# Chapter 1: The role of the immune system beyond the fight against infection


## Abstract

The immune system was identified as a protective factor during infectious diseases over a century ago. Current definitions and text book information are still largely influenced by these early observations and the immune system is commonly presented as a defence machinery. However, host defence is only one manifestation of the immune system's overall function in the maintenance of tissue homeostasis and system integrity. In fact, the immune system is integral part of fundamental physiological processes such as development, reproduction and wound healing, and a close crosstalk between the immune system and other body systems such as metabolism, the central nervous system and the cardiovascular system are evident. Research and medical professionals in an expanding range of areas start to recognise the implications of the immune system in their respective fields.

This chapter provides a brief historical perspective on how our understanding of the immune system has evolved from a defence system to an overarching surveillance machinery that strives to maintain tissue integrity. Current perspectives on the non-defence functions of classical immune cells and factors will also be discussed.


## Introduction - Our changing understanding of the immune system:

Our current understanding of the immune system varies drastically from the view that prevailed just over 20 years ago. Early observations during infectious diseases lead to a major focus on the immune system's ability to discriminate between self and non-self and defence against pathogenic micro-organisms. In its classical definition, the immune system comprises of humoral factors such as complement proteins, as well as immune cells and their products including antibodies, cytokines/chemokines and growth factors. This system of humoral and cellular factors is considered responsible for defending the host from invading pathogenic micro-organisms.

However, the effects of immune cells and factors are not limited to host defence, but extend to development, tissue homeostasis and repair (Figure 1). In addition, there are crucial immunological functions played by stromal and mesenchymal cells, which are not commonly considered part of the immune system, such as fibroblasts and endothelial cells. On top of that, it is now also appreciated that the inflammatory status of the environment is important in defining the type of response to any antigen

and that the immune system is in fact crucial for the maintenance and restoration of tissue homeostasis in both sterile and infectious situations.

**A brief historical perspective:**

What is believed to be the first record of an immunological observation dates from 430 BC. During a plague outbreak in Athens, the Greek historian and general Thucydudes, noted that people that were lucky enough to recover from the plague, did not catch the disease for a second time (1). The beginnings of modern day immunology are usually attributed to Louis Pasteur and Robert Koch. Pasteur, in contrast to common believe at the time, suggested that disease was caused by germs (2) and Robert Koch confirmed this concept in 1891 with his postulates and proofs, for which he received The Nobel Prize in Physiology or Medicine in 1905 (3, 4). These very early observations were fundamental for the first identification and early characterisation of the immune system, but also skewed all subsequent definitions towards a defence machinery against invading micro-organisms.

*The traditional view of immunity: evolution to protect from infectious micro-organisms.*

The immune system has long been considered to have evolved primarily because it provided host protection from infectious micro-organisms and correspondingly a survival advantage. Genes of the immune system have been suggested to be under particularly high evolutionary pressure due to the need to prevent pathogenic micro-organisms from harming the host. Hosts are therefore under selective pressure to resist pathogens, whereas pathogens are selected to overcome increasing host defences (5). This process of a stepwise increase in resistance by the host and subsequent mechanisms for evasion by the pathogen, is the basis for a well established co-evolutionary dynamics, the ‘host–pathogen arms race’ (6).

In 1989, Charles Janeway proposed his ‘pattern recognition theory’ (7), which still provides the conceptual framework for our current understanding of innate immune recognition and its role in the activation of adaptive immunity. Janeway proposed the existence of an evolutionary conserved first line of defence consisting of antigen-presenting cells equipped with pattern recognition receptors (PRR) which recognize common patterns found on micro-organisms, which are different and thus distinguishable from those of host cells. These innate cells take up foreign antigen,

present them to adaptive immune cells and thus determine the following adaptive immune response. Janeway's model also suggested, that the innate immune system evolved to discriminate infectious non-self from non-infectious self as microbial patterns were not present on host tissues (8). A few years later, the first family of pattern recognition receptors, the Toll-like receptors (TLRs) were indeed discovered (9). Notably, Toll-like receptors (TLRs) are also one of several striking examples of convergent evolution in the immune system (10). TLRs are used for innate immune recognition in both insects and vertebrates. The ancient common ancestor, a receptor gene with function during developmental patterning, subsequently evolved a secondary function in host defence, independently in insects and vertebrates, after the vertebrate and invertebrate lineage had separated (11).
All this seemed to strongly support the concept that the primary role of the immune system is to defend against potentially infectious micro-organisms.

*The danger view of immunity: evolution to protect from endogenous danger.*
Charles Janeway's model is still considered largely correct today, although too simplistic as it fails to explain certain aspects of immunity including sterile immune responses in the absence of infectious agents as well as the unresponsiveness to a variety of non-self stimuli such as dietary antigens and commensal microorganisms. In 1994, Polly Matzinger proposed the ‘Danger Hypothesis’ (12). Her model, again on purely theoretical grounds, suggested that the primary driving force of the immune system is the need to detect and protect against danger as equivalent to tissue injury. Importantly, in the same year, a group of scientists working on kidney transplantation, discussed the possibility that in addition to its foreignness, it was the injury to an allograft, which ultimately caused an immune response and rejection (13). Activation of innate immune events by injury-induced exposure of normally hidden endogenous molecules has since been demonstrated countless times (14, 15). Examples for such endogenous molecules include nucleic acids (16), heat shock proteins (17), cytoskeletal proteins (18), HMBG-1 (19), SAP130 (20), IL-33 (21) and IL-1a (22). In addition to proteins that are normally hidden from detection by the immune system, there are small molecules released as a result of endogenous stress including high glucose (23), cholesterol (24) and ATP (25). All these agents have been shown to contribute to sterile inflammatory responses and have been termed damage-associated molecular patterns (DAMPs).

Thus, an inflammatory environment caused by tissue injury (danger hypothesis) alerts the immune system and is the prerequisite to an adaptive immune response against foreign antigens (self versus non-self pattern recognition hypothesis).

*The integrative view of immunity: evolution as a system to establish and maintain tissue homeostasis.*

Considering the crucial importance of the innate immune response to tissue injury to initiate tissue repair processes and mount an effective adaptive response, the question arises if the early evolution of the immune system may have been driven by the need to maintain tissue homeostasis and the ability to deal with tissue injury rather than infection. Strikingly, the Russian developmental zoologist Ilya Metchnikoff discovered phagocytosis in echinoderms at the end of the 19th century and proposed the phagocyte and innate immunity as the center of the immune response. Metchnikoff's already developed a concept of immunity as a summary of all those activities that defined organismal identity, and which regarded host defence mechanisms as only subordinate to this primary function (26). The evolutionary development of the process of phagocytosis provides a very strong argument for the immune system being more than just a defence mechanisms. Evolutionary old organisms, such as ameba, already use this ancient mechanisms, albeit mainly for feeding (27, 28). In multicellular organisms, phagocytosis is first used during embryogenesis for the removal of dying cells and the recycling of their molecules. In adults, phagocytosis continues to play a crucial role during tissue remodeling (29, 30). Only the evolutionary appearance of the major histocompatibility complex (MHC) locus in jawed fish seems to have allowed the phagosomes to play a role in the establishment of adaptive immunity (31).

Decades of research using ever more sophisticated technologies allow the conclusion that defence against ‘non-self’ is only one of many layers of how the immune system protects us from disease. This is most evident in the evolutionary ancient mechanism of phagocytosis, which is still the most fundamental basis for tissue development, homeostasis and repair.

***Functions of immune cells beyond host defence:***

In this section, examples of non-defence functions of classical immune cells during reproduction, embryonic development, angiogenesis, and post-injury repair and regeneration will be discussed.

*Reproduction:* The immune system plays a crucial role in reproduction both before and during pregnancy and leucocytes are found in male and female reproductive tissues (32-34).

Several classical inflammatory mediators participate in the process of ovulation. Granulocytes, macrophages and T-lymphocytes migrate to the ovulation site and are activated locally, suggesting an active role of leukocytes in the tissue remodelling which occurs during ovulation (35).

Mice deficient of the major macrophage growth factor, colony-stimulating factor-1 (CSF-1) show severe fertility defects, as CSF-1 is involved in maternal-fetal interactions during pregnancy and has a crucial role in the development of the mammary gland (36-39). Eotaxin, a major chemokine for local recruitment of eosinophils into tissue, also contributes to mammary gland development (40, 41).

Establishment and maintenance of feto-maternal tolerance during pregnancy has intrigued immunologists for a long time, and to date a set of anatomical, cellular and molecular regulatory mechanisms that protect the fetus from immune-mediated rejection has been uncovered (42). The maternal-fetal interface is an immunologically highly dynamic site rich in cytokines and hormones (43, 44). During the first few weeks after fertilization, interstitial and endovascular infiltration of trophoblast cells leads to the recruitment of maternal immune cells and the production of pro-inflammatory cytokines (45). Maternal immune responses have been proposed to protect from trophoblast over-invasion while allowing for the acceptance of the semi-allogeneic fetal-placental unit. 40% of cells in the decidua during the first trimester are CD45+ leukocytes. 50-60% of decidual leukocytes are a unique type of natural killer (NK) cells which is not present outside the context of pregnancy and has crucial trophic function by helping to remodel the spiral arterioles of the uterus that supply the placenta with blood (46). Failure to sufficiently remodel these vessels leads to inadequate placental perfusion, which in turn leads to intrauterine growth restriction and pre-eclampsia, two important obstetrical complications (47). The remaining leukocytic infiltrate are roughly 10% T-lymphocytes, 1-2% dendritic cells (DCs), and 20-25% decidual macrophages (48).

The decidual macrophage population are subdivided into a CD11c high and CD11c low population, which are responsible for antigen processing and presentation. Depending on the macrophage subset, antigen presentation leads to either an induction of maternal immune cell tolerance to fetal antigens (CD11c high) or homeostatic functions including the clearance of apoptotic cells during placental construction (CD11c low) (49, 50). Thus, besides being a potential threat to the developing fetus due to allorecognition of fetal antigens, decidual leukocytes play a crucial role in the development of the fetal-placental unit (51).

*Development:* Macrophages both initiate and respond to developmental apoptosis (52, 53). Notably however, and a major sign of the fundamental role of the phagocytic process, non-immune cells are able to take over phagocytosis if necessary. In mice lacking macrophages due to a deficiency for the haemopoetic-lineage-specific transcription factor PU.1, the task of developmental phagocytosis is taken over by mesenchymal cells, although they are significantly less efficient than professional macrophages in recognition, engulfment and degradation of apoptotic debris (54). Comparable roles of macrophages in developmental apoptosis have been reported in evolutionary older vertebrate species and insects. In the frog *Xenopus laevis*, macrophage phagocytosis is involved in programmed cell death of tail and body muscle during metamorphosis (55). In the Drosophila embryo, the development of the tracheal system is created by a system of cell migration, rearrangements, and elimination of cells, which are engulfed and removed by macrophages (56).

*Bone development: Bone* osteoclasts are multinucleated cells that resorb bone material during development and form by fusion of mononuclear precursors of the monocyte/macrophage lineage. CSF-1 is an important factor involved in osteoclast differentiation (57). The toothless (tl) mutation in the rat is a naturally occurring, autosomal recessive mutation in the Csf1 gene and causes severely reduced numbers of macrophages and a profound deficiency of bone-resorbing osteoclasts and peritoneal macrophages. This results in severe osteopetrosis, with a highly sclerotic skeleton, lack of marrow spaces and failure of tooth eruption (58). Administration of CSF-1 can correct these defects demonstrating the crucial importance of macrophages in bone development (59).

*Brain development*: Brain microglia are highly motile phagocytic cells that infiltrate and take up residence in the developing brain, where they are thought to provide surveillance and scavenging function (60). They assist during embryonic development by mediating induced cell death of neurons (61). Both CSF-1 and its receptor are expressed in developing mouse brain, and CSF-1 deficiency induces neurological abnormalities (62). During postnatal brain development, microglia actively engulf synaptic material and play a major role in synaptic pruning (63). They can remove entire dendritic structures after depletion of appropriate inputs, a process termed synaptic stripping. They accumulate, through signaling mediated by the chemokine receptor CXCR3, at the lesion site and dendritic structures are removed within a few days (64, 65). Microglia cells may also be a source of other brain cells, as isolated microglia cells in culture have the potential to generate neurons, astrocytes and oligodendrocytes (66, 67).
Microglia also release factors that influence adult neurogenesis and glial development (68, 69). They secrete neurotrophins of the nerve growth factor (NGF) family, suggesting that they promote development and normal function of neurons and glia (70) and have autocrine function on microglial proliferation and phagocytic activity in vitro (71)

*Angiogenesis:* The formation of blood vessels is essential for tissue development and tissue homeostasis in all vertebrates. Monocytes and macrophages are known to be involved in the formation of new blood vessels and are involved in all phases of the angiogenic process. They are capable of secreting a vast repertoire of angiogenic effector molecules, including matrix-remodelling proteases, pro-angiogenic growth factors (VEGF/VPF, bFGF, GM-CSF, TGF-alpha, IGF-I, PDGF, TGF-beta), and cytokines (IL-1, IL-6, IL-8, TNF-alpha, substance P, prostaglandins, interferons, thrombospondin 1) (72). The expansion of the blood vessel network during angiogenesis starts with sprouting and is followed by anastomosis. Vessel sprouting is induced by a chemotactic gradient of the vascular endothelial growth factor (VEGF), which stimulates tip cell protrusion to initiate vessel growth (73). Macrophages are crucial for the fusion of tip cells to add new circuits to the existing vessel network by physically bridging and guiding neighboring tip cells until they are fused (74).

*Tissue homeostasis, regeneration and repair:* The immune system is crucial in wound healing and regeneration after tissue damage. There is a wealth of information available about the involvement of immune cells in the repair of all major organs including the skin (75, 76), skeletal muscle and heart (77-82), kidney (83, 84), liver (85), brain (86, 87) and the gut (88). If damage to blood vessels is involved, the activated coagulation system initiates the first stages of healing with the release of chemical mediators that promote vascular permeability and leukocyte adhesion and recruitment. Coagulation activates platelets which produce growth factors such as transforming growth factor-β (TGFβ) and platelet-derived growth factor (PDGF), which activate fibroblasts and act as chemoattractants for leukocytes (89). However, even without activation of the coagulation cascade, alarmins released from necrotic cells recruit leucocytes. Infiltrating neutrophils and macrophages remove dead cells and secrete chemokines and cytokines, including tumour necrosis factor (TNF) and interleukin-1 (IL-1), which further upregulate leukocyte adhesion molecules to increase immune cell recruitment and induce the production of additional growth factors and proteases such as matrix metalloproteases. Matrix metalloproteases degrade the extracellular matrix which allow for tissue remodelling. fibroblast growth factor (FGF), PDGF, prostaglandins and thrombospondin-1, promote new blood vessel growth, fibroblast proliferation and collagen deposition. Tissue remodelling is accompanied by parenchymal regeneration or regrowth of the epithelial cell layer with resolution of the healing process (90).

Recently, several innate-type lymphoid cell (iLC) subsets have been identified and characterized, that seem to play a particularly important role in sterile inflammatory settings. These novel cell types include lymphoid tissue-inducer cells, innate type 2 helper cells, and γδ T-lymphocytes (91). These cells rapidly express effector cytokines that are commonly associated with adaptive T helper cell responses such as IL-17, IL-13, IL-4 and IL-22 (92, 93). Their role in wound healing and regeneration is strongly mediated by the cytokines they produce. LTi cells play a central role in promoting appropriate thymic regeneration in sterile inflammatory settings, an effect which is mediated largely through the cytokine IL-22 which promotes epithelial repair and tissue regeneration (94). Further, the endogenous alarmin IL-33 has profound effects on innate type 2 helper cells and thereby plays a central role in driving type 2 immunity under sterile and infectious settings (95, 96). Tissue repair processes following injury are dominated by type 2 immune cells producing cytokines such as

IL-4, IL-5, IL-10, and IL-13. Many Th2 processes promote the “walling off” of large invaders through granuloma formation and matrix deposition, which are the same mechanisms employed to close open wounds (97). Shifting the inflammatory response towards a type 2 response is beneficial for quick wound healing, which likely was the evolutionary most cost-effective approach to deal with large parasites or insect bites, although this may come at the cost of fibrotic repair and long-term loss of tissue functionality (80, 98). Intense research efforts in the field of regenerative medicine are trying to find the right balance between pro-inflammatory Th1 and reparative Th2 responses to prevent scarring and fibrotic repair, and boost regenerative healing instead.

**Concluding remarks**

Both evolutionary development and functional variety in current day organisms strongly support a notion of the immune system as an all-encompassing machinery to ensure system integrity. Protection from disease caused by invading pathogenic micro-organisms is, although the most easily observed, only one manifestation of the workings of this machinery. Instead, the immune system is essential for development, surveillance, protection and regulation to maintain or if necessary re-establish homeostasis.

**Figure Legends:**

**Figure 1: The fundamental roles of the Immune System beyound host defense:** The Immune system is essential for reproduction, development and homeostasis. Sterile tissue damage such as physical trauma or ischaemia/reperfusion injury (e.g. myocardial infarct) induces an inflammatory reaction to initiate wound healing and/or regenerative mechanisms. The same basic immunological mechanisms will eliminate microbes if they are present due to injury at a barrier sites (e.g. skin) or primary infectious tissue damage (e.g. viral myocarditis). Necrotic cells in damaged tissue release danger associated molecular patterns (DAMPs) such as HMGB1, IL-33, ATP, heat shock proteins, nucleic acids and ECM degradation products. Microbes are recognised by the immune system through their expression of pathogen associated molecular patterns (PAMPs)

such as LPS, flagellin, dsRNA, unmethylated CpG motifs in DNA. ATP: adenosine triphosphate, HMGB1: high mobility group box 1, ECM: extracellular matrix.

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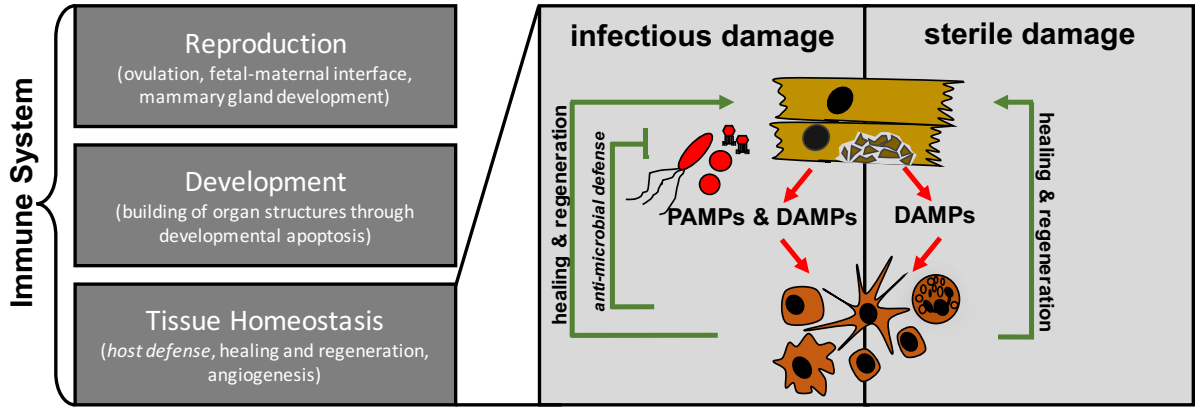
Figure 1


Immune System
Reproduction
(ovulation, fetal-maternal interface, mammary gland development)
Development
(building of organ structures through developmental apoptosis)
Tissue Homeostasis
(host defense, healing and regeneration, angiogenesis)
infectious damage
sterile damage
healing & regeneration
anti-microbial defense
PAMPs & DAMPs
DAMPs
healing & regeneration