Archives of Medical Research 48 (2017) 1−11

Archives of Medical Research

REVIEW ARTICLE

Role of Adaptive Immunity in the Development and Progression of Heart Failure: New Evidence

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Received for publication March 18, 2016; accepted December 13, 2016 (ARCMED-D-00175).

Heart failure (HF) is considered the endpoint of a variety of cardiac diseases, which are the leading cause of death in adults and considered a growing pandemic worldwide. Independent of the initial form of cardiac injury, there is evidence linking the involvement of the immune system. In HF there is evidence of the participation of T_H1, and T_H17 cells, which account for sustained pathological chronic inflammation, cell migration, and the induction of specific pathological phenotypes of mononuclear cells. Of equal or even higher relevance are the B lymphocyte activation mechanisms that include production of pro-inflammatory cytokines, chemokines, and cardiac autoantibodies with or without activation of the complement proteins. Both of these unbalanced T- and B-cell pathways of the adaptive immune system are associated with cardiomyocyte death and tissue remodeling by fibrosis leading to a dysfunctional heart. At this time, therapy with neutralizing antibodies and the use of anti-cytokine immunomodulators to counteract the immune system effects have reached a plateau of mixed results in clinical trials. Nevertheless, recent evidence showed promising results in animal models that suggest that modulation of the adaptive immune system cells more than some of their effector molecules could have benefits in HF patients. This review summarizes the role of the adaptive immunity cells in HF, considering the sustained activation of adaptive immune system as a potential contributor to disease progression in humans and experimental models where its regulation provides a new therapeutic target.

Key Words: B cells, Heart failure, T cells, Adaptive immunity, Auto-antibody.

Introduction

The clinical syndrome of heart failure (HF) is the final common pathway for myriad diseases that affect the heart. Mortality is comparable to that of the most common cancers, with a 50% 5-year survival (1). One of the more recent and less understood mechanisms that leads to HF is the involvement of the innate inflammatory cascade, largely mediated by neutrophils and monocytes/macrophages (2). These cells secrete a range of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and interleukin (IL)-6 (3). A clear imbalance between inflammatory and anti-inflammatory cytokines (IL-10 and transforming growth factor beta [TGF-β]) favors the onset of accelerated and extensive fibrosis, resulting in inappropriate myocardium remodeling (4).

To date, identifying the mechanisms that determine the progression from well-compensated ventricular remodeling and hypertrophy to ventricular dilatation and subsequent HF has not been fully elucidated. A complex balance of molecular and cellular compensation seems to be mediated, at least in part, by an overly activated immune system. This

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0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2016.12.008

phenomenon appears not only in the acute phase, but also in the chronic phase, perpetuating and allowing the progression of HF and tissue damage (5).

The current literature suggests that there is an important contribution of the adaptive immune system in this process through reactivation and/or persistence of the inflammatory cascade (6). However, the mechanisms responsible for recruiting the lymphocytes to the heart have not been fully described (7,8).

By improving our understanding of the innate and adaptive immunological mechanisms involved in HF, we can identify future potential therapeutic targets. This knowledge can be focused on the prevention or reduction of the adverse wall remodeling mechanisms and thereby improve the morbimortality rates of these patients. In this review we describe the role of the adaptive immune system, focusing on heart diseases, emphasizing on HF, and providing an update compilation of the available evidence.

Adaptive Immunity in Heart Diseases

Innate and adaptive systems work simultaneously with constant feedback between them. Almost every type of lymphoid and myeloid cell is involved in the physiopathology of cardiovascular diseases, both circulating and heart hosted, and it is the balance of their effects that determines the healing or damage of myocardial cells (8,9). As in other organs, the heart's resident immune system cells are capable of recognizing and eliminating potential hazards through pattern recognition receptors, which identify pathogen- or damage-associated molecular patterns. This ability is a primary characteristic of the innate immune system. Most of the immune system cells in the heart are macrophages and only a small number of mastocytes and T- and B-lymphocytes are present. The roles of these cells as initiators and promoters of the inflammatory cascade after myocardial damage are not very well known (10).

Adaptive immunity, which comprises lymphocytes, is capable of launching an initial immunological response through cytokine production and antibody or antigen presentation through the major histocompatibility complex I and II (MHC-I, II). An important characteristic of these cells is that they can develop memory against perceived antigens and proteins, allowing a faster and more intense response to subsequent re-exposure. In recent years, increased attention has been given to the potential role of the adaptive system in many heart diseases, both as an initiation and/or perpetuating mechanism (9).

Immune-mediated mechanisms have been described in both ischemic and non-ischemic pathologies of cardiac tissue, which means they can play an important role in virtually all cardiovascular diseases (Figure 1).

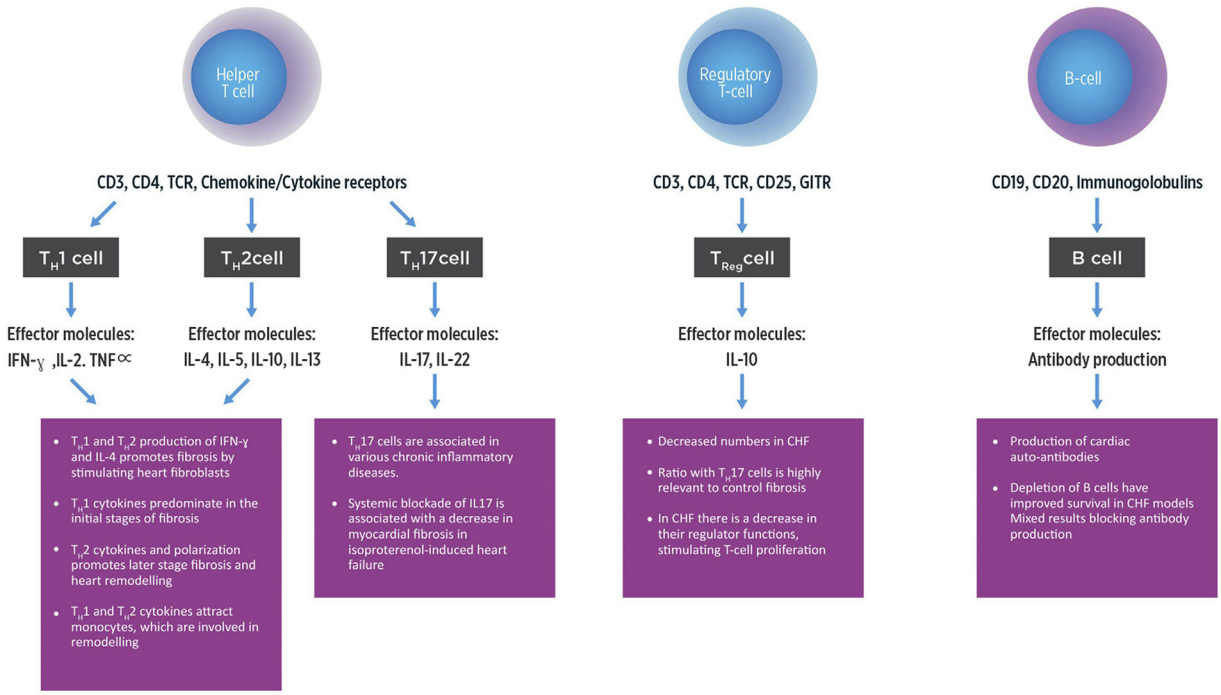

Figure 1. Role of lymphocytes in heart disease. Schematic representation of lymphocyte subtypes involved in the pathophysiology of heart disease. Each subtype expresses different effector molecules (cytokines and chemokines) with different functions. Although their effects are limited by a series of compensatory mechanisms, their unbalance is linked to a variety of pathological processes. Whereas T_H1 and T_H2 cells are involved in several autoimmune settings, in heart disease they are involved in the initial (T_H1) and perpetuation (T_H2 and T_H17) of fibrotic phenomena. T_{REGS} dysfunction and decreased numbers in CHF are associated with T-cell proliferation and pathological remodeling. Finally, B cells are associated with the production of autoantibodies and their removal by immunomodulatory agents has been associated with improved survival in animal models. (A color figure can be found in the online version of this article.)