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Potential role of IL-37 in atherosclerosis

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ABSTRACT

IL-37 is a member of the IL-1 family, but unlike most other members of this family of cytokines, it has wide-ranging anti-inflammatory properties. Initially shown to bind IL-18 binding protein and prevent IL-18-mediated inflammation, its known role has been expanded to include distinct pathways, both intracellular involving the transcription factor Smad3, and extracellular via binding to the orphan receptor IL-1R8. A number of recent publications investigating the role of IL-37 in atherosclerosis and ischemic heart disease have revealed promising therapeutic value of the cytokine. Although research concerning the role of IL-37 and its mechanism in atherosclerosis is relatively scant, there are a number of well-known atherosclerotic processes that this cytokine can mediate with the potential of modulating the disease progression itself. This review will probe in detail the effects of IL-37 on important pathological processes such as inflammation, dysregulated lipid metabolism, and apoptosis, by analyzing existing data as well as exploring the potential of this cytokine to influence these properties.

1. Introduction

Since its discovery in 2000 by *in silico* research, the Interleukin (IL)-1 family cytokine IL-37 has gained much attention due to its potent anti-inflammatory properties. Initially shown to prevent IL-18-induced inflammation via binding to the IL-18 binding protein (IL-18bp), the mechanisms by which IL-37 functions have been further elucidated in the last few years to include both intra- and extra-cellular pathways involving the transcription factor Smad3 and the orphan receptor IL-1R8, respectively. There are 5 known splice variants of IL-37, designated a-e [1]. The longest isoform, IL-37b, is predominantly found in immune cells, and is the most well characterized to date [2].

Notably, there is no known mouse homolog of human IL-37. However, a landmark 2010 publication by Nold et al. [3] showed that transgenic mice expressing human IL-37b are protected from acute inflammation. The finding that human IL-37 is functional in the mouse has paved the way for many studies using mouse models to investigate the role of IL-37 in a wide range of inflammatory diseases. It is worth noting that IL-37 does exist in many other rodents such as Guinea pigs and rabbits [4], which could be used to develop a knockout model for studying IL-37 deficiency *in vivo*.

Many correlation studies using human samples have shown a strong connection between IL-37 levels and various disease states. IL-37 expression has been strongly associated with many inflammatory diseases, both autoimmune [5–9], and infection-related [10,11]. Elevated plasma IL-37 levels have also been found in human patients with acute coronary syndrome [12] and atrial fibrillation [13]. Research using mouse models of pathogenic cardiovascular inflammation, including ischemia/reperfusion (I/R) injury [14,15], myocardial infarction (MI) [16,17], and vascular calcification [18,19], reveal significant benefit from IL-37 expression or treatment *in vivo*, indicating promising therapeutic value for use of the cytokine to treat the equivalent conditions in humans. Here we review the potential role of IL-37 in cardiovascular disease, with a specific focus on its protective effects against atherosclerosis development.

2. IL-37 modulates multiple atherogenic macrophage functions

The initiation of atherosclerosis occurs when circulating LDL particles become trapped within the arterial wall and become modified, eliciting an inflammatory response. Signaling molecules produced by cells of the vessel wall, such as endothelial cells and smooth muscle cells, lead to activation of the innate immune response. Although the role of IL-37 has been examined in various inflammatory diseases of both acute and chronic nature, there is limited research on the therapeutic potential of IL-37 to reduce the chronic inflammation and dysregulated cholesterol homeostasis that drive the pathogenesis of atherosclerosis. However, the known protective effects of IL-37 on the various cell types involved in atherogenesis, especially macrophages, suggest a therapeutic role for the cytokine in preventing or suppressing

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