CHAPTER 2
Literature review
2. Literature review

2.1. Coronary artery disease

Cardiovascular diseases (CVD), is the most significant cause of global mortality despite advances in medicine and drug development[46,47,48]. An estimated 17.9 million people died in 2016 from cardiovascular diseases (85%), due to heart attack and stroke representing 31% of global mortality. CVD can be prevented by addressing lifestyle-related risk factors such as smoking, physical inactivity, unhealthy food habits, and obesity. Stress and inflammation are emerging as novel risk factors for CVD in recent years.

Atherosclerosis is the underlying cause of CVD, and when it affects the coronary arteries it is termed as coronary artery disease (CAD). Atherosclerosis develops early as lesions in coronary arteries start appearing early in childhood [49]. The disease is prone to develop in the arterial curvatures especially at the branching points of the coronary artery [50]. The disease is now accepted as a chronic autoimmune inflammatory disease, based on our increased understanding of the role of the immune system in the disease pathology [51]. It is a complex disease wherein the immune system can have both protective and a pathological role in the development of the disease [13].

2.2. Indian scenario of coronary artery disease

India is an epicenter for coronary artery disease accounting for 25% of all mortality [52]. Indians get affected with a more severe form of coronary heart disease at a much younger age which cannot be explained by conventional risk factors alone [44,53,54], [55]. South Asian migrants in different countries are more susceptible to acute
myocardial infarction [56]. Comparing to other ethnic populations heart diseases occur in Asian Indians 5-10 earlier [54]. They are also reported to have higher pathogen burden and antigen load [3,4,57]. Thus Asian Indian population belongs to a high-risk group for developing the atherothrombotic disease, which is not explained by the conventional risk factors [44].

2.3. Immune system in Coronary artery disease

Classically the immune system is divided into an innate and adaptive response which is complementary to each other. The innate response is the nonspecific reaction to invading pathogen or foreign substance, while an adaptive response is highly specific. The innate response recognizes the damage associated molecular patterns and initiates a rapid inflammatory response. The pathogen is then internalized and processed by the antigen presenting cells (APC), represented by macrophages and dendritic cells, which then present the processed antigens to the lymphocytes for an adaptive response. Lymphocytes, initiate a specific inflammatory response towards the pathogen and retain the information about the pathogen as memory T and B cells for a quicker recall response during a second invasion by the same pathogen.

The role of the immune response in the pathogenesis of myocardial infarction has been demonstrated by several studies [58,59]. Activated inflammatory cells are found in the coronary plaques as well as the peripheral circulation in patients with acute coronary syndrome [60,61,62,63]. Different subsets of monocytes and T cells are involved in the pathogenesis of atherosclerosis. The immune system is being considered as a potential target for the prevention of cardiovascular diseases.
2.4. Circulating blood cells in CAD

Circulating peripheral blood mononuclear cells (PBMC), are exposed to the systemic environment, which includes metabolic factors and inflammatory molecules produced by different organs and tissues, which can alter their phenotype [64]. During acute inflammation, removal of stimuli leads to resolution of inflammation while it is sustained and unresolved in chronic inflammatory diseases [65]. Inflammatory monocytes (CD14++CD16−) and different subsets of T cells (Th1, Th2, Th17 and Tregs) are found in the atherosclerotic plaques of animal and human samples, with varying frequencies at different stages of the disease [10,21,25,27,66,67]. Treg cells are known to decrease during atherosclerosis, thus skewing the balance between the effector and regulatory T cells in circulation [68]. Apart from the T cells, the monocyte population also plays a variable role in atherosclerosis. These are the key inflammatory cells which enter the inflammatory tissue or growing plaque, mediated by the expression of the chemokine receptor, CCR2 [69,70]. Delineating the molecular and functional phenotype of circulating monocytes and T cells could be an indication of subclinical inflammation, which can precede the development of a disease.

2.4.1. Monocytes

Human monocytes are classified based on the surface expression of CD14 and CD16 as classical monocytes (CD14++CD16−) which respond to tissue damage and produce inflammatory cytokines, intermediate monocytes (CD14++CD16+), which are highly phagocytic, produce ROS and inflammatory mediator and non classical monocytes (CD14+CD16++) which are patrolling cells that remove debris and produce high levels of anti-inflammatory factors. The association of inflammatory monocytes with Crohn’s
disease rheumatoid arthritis, coronary artery disease, atherosclerosis, and obesity have shown in several clinical studies [66,67,71,72]. Monocyte count was also demonstrated to be an independent risk factor of CVD [73]. Multiple subsets of monocytes, from inflammatory (classical- CD14+CD16−) to anti-inflammatory (alternatively activated-CD14+CD16++) and intermediate cells (CD14++CD16+) are distinguished by cell surface markers [74]. The human classical inflammatory subset CD14+CD16− is elevated in circulation following inflammatory injury [75]. Expression of CCR2 on the surface is required for their high mobilization [76]. The chemokine receptor CCR2 is highly expressed in classical monocytes binds to monocyte chemoattractant protein 1(MCP1), and mediates monocyte infiltration into inflamed tissue [69]. Conversely, mice lacking CCR2 showed reduced lesion formation [77]. Apart from CCR2, other chemokines are also involved in homing of monocytes to the atherosclerotic lesion, which includes CCL5, CXCL1 and CX3CL1. Blockade of the chemokine receptors CCR2, CCR5 and CX3CR1 reduce atherosclerotic development [78,79]. The role of nonclassical monocytes in CAD is less well defined.

Macrophages are actively involved in atherosclerosis and were one of the first cells associated with atherosclerosis and are the main component of atherosclerotic plaque and take place in vascular remodeling. The macrophage in atherosclerotic lesions accumulate lipid (Oxidatively modified LDL), and with retention, it transforms to foam cell. M1 and M2 macrophages are polarized macrophages phenotyped based on their cytokine production. The M1 macrophages are inflammatory macrophages which secrete the inflammatory cytokines such as IFN-γ, TNF-α, IL-1β, IL12 and IL23 which aggravates the disease. The M2 macrophages secrete anti-inflammatory cytokines like
IL4 and IL10 which have a protective role in atherosclerosis [80]. Classical monocytes are recruited into growing plaque and differentiate into macrophages. M1 and M2 macrophages differentiate based on the expression of Th1 and Th2 respectively.

2.4.2. Mast cells

Mast cells another cell type which has a protective role in the host defense mechanism but known to take part in atherosclerosis disease progression and also known to involved in plaque destabilization. Mast cells respond to allergic response and also in both innate and adaptive immune responses. Mast cells are found in human atherosclerotic plaque and recruited into growing plaque. CXCR2, CCR3, CXCR4 and CCR5 are the chemokine receptors that help in chemotaxis and migration of mast cell into tissues [81]. The CCR3 expressed on mast known to be involved in their recruitment into plaque. Inhibition of CCR3 in mice reduced the recruitment of mast cells into tissues and prevented the progression of plaque [82]. The CCR3 and CCL11 expression in atherosclerotic plaque might also play an important role in their recruitment into the plaque. Lipid uptake of macrophages is reported to be enhanced by mast cells. Mast cell-derived mediators are known to be a potential promoter of atherosclerosis. Upon activation, mast cell secretes inflammatory cytokines like IL6, IFN a, IFN b, IL1 B, IL18. IL1 B and IL6 are crucial in Th17 differentiation. Mast cells secrete MMPs as MMP1 and MMP9, which has a potential role in plaque erosion and rupture.

2.4.3. Neutrophils

Neutrophils have a proinflammatory effect on atherosclerosis though it is considered as short lived. They have proteolytic enzymes and reactive oxygen species, which upon release lead atherosclerotic disease severity [83]. The proteolytic enzymes
and reactive oxygen species can affect the plaque stability and induce ER stress respectively. The monocytes, macrophages and dendritic cells are recruited and activated upon release of proteins by neutrophils [84,85]. Neutrophils are found in atherosclerotic plaque and also found in the most vulnerable plaque [86,87,88].

2.4.4. T cells

Naive T cells differentiate into distinct T cell subpopulations, including T helper (Th) cells and regulatory T (Treg) cells, in response to antigen and cytokine stimulation. The helper cells can be subdivided into Th1; Interferon-producing cells required for antimicrobial activity against intracellular pathogens, Th2; IL4 secreting cells with antiparasitic activity, Th17; IL17 secreting inflammatory cells with a pathogenic role in autoimmune diseases [89,90]. Treg cells are critical for the induction and maintenance of immune homeostasis and tolerance [91].

T lymphocytes are involved in the initiation, progression and destabilization of atherosclerotic lesions and demonstrated in the atherosclerotic plaques from humans and experimental animals [58,92,93,94]. Inflammatory T cell response to lipoproteins, heat shock proteins, and molecular mimicry with microbial antigens are believed to initiate the autoimmune reactions during atherogenesis [13]. The Th1 and the Th17 cells contribute to the proatherogenic T cell response while the influence of Th2 cells on atherosclerosis is inconsistent. Regulatory T cells (Tregs) are known to suppress the inflammatory response and have a protective role in atherosclerosis [29]. Naturally occurring Treg cells, characterized by the intracellular expression of fox head transcription factor (CD4⁺CD25⁺Foxp3⁺) maintain the immune homeostasis and suppress the inflammatory immune response [95]. Reduction in Tregs and their activity is seen in inflammatory and
autoimmune diseases [96]. In contrast, the Th17 cells play a critical role in the pathology of allergy and autoimmune response [97]. Since these two cell types have an opposite effect on the immune response, their balance is important in the development of autoimmune and inflammatory diseases [98,99,100].

2.4.4.1. Th1 cells

Th1 cells are the main face of the adaptive immune response, which afford protection against bacterial infections. They are also known to play a significant role in T cell-mediated injury in coronary atherosclerosis and are involved in disease progression and complications [101]. The IFN-γ secreted from Th1 cell induce macrophages to adhere to the endothelial wall. IL2 and IL18 induce the Th1 cells to secrete IFN-γ, which are associated with exacerbation of atherosclerosis [102]. Th1 cell which infiltrated from circulation is differentiated in draining lymph node by antigen stimulation which presented by DCs. In the plaque the most of Th1 cells found are clones, and this was stimulated within the plaque by antigens present in plaque, and they are present in the all the stages of the disease and the initiation stage of disease Th1 cells secrete cytokine TNF-α which activate the macrophages in foam cell formation. Th1 cells secrete the cytokines IFN-γ, IL-2, TNF-α and β, IL-6 and induce secretion of IgG2a antibodies by B lymphocytes [103], [104]. The cytokines produced from the Th1 cell are known to promote inflammation, plaque instability, macrophage activation. The Th1 cells are also involved in macrophage polarization of M1 and M2. The cytokines from Th1 cells induces the secretion of plaque destabilization cytokines and chemokines. It is reported that reduced lesion development and enhanced plaque collagen was found in an
experimental with IFN-γ receptor or IFN-γ deficiency [24,105] and enhancement of the lesion development was found with the exogenous administration of IFN-γ [105].

T cells plasticity polarize the T cell which can be pathogenic to the disease. The CD8 cells presence in atherosclerotic plaque have been reported and the cytotoxic T cells (Tc1) also fight against the infection. The CD8 is also known to secrete Th1 cytokine IFN-γ which are evident in driving the disease. IFN-γ is one of the driving factors in atherosclerotic pathophysiology and CD8 cells can secrete IFN-γ in response to antigen stimulation [106]. Tc1 cells along with IFN-γ also produce ROS upon activation [107]. ROS have a severe proatherogenic role in disease.

2.4.4.2. Th2 cells

Th2 cells are another type of T cells which also found in circulation and atherosclerotic plaque, characterized by secretion of IL-4, IL-5, IL-10, and IL-13 and help B cells in production of IgG1a and protective IgM antibodies [9]. The role Th2 in atherosclerosis is controversial but their cytokines IL4 and IL10 known to have an antiatherogenic effect. They are reported to play both atherogenic and anti-inflammatory role. Th1/Th2 skewed ratio was reported in CAD patients. The IL4 and IL10 from Th2 cells suppress the production of IFN-γ and differentiation of Th1 thus showing the anti-inflammatory property. CD8 cells also secrete Th2 cytokines, which represented as Tc2 have an anti-inflammatory role and suppress the inflammation [108]. Tc2 have atheroprotective property through its cytokine production and antiatherogenic role [109].

2.4.4.3. Th17 cells

Th17 is a helper cell subtype characterized by the production of IL17 beneficial in protecting the host from extracellular pathogens [110]. Although they have an important
role in host defense, these cells are associated with several autoimmune and inflammatory diseases such as arthritis, multiple sclerosis, psoriasis, and atherosclerosis [111]. Th17-producing cells are characterized by the expression of retinoic acid receptor-related orphan receptors (RORγt) transcription factor [90]. Th17 cells are derived from naïve CD4+ cells and produce characteristic inflammatory cytokines like IL-17A, IL-22 and IL-23 which in turn can induce the expression of an array of pro-inflammatory cytokines and chemokines (TNF-α, IL-1, IL-6 CXCL1, CXCL2, and CCL7) to intensify inflammation [112]. IL-17 has been implicated in several autoimmune diseases found to induce apoptosis of smooth muscle cells and endothelial cells which could lead to plaque rupture [113]. Th17 cells can aggravate the development of atherosclerosis and recently shown to be involved in the disruption of vulnerable plaque in mice model, suggesting their role in triggering an acute event [22,114].

In another study T cells infiltrating the coronary arteries were found to produce IL-17 concomitantly with IFN-γ and induce pro-inflammatory responses in vascular smooth muscle cells [30]. The cytokine IL-23 is known to enhance IL17 expression in activated cells but not on naïve T cells and thus is essential for Th17 differentiation, expansion, and survival [115]. The IL-23/Th17 pathway is also involved in the pathophysiology of autoimmune diseases [116,117]. Prolonged exposure to an inflammatory environment consisting of IL-1 and IL-23 induces Th17 cells to recruit inflammatory myeloid cells which cause severe local tissue injury which is most often observed in autoimmune diseases [118,119]. Patients with ACS have a higher number of Th17 cells and IL17 in peripheral circulation compared to control [28,120].
Although it is known that CD8 T cells may also contribute to the pathogenesis of acute MI, changes in circulating CD8 cells have not been explored in detail [121]. IL-17 producing CD8$^+$ T cell subpopulation, termed as Tc17 with a distinct role in the pathogenesis of autoimmune diseases including multiple sclerosis, psoriasis and autoimmune encephalomyelitis was recently described in human and mice [122,123,124].

2.4.4.4. CD4$^+$CD28$^-$ T cells

CD4$^+$CD28$^{\text{null}}$ T cell another T cell reported in atherosclerosis is associated with plaque vulnerability. Patients with unstable angina (UA) were reported to have an increased frequency of CD4$^+$ T lymphocytes lacking the co-stimulatory molecule CD28 (CD4$^+$CD28$^{\text{null}}$), which secrete high level of IFN$\gamma$ and perforin [61,125]. High levels of IFN$\gamma$ are reported in patients with unstable angina. It was also suggested that CD4$^+$CD28$^{\text{null}}$ can constitute up to 50% of the total CD4$^+$ compartment and are a dominant population of IFN$\gamma$ producing cells in patients with Unstable Angina [61,125]. The amount of CD4$^+$CD28$^{\text{null}}$ T cells in ACS with UA was ninefold higher than in CSA [60]. Several recent studies have reported that the expansion of CD4$^+$CD28$^{\text{null}}$ cells can mediate plaque instability and recurrence of AMI [60,126].

2.4.4.5. Tregs cells

Regulatory T cells (Tregs) can limit the inflammation and exert an immune regulatory function and are known to have an anti-atherogenic effect [127]. Adoptive transfer of Treg cells can reduce the plaque development [128] and depletion of Tregs enhances atherosclerosis in mice models, suggesting a protective role for these cells. Patients with unstable angina were reported to have lower Tregs [33]. Dysfunction of
Treg cells was also reported in experimental animal models of atherosclerosis [129]. Regulatory T cells are reported to suppress the recruitment of macrophages and foam cell formation in the lesion, increase phagocytosis, and collagen biosynthesis, thus resolving inflammation [130,131]. Regulatory T cells are pivotal for preventing autoimmune diseases in both human and mice and the numbers of Tregs found in the peripheral blood are determined by their development, persistence, and proliferation at the site of inflammation [132].

Like CD4+CD25+ the CD8+CD25+ regulatory cells are also reported to reduce the atherosclerotic plaque. These have suppressor activity and able to reduce atherosclerosis in mice when they were adoptive transfer to apoE(−/−) mice[133]. In another study it is reported that anti-CD3 induced CD8 Tregs were able to suppress the IFNγ and IL17 production of T cells [134].

2.5. **Imbalance in regulatory and effector cells**

The imbalance between inflammatory and regulatory cell type is associated with the disease. Earlier studies have shown that circulating pro-inflammatory T cells secreting IL-17 and IFN-γ with increased frequency and a reduction in the number of naturally occurring Tregs with compromised suppressive properties in MI patients [28,30,31,32,33,34]. Th1/Th2 skewed ratio reported in CAD patient was also to be involved in macrophage polarisation. Cheng et al showed that Th17/Treg balance controls inflammation and may be important in the pathogenesis of plaque destabilization and the onset of the acute coronary syndrome [28]. Imbalance in Th17/Treg was also found to be associated with infarction related cardiogenic shock [135].
2.6. **Systemic inflammation, Classical risk factors and metabolic factors**

Systemic inflammation is reported to be an independent risk factor for metabolic disorders as well as heart diseases [63, 136] which is characterized by high concentrations of inflammatory cytokines (TNF-α, IL 1β, IL6 and IL17), and an increase in macrophages and T cells infiltration [136, 137, 138, 139].

Hyperglycemia is known to acutely increase the inflammatory properties of monocytes and circulating cytokine concentrations and exaggerates inflammation [140, 141, 142]. One of the well known risk factor for cardiovascular diseases and stroke is smoking [143]. The soluble components of cigarette smoke are known to promote oxidative stress in blood cells [144]. Smoking can induce inflammation by downregulating the Nrf2/ARE pathway [145] and change the DNA methylation pattern in peripheral mononuclear cells affecting the immune inflammatory response [146]. Earlier studies have reported a strong correlation between subclinical inflammation with metabolic abnormalities in hypertension [147].

It is now generally accepted that systemic inflammation precedes metabolic diseases which in turn can accelerate acute coronary disease [148]. Major public health issues faced in the industrialized countries are being the Type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD) [149, 150]. The development of atherosclerosis influenced by various mechanisms and T2DM a major independent risk factor for CAD accelerates the disease [151].
2.7. **Metabolic factors**

High prevalence of CVD by a high frequency of diabetes and insulin resistance, high body fat, elevated levels of fibrinogen, homocysteine, and plasminogen activator, low HDL, and higher incidence of infection and inflammation [45]. Many of these factors have a direct influence on the immune system and the circulating lymphocytes. According to the World Health Organization, CVD can be prevented by addressing behavioral risk factors such as obesity, smoking and excessive alcohol use and lifestyle changes such as diet and physical activity [47].

The metabolic syndrome is associated with adverse cardiovascular events and related comorbidities, a group of symptoms which include high blood pressure, obesity, decreased HDL, elevated triglycerides, diabetes and insulin resistance [152], characterized by chronic low-grade inflammation [153,154,155,156]. It is now well accepted that cardiovascular diseases is not just an accumulation of cholesterol in the vessel wall but involves inflammation which affects the endothelial wall [157]. The source of this inflammation could be the infection, comorbidities like hyperglycemia, hypertension, obesity, and habits including smoking and excess alcohol consumption [158,159]. These stimuli induce the activation of the immune system and release of inflammatory biomarkers, adhesion molecules and chemoattracting factors [13].

2.8. **Hyperglycemia**

Association between the stress hyperglycemia and the poor cardiac outcome has reported in MI patients [160]. High blood sugar levels are known to have proinflammatory action and can increase circulating concentrations of IL-6, IL-18 and TNF-α [161]. IL-6 is a pleiotropic cytokine and can influence T cell development. Naïve
cells are known to differentiate into Th17 cells in the presence of IL-6 and TGF-β [162]. Untreated hyperglycemia in young adults is likely to influences the differentiation of Th17 cells which in turn augments inflammation and pathogenesis associated with the acute coronary syndrome. Cells of the immune system, especially macrophages in adipose tissue, are a major contributor to inflammation. In obese individuals, activation of these cells is associated with systemic inflammation and increased expression and production of TNF-α, which has a direct role in obesity-induced insulin resistance [163,164]. Immune cells are known to increase and secrete proinflammatory cytokines in pancreatic islets before the onset of type 2 diabetes [165].

2.9. Cytokines, chemokines and Infection

Cytokine and chemokines play a key role in acute and chronic inflammation. TNF-α, IL-1, IL-2, IL-3, IL5, IL-6, IL-10, IL-12, IL-15, IL-18, CXCL8, IFN-γ, M-CSF, TGF-β1, TGF-β2 and TGF β3 are found in atherosclerotic plaque and circulation [166]. IFN-γ, IL17, IL6 cytokines produced by Th1, Th17 and classical monocytes respectively have a proinflammatory role in the disease. IL10, IL4 and TGF-β have an anti-inflammatory role and have the ability to suppress inflammation. The IL5 and IL4 from Th2 can suppress the Th1 differentiation and its production of IFN-γ. Reciprocal developmental pathways involved in the generation of T cells like pathogenic effector Th17 cells and regulatory Treg cells. The TGF-β, an anti-inflammatory cytokine under the presence of IL6 is known to induce Th17 differentiation [167].

IL-17 was reported to induce apoptosis of aortic smooth muscle cells as well as endothelial cells in a mouse model and thus Th17 cells thought to be involved in the disruption of vulnerable plaques [114,168]. IL-6 has been reported to be higher in AMI
patients and identified earlier as an independent risk factor [169]. MCP 1 is found in both human and mice atherosclerotic plaque, and the mice which lack the MCP1 gene have showed reduced lesional formation. It is involved in the development and progression of the disease. CCR2 and CCR4 chemokine receptors expressed respectively in classical monocytes, and Tregs helps them in transmigration and recruitment into the plaque. CCR3 expression helps mast cells in recruitment into the atherosclerotic plaque. Leukocyte recruitment and regulation in atherosclerosis are mediated by chemokines (CXCL1, CCL2, MIF (macrophage migration inhibitory factor), CXCL16, and CX3CL1) and their receptors CXCR2, CCR2, CXCR2 and CXCR4, CXCR6, and CX3CR1 [170].

Infection is another possible reason for increasing inflammation and inflammatory cells in circulation. Infection along with hyperglycemia is one of the various factors that induce ER stress. High level of seropositivity is found to cytomegalovirus or Chlamydia pneumonia in the Indian population [57,171]. Chlamydia pneumonia (C.pn), Helicobacter pylori (H.py), Hepatitis A (Hep.A), Herpes simplex virus (HSV) and cytomegalovirus (CMV) are important among the various infection associated with atherosclerosis [172,173,174,175] and other studies also reported of that they have not associated the disease [176]. Pathogen burden due to infection through various pathogens instead of infection by any single pathogen are more susceptible towards the progression of CAD and related complications [174,177,178]. Indian population is reported to have high pathogen burden [179].

2.10. Autoantigens and autoantibodies

Autoantigens present in atherosclerotic plaque of CAD mediates the antigen-specific stimulation and expansion of T cells. Antigens like modified LDL leads foam
cell formation. Antigens which have been studied in greater detail as the possible autoantigens which initiate an autoimmune response are Oxidized low-density lipoprotein (Ox-LDL), Apolipoprotein B (ApoB) and Heat shock protein (HSP)60 [13,180,181,182,183]. Since human HSP60 shares a high level of homology with microbial HSP65, enhanced expression of HSP60 triggers a cross-reactive autoimmune reaction, which was originally primed by microbial infection [184]. Oxidized LDL is an immunogen which is taken up by macrophages to form foam cells during the early stages of atherosclerosis [185,186].

Several antigens, including oxidized LDL (Ox-LDL), heat shock proteins (HSP) are known to be important for the development of atherosclerosis [15,17]. Recently it was suggested that heat shock proteins could induce IL-12 and IL-23 expression by dendritic cells. IL23 is required for the sustenance of Th17 cells and therefore HSP60 may be one of the potential antigens for Th17 expansion [187].

Autoantigens also reported to have a protective role as several studies in the last decade have reported about the protective role of the regulatory immune response of atherogenic antigens [13,188,189,190,191,192,193,194,195]. Studies reported immune tolerance to ApoB and HSP60 derived peptides can protect against atherosclerosis in animal models [190,191,192,193,196]. Immune response to potential auto-antigens, also promote activation of the Th17 pathway [197,198].

The role of specific antibodies in atherosclerosis has been studied extensively. A positive association between anti-Ox-LDL antibodies and coronary artery disease have mentioned in several studies [199,200,201], while others find no such associations [202,203,204]. Circulating IgG antibodies against copper-oxidized LDL were associated
with a higher risk of cardiovascular disease (CVD), while IgM antibodies were associated with lower risk [205]. Both IgG and IgM antibodies to modified LDL were not found to be independent biomarkers to predict CVD by the EPIC Norfolk study [206]. Association of low levels of antibodies to malondialdehyde-modified apolipoprotein B-100 peptides p45 and p210 with a higher risk of coronary events were reported in a recent study [207]. Lower circulating antibodies to p210 and p45 from ApoB protein was shown to be associated with a lower risk of ACS and severity of coronary atherosclerosis in earlier studies [208,209],[210]. In a large population of more than 5000 subjects with 15 years follow up, subjects who developed ACS had a lower basal level of IgM antibodies to ApoB 100 derived peptides (p45 and p210) and lower IgG to P210 [207].

Apart from their role as molecular chaperones, heat shock proteins are also immunodominant molecules [211]. Higher levels of anti HSP65 antibodies were found to be associated with cardiovascular severity and mortality [212,213,214]. These antibodies were also found to mediate endothelial cytotoxicity, further strengthening their pathogenic role [215]. Subsequently, anti HSP60 antibodies were also reported to be higher in patients and predict the risk of cardiovascular diseases [172,216]. On the contrary, several studies in the last two decades have reported an immunoregulatory phenotype for HSP60 suggesting that these autoantigens also have the potential to induce a suppressive immune response to control chronic inflammatory diseases like atherosclerosis [183,188,190,217,218,219].