Already in 1858, Rudolph Virchow, one of the founding fathers of cellular pathology lectured on the inflammatory nature of the ‘atheromatous affection of arteries’. According to Virchow, three stages of this disease can be distinguished: A stage of ‘fatty metamorphosis’, a stage of ‘irritation’ comparable to the stage of swelling and enlargement seen in other inflammatory states, and the stage of ‘atheromatous degeneration’ (1). This viewpoint was largely ignored in the 20th century, where atherosclerosis was considered to be the consequence of passive deposition of lipoproteins in the vessel wall or of smooth muscle cell proliferation and migration (2). However, research and numerous experiments in the past three decades have proven that the fundamentals of Virchow’s interpretation of the process of atherosclerosis were right. Atherosclerosis is indeed a chronic inflammatory disease (3).

Over the years, insights in how inflammatory processes modulate atherogenesis have become more sophisticated. At first the innate immune system was thought to be the key for the initiation and progression of the atherosclerotic plaque. Shear stress and oxidative stress induce endothelial cell activation, followed by monocyte adhesion and diapedesis into the intima. Subsequently, these monocytes within the intima differentiate into macrophages, which phagocytose modified lipids and become foam cells that are ‘building bricks’ of the atherosclerotic plaque (4). Clearly, the recruitment of macrophages is a rate limiting step in atherogenesis (5).

Nevertheless, research of the past years has shown that cells of the adaptive immune system such as T cells, B cells and antigen-presenting cells, although only present in small quantities in the plaque, were powerful mediators of atherosclerosis as well (6).

Our insights into how immunological processes mediate the initiation and progression of atherosclerosis have advanced dramatically in the past decade (7, 8). It has become clear that previously well-defined cell-types within the immune system actually consist of a collection of subtypes that exert a specific function within the inflammatory cascade that occurs during atherosclerosis. For example, we now clearly distinguish a pro-atherogenic role for the Th1 cells, whereas regulatory T-cells play a protective role in atherosclerosis (7, 8). We also discovered that there is an intricate interplay between the different immune cells, and that co-stimulatory molecules are key in modulating the consequences of these interactions (9). Similarly, different subsets of B cells – although barely present in atherosclerotic lesions – were found to play diverse roles in atherogenesis. Recent data suggest that conventional B2 cells possess proatherogenic properties, while innate-like B1 cells mediate atheroprotection via the secretion of natural IgM antibodies (10, 11). The latter property may largely depend on the capacity of natural IgM to recognise oxidation-specific epitopes on oxidised low-density lipoprotein (LDL) and cellular debris (12). Also new players have entered the field. Mast cells, natural killer (NK)-cells, neutrophils and dendritic cells are now considered key players in vascular disease. Moreover, co-morbidities such as systemic lupus erythematosus (SLE), human immunodeficiency virus (HIV) and exposure to the different pathogens were found to accelerate atherosclerosis significantly.

In this theme issue of Thrombosis and Haemostasis we have collected 13 review articles by experts in the field of cardiovascular immunology covering the most recent insights of the role of the different immune cells and their subtypes, the role of co-stimulatory molecules, and the effects of the different co-morbidities on the pathogenesis of atherosclerosis.

M. Hristov and C. Weber highlight the newest insights in how monocyte subpopulations guide the different aspects of atherosclerosis (13). Wolffs et al. describe how the classical M1/M2 paradigm does not fully apply in atherosclerosis and how the microenvironment determines the phenotype of the plaque macrophage (14). H. Manthey and A. Zernecke have entered the complex field of vascular dendritic cell biology (15). D. Ketelhuth and G. Hansson focus on the roles of the different T-cell subsets and elaborate on their recent findings of antigen specific T-cells in atherosclerosis (16). M. Butcher and E. Galkina describe the complex role of Th17 and other IL17 producing cell-types (17), while S. de Jaeger and J. Kuiper explore vaccine as a strategy to treat atherosclerosis (18). N. Gerdes and A. Zirlik highlight the important, but – sometimes – counterintuitive role of co-stimulation in cardiovascular disease (19). Getz et al. describe the newest insights on NK cells (20), I. Bot and E. Biessen on mast cells (21), D. Lievens and P. von Hundelshausen on platelets (22), and M. Drechsler and O. Soehnlein on neutrophils (23) in atherosclerosis, cell types that have only recently emerged in atherogenesis. Lastly, the papers by N. Wade and A. Major (24) and by M. Rosenfeld and L. Campbell (25) show that co-morbidities such as SLE and exposure to different pathogens have a major impact on cardiovascular disease.

From these reviews it becomes clear that the immune system plays a major role in

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atherosclerosis, and that we are getting a bit closer to a complete understanding of the processes contributing to plaque initiation, progression and the favourable regression. One of the major questions that remain to be addressed is the thorough identification of the key antigens that trigger these responses. Clearly, further research is needed to eventually allow the translation of immunological insights into novel therapeutic approaches for the prevention and treatment of atherosclerosis.

Conflict of interest
None declared.

References