



PART I

Immune dysfunction
leading to heart
disease: induction by
physiological changes

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CHAPTER 1

Immunosuppression by ultraviolet light-B radiation: a mediator of cardiac remodeling

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Introduction

Heart failure (HF) represents a major public health problem, affecting approximately 5 million patients in the United States and more than 550,000 new cases each year [1]. Heart failure has an extremely complex multidimensional pathophysiology involving structural and functional cardiac disorders and increased neurohormonal activity, primarily mediated through the sympathetic nervous system and the renin–angiotensin–aldosterone axis. Despite the diversity of HF etiologies, a crucial process in the progression of most forms of HF is left ventricular remodeling. Increasing evidence suggests the immune response-mediated regulation of cardiac extracellular matrix (ECM) remodeling.

Ultraviolet (UV) radiation presents one of the most important environmental factors that influence human health. Besides its well-known advantages, UV radiation also has well-documented adverse health effects, including premature skin aging, skin cancer, cataracts, and exacerbation of infectious diseases. Conclusive evidence has demonstrated that exposure to UV-B light induces photoimmunosuppression, which mediates several of these hazardous health effects. Estimation of over 1 million new cases of nonmelanoma skin cancer, and about 50,000 cases of in situ melanoma in the United States in 2006, according to the American Cancer Society [2], suggests the number of people who likely have UV-B exposure with likely enhancement of carcinogenesis with immunosuppression. However, do the UV-induced immunosuppressive

changes in the skin become significant enough to have systemic effects that could affect heart structure?

Role of T_H1/T_H2 imbalance in development of cardiac ECM remodeling

Cardiac remodeling, a determinant of the clinical progression of HF, is defined as alternation of genome expression resulting in molecular, cellular, and interstitial changes and manifested clinically as changes in size, shape, and function of the heart [3]. Changes in the myocardial ECM, including the activation of proteolytic enzymes, matrix metalloproteinases (MMPs), and alteration in the myocardial collagen organization, contribute to the remodeling process [4]. Not only neurohormonal and autonomic nervous systems have been described as effector pathways in myocardial ECM reorganization, but also $CD4^+$ T lymphocyte has been shown to play a fundamental regulatory role in cardiac ECM composition through modulation of collagen synthesis and degradation.

$CD4^+$ T helper (T_H) cell subsets can be classified by the pattern of the cytokines they express upon activation. T_H1 cells produce mainly interleukin (IL)-2, -12, -15, and -18, interferon (IFN)- γ , and transforming growth factor (TGF)- β and promote cell-mediated immunity, whereas T_H2 cells secrete IL-4, -5, -6, -10, -13, -17, associated with humoral immune responses [5]. The T_H phenotypes have been shown to differentially alter cardiac

ECM composition. Selective induction of T_H1 lymphocytes in young mice increased left ventricular stiffness, through decreased pro-MMPs expression, MMPs activity, and increased total and cross-linked collagen synthesis. However, T_H2 induction resulted in dilated cardiomyopathy associated with decreased left ventricular stiffness, increased MMPs expression and activity, and decreased myocardial total and cross-linked collagen synthesis [6]. An important observation was the finding that the immune background of the mouse affects the cardiac remodeling processes in response to the induction of hypertension. In this study, T_H2 predominant strain was associated with increase in collagen synthesis and deposition, and ventricular stiffness, whereas no significant changes was observed in T_H1 predominant strain [7]. Moreover, the T_H2 murine model of HIV has been shown to be associated with a significant diastolic dysfunction [6]. Interestingly, in a recent clinical study, increased peripheral T_H2 subtype of $CD4^+$ T lymphocytes has been hypothesized as an immunological pathogenesis underlying dilated cardiomyopathy [8].

Ultraviolet light-B-induced immunosuppression

The immunosuppression results mainly from the effect of UV-B light on skin dendritic cells (DC) and T lymphocytes, which is a consequence of the formation of pyrimidine dimers in UV-irradiated epidermal Langerhans cells [9]. It has been shown that solar-simulated UV radiation induces a defective maturation and an anomalous migratory phenotype of DC, accompanied by decreased expression of molecules involved in antigen capture, diminished endocytic capacity, enhanced expression of molecules involved in antigen presentation, and a significant increase in their capability to stimulate T cells [10]. Moreover, it has been indicated that UV-B exposure impairs antigen presentation to T_H1 cells, whereas enhances the antigen presentation to T_H2 cell [11, 12]. Therefore, a shift in the activation of the T cells from a T_H1 - to a T_H2 -type immune response may mediate, in part, the immunosuppressive effect. This T_H1/T_H2 imbalance was confirmed in another study in which the proinflammatory T_H1 cytokines, $IFN-\gamma$ and IL-12, were depleted from the murine epidermis by UV-B

by 24 hours, whereas expression of the T_H2 cytokine IL-10 was unregulated, peaking at 72 hours [13].

The UV-B effect has been thought to be mediated, in part, by a subset of T regulatory cells. The UV-B-induced $CD3^+$, $CD4^+$, and $CD8^-$ regulatory T cells mediate their suppressive effects by releasing the immune regulatory cytokines IL-4 and IL-10 [14]. Recently, this subtype of regulatory T cells, with the ability to transfer UV-induced immune suppression to the UV-B unexposed recipient mice, have been shown to express CTLA-4, a negative regulatory T cell-associated molecule [15]. Upon in vitro expansion, CTLA-4⁺ T cells secrete variety of cytokine, including IL-2, IL-10, TGF- β , and $IFN-\gamma$, resembling a T regulatory 1-like cytokine pattern [16]. IL-10 monoclonal antibody not only has been shown to neutralize the suppressive activity of CTLA-4⁺ T cells in vivo [15], but also to reserve both the failure to present to T_H1 cells and the enhanced presentation to T_H2 cells [17]. These findings suggest the involvement of CTLA-4⁺ T cells in induction of T_H1/T_H2 imbalance.

Supporting the observed immunosuppressive effect of UV in experimental studies, UV exposure suppresses the induction of immunity in human volunteers [18, 19]. Many of the mechanisms involved in UV-induced immune suppression in humans are similar to those described previously in experimental animals. Induction of delayed-type hypersensitivity and contact hypersensitivity are suppressed after a single or short-term exposure to UV radiation [20], indicative of impaired cell-mediated immunity and T_H1/T_H2 imbalance. Moreover, UV-B irradiation of antigen-presenting cells selectively impairs T_H1 -like responses, a phenomenon caused by reduced IL-12 production by human monocyte [21]. There is also evidence that UV-B irradiation in healthy volunteers initiates a rapid proinflammatory response followed by a combined T_H1/T_H2 response in which ultimately T_H2 cytokines, IL-4 and IL-10, predominated after 24 hours [22].

Conclusion

These epidemiologic and experimental animal studies lead us to the hypothesis that UV-B through its immunosuppressive effect may initiate or attenuate the adverse cardiac remodeling, which may in

turn contribute to the clinical syndrome of HF. In light of the fact that exposure to UV-B radiation occurs daily and may be increasing due to the effects of atmospheric pollution on the ozone layer, it is critically important to investigate the potential role of UV-B radiation on cardiac ECM remodeling.

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