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The Immunology of Cardiovascular Homeostasis and Pathology

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Preface

Cardiovascular immunology is a newly emerging research area based on the increasingly evident existence of several layers of crosstalk between the cardiovascular and the immune system. Nevertheless, there is still little overlap between research into cardiovascular biology and immunology. However, emerging knowledge is challenging this paradox and forcing communication between the two fields. As a result, we are now approaching a time where the immune system is rapidly being appreciated for its role other than fighting infections, particularly in the cardiovascular sciences.

For this book, we have sought to bring together experts on various aspects of cardiovascular immunology, with the aim of providing an overview of the crosstalk between the cardiovascular and the immune system under homeostasis and during disease. First, we discuss our changing understanding of the immune system and its various roles in physiological processes other than host defence. We then describe the immunological capacities and functions of the most important cardiovascular cell types, including cardiomyocytes, fibroblasts, endothelial cells, pericytes as well as resident macrophages, the most prominent cardiac immune cell population. This is followed by an exploration of areas, in which disturbance of immune regulation and aberrant activation of the immune system is causative in the development of cardiovascular disease including atherosclerosis and cardiac and cardiovascular autoimmunity. We conclude with two chapters on the crucial role of the endogenous innate and adaptive immune system in heart repair and regeneration after tissue damage.

With this comprehensive coverage of state-of-the-art knowledge on the mutual and interdependent link between the cardiovascular and the immune system, we hope to provide a valuable resource for readers with either immunology or cardiovascular background.

London, UK — Susanne Sattler
London, UK — Teresa Kennedy-Lydon

Introduction

Most textbooks still describe the immune system largely in the light of infectious disease. However, we now know that defence against invaders is only one of several roles of the immune system aiming for the maintenance or restoration of tissue integrity. Non-self-recognition and defence against infectious microorganisms even seem to be an evolutionary younger addition to the ancient mechanism of phagocytosis, which is the crucial basis for fundamental physiological processes during development and homeostasis.

As such the immune system cannot be separated from the rest of the body but is an integral part of any organ system or physiological process. To name just a few striking examples, ovulation, mammary gland development, the establishment of a successful pregnancy through fetomaternal tolerance, embryonic development through developmental apoptosis, angiogenesis, bone and brain development and of course wound healing and regeneration of adult tissues are all dependent on a variety of immune effector cells or molecules.

A crucial role of the immune system beyond the control of infectious diseases has also become evident in the cardiovascular system. Immune cells and molecules play critical roles as effectors in cardiovascular health and disease. The heart itself contains a diverse population of tissue-resident immune cells, which are crucial in the continuous maintenance of tissue integrity. Moreover, the vasculature is in intimate contact with immune effectors in the blood and thus particularly susceptible to inflammatory changes. Conversely, parenchymal and stromal cells of the heart and vasculature have a wide range of crucial immunological functions and are active players in shaping immune responses.

Although the field of cardiovascular immunology is still in its infancy, it's becoming increasingly evident that a tightly controlled interplay between the two systems is essential to maintain cardiovascular health. Taking into account the effects on both systems will have potential to significantly improve future therapeutic strategies.

Contents

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Part I
The Immune System in Tissue and Organ Homeostasis

Chapter 1
The Role of the Immune System Beyond the Fight Against Infection

Susanne Sattler

1.1 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 microorganisms. 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 pathogens.

However, the roles of immune cells and factors are not limited to host defence, but extend to development, tissue homeostasis and repair (Fig. 1.1). 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.

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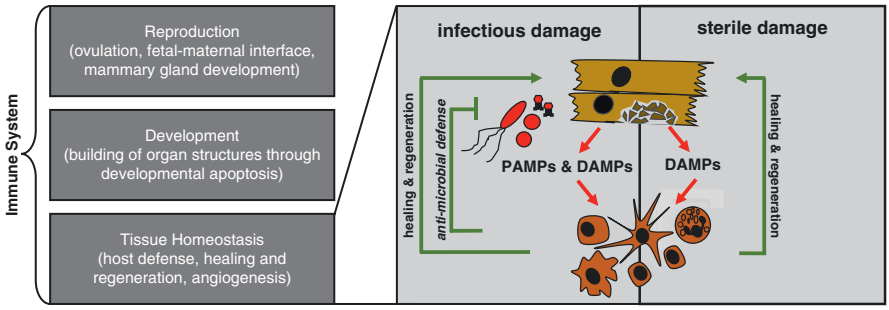

Fig. 1.1 The fundamental roles of the immune system beyond host defence: The immune system is essential for reproduction, development and homeostasis. Sterile tissue damage such as physical trauma or ischemia/reperfusion injury (e.g. myocardial infarct) induces an inflammatory reaction to initiate wound 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 damage/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 and unmethylated CpG motifs in DNA. *ATP* adenosine triphosphate, *HMGB1* high mobility group box 1, *ECM* extracellular matrix

1.2 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 Thucydides 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 belief 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 microorganisms.

1.2.1 The Traditional View of Immunity: Evolution to Protect from Infectious Microorganisms

The immune system has long been considered to have evolved primarily because it provided host protection from infectious microorganisms 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 microorganisms 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 recognise common patterns found on microorganisms, which are different and thus distinguishable from those of host cells. These innate immune cells take up foreign antigens, 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. This happened 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 microorganisms.

1.2.2 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