

## **Editorial**

### **Does a myocardial infarction boost your (B cell) memory?**

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The evolution of atherogenesis in humans is the result of episodic cycles of lesion progression, whereby subclinical thrombus formation leads to plaque accrual with the accumulation of layers of fibrotic tissue<sup>1,2</sup>. Multiple simultaneous coronary fissure and thrombi that have been described in patients with acute coronary syndromes may be explained by inflammatory activity within the vessel wall<sup>3,4</sup>. Enhanced understanding of the contribution of inflammation to cardiovascular disease (CVD) is leading to the discovery of additional mechanisms through which remote acute events might accelerate plaque formation. The evidence is mounting that the occurrence of a myocardial infarction (MI) can worsen atherosclerosis. In a seminal paper, Nahrendorf *et al.*, previously showed that following MI, a swarm of monocytes from the bone marrow and spleen invade the blood and reach remote plaques, building atheroma<sup>5</sup>.

This editorial refers to the publication by Kyaw *et al.* published in this issue of the European Heart Journal. Kyaw *et al.*, provide another - more insidious and long-lasting - mechanism to explain why MI can worsen atheroma: the establishment of autoreactive B cell memory. The manuscript reveals a previously unidentified risk of autoimmunity against the vessel wall after experimental MI<sup>6</sup>. MI induces an increase in aortic atherosclerotic lesions in apolipoprotein E-deficient (ApoE<sup>-/-</sup>) mice that is dependent on B cells and their ability to make antibodies (Figure 1). The authors provide evidence that there is a significant accumulation of IgG in aortic atherosclerotic lesions following MI. Depletion of B cells using an anti-CD20 antibody - a biologic used in rheumatoid arthritis - one week after MI attenuated atherosclerosis progression and IgG deposition. The authors show evidence that adoptive transfer of these autoreactive B cells enhances atherosclerosis in mice that did not see the same antigens because they did not suffer an MI, proving that the B cells themselves are key for the lesion enhancement and fulfilling a key criterion for autoimmunity.

B cells exemplify the contrasting roles of immune cell subsets in CVD. Two lineages of B cells exist, B1 cells of foetal liver origin and B2 cells that originate in the bone marrow. These lineages can be further separated into B1a and B1b subsets and B2 cells mature into follicular B cells and marginal zone B cells<sup>7</sup>. Following experimental MI, B cells are recruited to the injured myocardium and, via CCL7 production, they mobilise inflammatory monocytes to be recruited to the injured tissue. Systemic B cell depletion with an anti-CD20 antibody, leads to smaller infarct size and improved cardiac function<sup>8</sup>, suggesting a new strategy for the treatment of MI. In atherosclerosis, the role of B cells is more complex, and different B cell subsets carry out both pro- and anti-atherogenic functions (reviewed in<sup>7</sup>). B cell depletion in atherosclerosis-prone mice using an anti-CD20 antibody attenuates atherogenesis and the activation of dendritic cells and T cells<sup>9</sup>. B2 B cells are responsible for these pro-atherogenic effects<sup>10</sup>. In hypercholesterolaemia, a granulocyte macrophage colony-stimulating factor producing subset of B cells, known as innate response activator (IRA) B cells emerges in the spleen. These cells exacerbate atherosclerosis via promoting dendritic cell expansion leading to T-helper 1 cell generation<sup>11</sup>. In contrast, B cell immunity in the spleen has anti-atherogenic properties<sup>12</sup>, where marginal zone B cells regulate follicular T cell activation via PDL1<sup>13</sup>. Regulatory B cells are enhanced by hypercholesterolemia and exert athero-protection via other pathways including cytokine (IL-10) production<sup>14</sup>.

Where do B cells go to acquire their long-lasting memory? B cells acquire their long-lived immunological memory to antigens in germinal centres with T follicular cell help. Germinal centres are located in lymphoid organs or in the adventitia<sup>15</sup>. Somatic rearrangement of their genome leads to generation of cells that encode memory of antigens and can produce antigen-specific antibodies. The manuscript presents evidence that after MI, germinal centres are activated, which is an essential step towards the generation of high-affinity antibodies required for long-term serological immunity. Hypercholesterolemia itself is known to activate germinal centre formation<sup>15</sup>. Recently, Centa *et al.*, examined the contribution of germinal centre-derived IgG to atherosclerosis. B cell-specific deletion of PR domain zinc

finger protein 1 (*Prdm1*), which is required for establishing plasma cells, in ApoE<sup>-/-</sup> mice resulted in attenuated plaque development<sup>16</sup>. However, these smaller lesions displayed a more vulnerable phenotype with increased lipid and reduced smooth muscle cell content further highlighting the complex role for B cells and antibodies in atherosclerosis and the careful tightrope that must be walked when considering potential therapeutic targets.

What antigens are recognised by B cells post myocardial infarction? Kyaw *et al.*, hypothesise that the B cells respond to the release of intracellular proteins including alarmins. In humans, the levels of CD86<sup>+</sup> B cells (activated) and CCR7<sup>+</sup> B cells (B cells that have possibly encountered antigen) are increased after myocardial infarction, suggesting B cell activation. Autoreactive clones are usually eliminated in the thymus. In thyroiditis, inflammation and death reveal thyroglobulin and other crypto-antigens and start an autoimmune reaction. Here the authors hypothesise that alarmins and other crypto antigens can be revealed during myocardiocyte death and spill over into the circulation. The spleen starts an immune process in its germinal centre and long-term memory of B cells is built. This immunity does not attack the heart, the assault is carried out on distant arteries (Figure 1). It is difficult to conclude that alarmins are the only potential antigens, as they are often released during cellular activation by inflammatory stimuli. Alarmins may also activate other immune cells, boosting inflammation and antigen presentation, indirectly affecting B cells<sup>17</sup>. Other cryptoantigens might be at play and more research is necessary on the molecular mimicry linking the heart and arteries. No systemic changes in antibody production are seen after MI<sup>6</sup> and further validation of an antibody-mediated effect in human will also be required. Where are these antibodies produced? Is their production local to the vessel wall, where B cells are detectable in the adventitia?

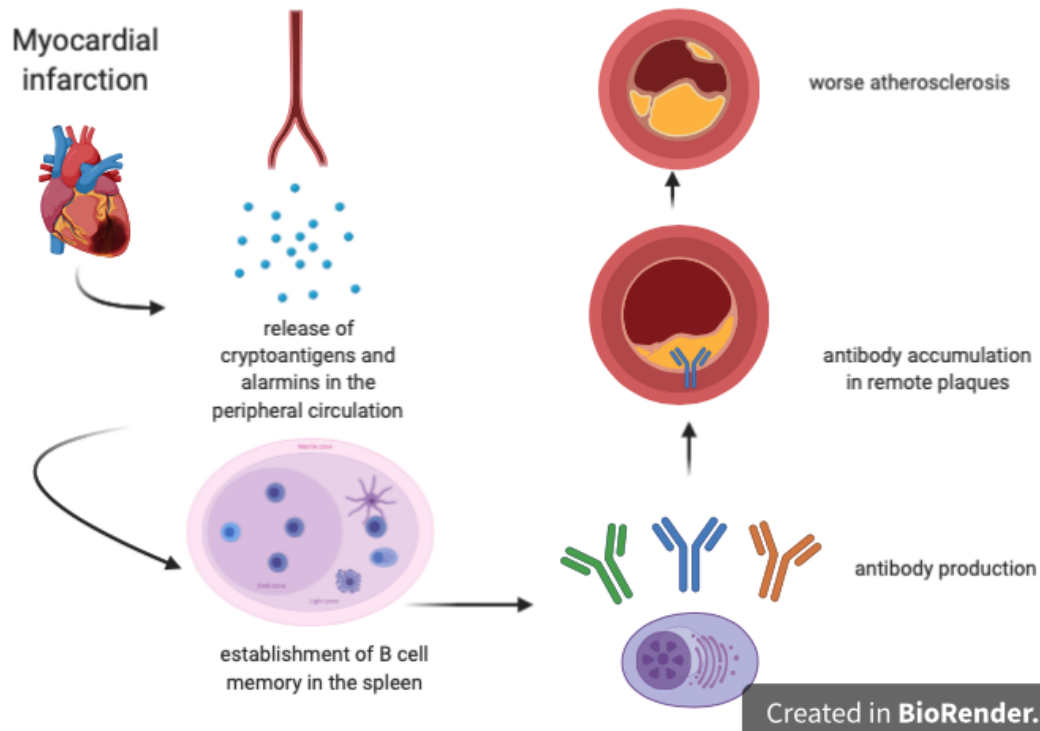
Atherosclerotic plaques in mouse and man are little cemeteries of dead foam cells at the side of the artery. Antibody production by B cells against dead cells and lipoproteins is a key feature of atherosclerosis. Protective natural IgM antibodies, produced by B1a B cells<sup>18</sup> recognise the phosphocholine within oxidised (ox) LDL and apoptotic cells<sup>19</sup> and they exert atheroprotective function probably via blocking LDL binding to scavenger receptors<sup>20</sup>. In CVD, there are several types of antibodies against lipoprotein particle components. B cells can protect from disease via the release of IgG antibodies against major components of lipoproteins such as ApoB100<sup>21</sup>. Not all antibody production by B cells is beneficial. Targeting plasma cell antibody production using loss of B cell X-box binding protein 1 in low density lipoprotein-deficient (LDLR<sup>-/-</sup>) mice via bone marrow transfer results in accelerated atherogenesis and lesions with larger necrotic cores<sup>22</sup>. Kyaw *et al.*, now show that B cells can acquire memory of myocardial infarction and perpetuate damage to the vessel wall by producing antibodies against antigens exposed and/or released by the death event. The mechanism through which these antibodies act remains unclear. The authors detect increased IgG in the lesions and also detect some cytotoxic cells that could use IgG to injure cells. They show that deficiency of MyD88 – a signalling adapter downstream of the interleukin-1/toll-like receptor superfamily -protects from the enhancement of atherogenesis, possibly through reduction of macrophage activation. However, due to the slow development of atherogenesis, MyD88 might mediate an indirect effect of cytokine release. Autoantibodies are known to activate TLR signalling. In systemic lupus erythematosus, autoantibodies against nucleoproteins activate endosomal TLRs driving chronic activation of the interferon pathway<sup>23</sup>. Autoantibodies against apolipoprotein A-1 activate TLR2 and TLR4<sup>24</sup>.

What is the evidence that acceleration of atherosclerosis post-MI is happening in humans? The risk of reinfarction or another acute coronary syndrome is very high in MI survivors<sup>25</sup>. Complex coronary<sup>3</sup> and carotid plaques<sup>26</sup> are found in MI survivors. Is the immune system involved? Are monocytes involved? Are B cells involved? We don't know. Yet. The reverse connection between myocardial infarction and atherosclerosis is increasingly being proven to be biologically plausible. We had better heed the warnings and start looking into this

mechanism of atherosclerotic progression in clinical prospective studies. The possibility of immune memory is a fascinating new hypothesis that makes CV immunology more intriguing than ever and one hopes that it will spark more verification of these mechanisms in human CVD.

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**Figure 1. Establishment of an autoreactive B cell memory after myocardial infarction: a working hypothesis.** The demise of cardiac cells leads to the release of cryptoantigens that induce a humoral immune response that leads to accumulation of immunoglobulins in plaques and eventually amplifies atherogenesis at remote sites.

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