opposed T-cell identity and a profound vasculature involvement. From a simplistic standpoint, atherosclerosis could be referred to as a physical plumbing issue that leads to pipe clots, pressure changes and ruptures. Yet, atherosclerosis still stands as a major cause of mortality worldwide, with a dearth of curative treatment options, which unveils the intricate maze that it represents.

The repercussion of acute and late allergic inflammation in atherosclerosis remains poorly characterized. From a broader perspective, acute allergic reactions are the result of an inflammatory program that ultimately acts on the endothelium favouring cell diapedesis to respond to a threat. The fast-acting ability of this Ig-mediated response allows the immune system to react promptly to danger, but it comes with an endothelial toll, likely favouring the initiation or exacerbation of atherosclerosis.

The atherosclerotic role of several components classically associated with Th2 immunity has been studied, but mostly under non-allergic conditions and on an individual basis. However, Th2 responses are an integral part of a broader program, termed type 2 immunity, which has evolved not only to control parasites and non-microbial noxious substances, but also to regulate other homeostatic processes. Thus, understanding type 2 immunity and, particularly, atherogenic mechanisms of allergic diseases, requires a holistic approach that assesses the role of each cellular/molecular player in the allergic arena.

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CONFLICT OF INTEREST

All the authors have no conflict of interest within the scope of the submitted work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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