15.1 Introduction

The view of atherosclerosis as an inflammatory disease has been strongly supported by studies demonstrating the ability of both the innate and adaptive immune system to modulate its initiation and progression. Different explanations exist as to why the immune system is involved in atherogenesis: While the adaptive immune responses involve certain autoimmune characteristics that likely develop as a consequence of chronic tissue damage in the vasculature, the involvement of the innate immune system may initially represent a defensive host responses that becomes exhausted or inadequate due to the long persistence of the pathogenic insult [1–6]. Indeed recent evidence suggests that atherosclerosis is profoundly propagated by the retention, accumulation and persistence of modified LDL, apoptotic cells and cellular debris, as impaired clearance mechanisms of innate immunity result in accelerated lesion growth [7–9]. Natural antibodies (NAbs) represent a major layer of innate immunity that have been suggested to convey “house keeping” functions by promoting the clearance of cellular waste, which is necessary for maintaining immune homeostasis [10]. Although, B-cells are rarely found within atherosclerotic lesions, antibodies – including NAbs – as their major product are regularly found to be present. Recent evidence now shows that NAbs are not merely present, but that they actively modulate the atherosclerotic disease process [11]. Their involvement in atherogenesis has not only contributed to the understanding of the pathogenesis of atherosclerosis, but provided also important insights into the hypothesized “house keeping” functions of NAbs in general.
15.2 Definition and Function of Natural Antibodies

NAbs are defined as pre-existing antibodies with germline or close to germline encoded variable regions. In lower vertebrates NAbs mainly consist of IgM antibodies with restricted epitope specificity and functions, whereas in higher vertebrates NAbs are of the IgM, but to some extent also of the IgG and IgA isotype. The term “natural” stems from the fact that they are found in normal quantities in the blood of mice housed in completely “germ” free conditions, thus also lacking commensal bacteria in the gut [12, 13]. Hence, NAbs develop without apparent immune exposure. They are produced very early in life by a specialized subset of B cells, termed B1 cells in mice. These cells have a self-replenishing capacity and differ from conventional B2 cells by their surface marker expression, activation requirements and anatomical localization, i.e. in pleural and peritoneal cavities [14, 15]. B1 cell development occurs primarily during fetal or perinatal life, and two models have been suggested regarding the ontogeny of B1 cells: the lineage model suggests distinct progenitors for B1 and B2 cells, while the selection model proposes their development from a common progenitor based on antigenic selection at the sIgM+ stage [16–21]. However, little is known what drives the selection of NAbs.

NAbs display reactivity to phylogenetically conserved structures of nucleic acids, (glyco)proteins and (phospho)lipids, all of which can be found in a wide range of both microbial as well as (altered) self antigens. Therefore, NAbs possess a rather broad specificity that is often described as “polyreactivity” [13], which however may only reflect the ubiquitous presence of these structures. Because of these binding properties, NAbs have a well established and critical function in providing a first line defense against invading pathogens; on the other hand, they have been suggested to mediate tissue homeostasis by regulating the clearance of damaged molecules and cellular debris [12, 13]. For example, in agreement with the importance of proper clearance of apoptotic cells in preventing certain autoimmune diseases, it has been shown that mice deficient in secreted IgM (sIgM), which are at large NAbs, show a higher propensity of developing an autoimmune phenotype upon LPS injection or when crossed with lupus prone lpr mice [22]. Moreover, this activity of NAbs has been shown to be aided by the activation of the classical complement pathway. IgM antibodies have been shown to be required for C1q mediated clearance of apoptotic cells both in vitro and in vivo. Moreover IgM antibodies are required for the C3 deposition on opsonised apoptotic cells [23]. In addition, natural IgM are also capable of inducing tolerance by presenting self antigens to immature B cells, [24] and thereby play a very important role in regulating B cell maturation, maintenance and survival. Studies in sIgM ko mice have shown that B1 cell as well as marginal zone B (MZB)-cell compartments are strongly increased in both young and adult mice, demonstrating a physiological feedback regulation by natural IgM [25, 26]. Young sIgM ko mice have also increased IgA, IgG3 and IgG2a levels, and exhibit impaired responses to T cell dependent antigens at suboptimal dosages. All this indicates that the efficiency of adaptive B2 cell antibody responses is at least partially regulated by natural IgM