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Review Article

The varying faces of IL-6: From cardiac protection to cardiac failure

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ABSTRACT

IL6 is a pleiotropic cytokine that is made in response to perturbations in homeostasis. IL6 becomes elevated in the acute response to host injury and can activate immune cells, direct immune cell trafficking, signal protective responses in local tissue, initial the acute phase response or initiate wound healing. In the short term this proinflammatory response is protective and limits host damage. It is when this acute response remains chronically activated that IL6 becomes pathogenic to the host. Chronically elevated IL6 levels lead to chronic inflammation and fibrotic disorders. The heart is a tissue where this temporal regulation of IL6 is very apparent. Studies from myocardial infarction show how short-term IL6 signaling can protect and preserve the heart tissue in response to acute damage, where long term IL6 signaling or an over-production of IL6R protein plays a causal role in cardiovascular disease. Thus, IL6 can be both protective and pathogenic, depending on the kinetics of the host response.

1. Introduction

IL6 is a pleiotropic cytokine which bridges the innate and adaptive immune systems [1]. Perturbations or dysfunction in the transition from innate to adaptive immunity have long term consequences for inflammation and autoimmunity [2]. The acute response to IL6, which is largely protective, to chronic, long term signaling leading to pathogenic inflammation and autoimmunity is an example of the varying faces of IL6 [3].

IL6 has a wide array of biological functions and is produced by many cells of the body. Originally identified as a B-cell differentiation factor, IL6 is now recognized as a cytokine that regulates many processes such as the acute-phase response, inflammation and hematopoiesis. IL6 can be made by most tissues as well as virtually all cells of the immune system. IL6 can signal either through membrane-bound receptors or, uniquely within the IL-6 family of cytokines, can signal in trans, with a soluble form of its receptor. IL6 has been shown to participate in neurogenesis, wound healing and hepatic regeneration [4–6]. Acutely, IL6 responds to almost all perturbations of homeostasis. However, when IL6 remains elevated chronically, the protective roles IL6 have maintaining tissue integrity and signaling the immune response, are no longer required and constant signaling becomes associated with fibrosis and chronic inflammation. This dual role of IL6, from acute and beneficial to chronic and harmful, is the subject of this review.

2. Population based studies

Meta-analysis of human studies has demonstrated that long-term elevation of IL6 levels more than double a person's life-time risk of coronary heart disease [7]. These studies, among many others, demonstrate an association between pathology and chronic IL6 levels. Recent studies have established a causal role of increased IL6R protein levels in coronary heart disease (CHD) [8–10]. Not understood is whether elevated IL6 was a byproduct of the cardiovascular disease (CVD) or was serving a pathogenic function. Where as association studies have suggested that long-term IL6 levels have adverse consequences for cardiac health, these 2 studies have finally given clear evidence that IL6, a proinflammatory cytokine, plays a causal role in determining CVD risk. The studies focused on a genetic variant in the population that is associated with increased IL6 levels circulating in the blood but decreased IL6R signaling. Interestingly, these groups when on to look at the effect of the variant compared to the anti-IL6R drug, tocilizumab, and found that the variant was associated with the same biological changes as the inhibiting drug. The findings of these studies suggest that targeting IL6 or, in particular IL-6R-mediated signaling, may be a possible therapeutic intervention for CVD, including a possible preventative measure in high risk individuals.

The many polymorphisms in the IL6 promoter region as well as polymorphisms in the IL6R gene locus which exist in the population

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are associated with inflammation and increased disease risk [11–14]. A particular polymorphism in the promoter region of IL6 was shown to lead to higher systemic levels of IL6 [11–13]. This variant is uniquely associated with susceptibility to systemic juvenile idiopathic arthritis and importantly, led to the use of anti-IL6R antibody for its treatment [14–17]. The polymorphisms associated with elevated protein levels of IL6R are also associated with inflammation and are predictive of adverse coronary outcomes such as cardiovascular disease [9] and abdominal aortic aneurism [18]. Elevated IL6 serum levels in patients may be predictive of poor outcomes, thus providing a potential prognostic tool, in a variety of heart-related diseases such as heart failure, myocardial infarction (MI), and angina [19–22]. Human studies clearly implicate IL6 signaling in the heart to be pathogenic over time, however some experimental data using animal models of acute insult to the heart, contradict these associations. The final outcome of IL6 signaling seems to be greatly dependent the duration of the signaling, as well as the downstream signaling cascades activated (see Fig. 1).

The identification and description of IL6 trans-signaling has begun to explain how IL6, uniquely in the IL6-family, has been shown to be protective in acute inflammation and disease such as septic shock but pathogenic in chronic disease [23–27]. Early in the study of IL6, chronic overproduction of the cytokine was implicated in the pathogenesis of many inflammatory conditions including rheumatoid arthritis (RA), Castleman's disease and cardiac myxoma [28–30]. In all these disease states, a constitutively increased IL6 level explained the pathogenic inflammatory symptoms of the patients. Because of this, a therapeutic antibody targeting IL6 signaling, anti-IL6R, which targets membrane-bound as well as a soluble receptor, has been used to treat RA, Castleman's disease and multiple myeloma in small studies [31–33]. Targeting the IL6R has been shown to be particularly effective in clinical trials for severe RA [34–36] and Crohn's disease [37] which is important because IL6 trans-signaling is particularly pathogenic in these diseases where high levels of sIL6R have been found in patients [38–41] and associate with worse disease outcomes [41]. Trans-signaling of IL6 may be more common in chronic IL6 pathology and thus a way to target chronic signaling in the long-term, while preserving classical IL6 signaling, which is required during acute tissue insult (see Tables 1 and 2).

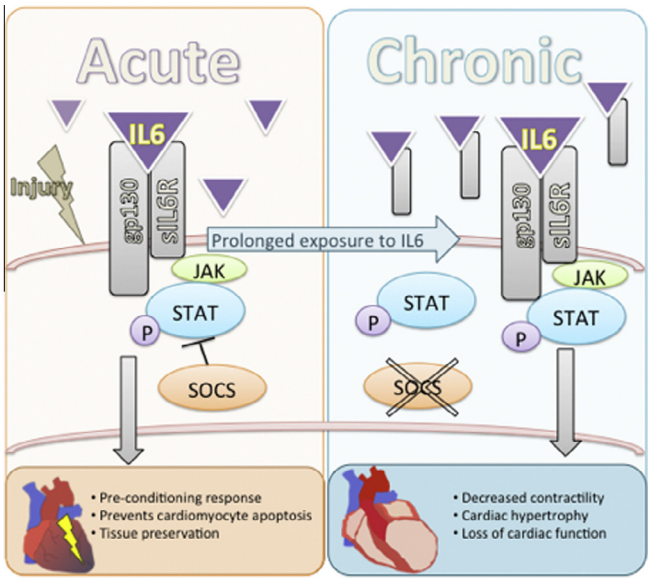

Fig. 1. The transition from acute, protective IL6 signaling, to chronic, pathogenic IL6 signaling on the cardiomyocyte. In the acute phase, IL6 preserves cardiac tissue by inducing an anti-apoptotic program in the myocyte and triggers the preconditioning response [44,45]. When IL6 signaling continues chronically, these protective responses become pathogenic and induce depressed myocyte function. There is decreased contractility, hypertrophic genes are turned and LV enlargement occurs [115,119,120].

3. IL6. biological functions and signaling

IL6 is a member of the IL6 family of cytokines that also includes cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF) leukemia inhibitory factor (LIF), neuropoietin (NPN), and oncostatin M [49–51].

As a multi-functional cytokine, IL6 acts on the immune system as well as other local tissues. Within the immune system, IL6 can direct the development and activation status of both innate and adaptive immune cells. IL6 signaling up-regulates anti-apoptotic molecules in T cells [52–54]. In addition, IL6 is required for Th17-lineage differentiation through STAT3 dependent mechanisms [55,56]. This is particularly important because the Th17 lineage has been implicated as a contributor to pathogenesis in many autoimmune diseases. IL6 also has functions in the innate immune system, where it induces the differentiation of monocytes to macrophages rather than dendritic cells [57]. IL6 may also influence DC activity as it can suppress DC CCR7 expression and IL6 secretion by DCs can affect the immunosuppressive activity of Tregs [58–60], thus bridging the innate and adaptive immune responses. And importantly for the initiation of many inflammatory responses, in the tissue IL6 suppresses neutrophil infiltration while promoting the infiltration and activation of mononuclear leukocytes [61–65]. Together, these studies show how IL6 can direct a proinflammatory immune response that can trigger an auto-aggressive response through the Th17 lineage if not properly controlled.

The IL6 cytokine family signals through a cytokine-specific receptor complexed with at least one subunit of the signal-transducing protein gp130 [50]. IL6 specifically signals through a complex of the IL6R (also known as IL6R-alpha) [66] and the IL6-family common receptor gp130 [67,68]. GP130 signaling mediates a variety of cellular processes including cell survival, apoptosis, growth, proliferation, differentiation and survival [47,69–71]. GP130 is part of the receptor complex for CNTF in the brain, LIF, oncostatin M, NPN, cardiotrophin (CT-1) in the heart, IL11, IL27 and IL31 [72–78]. Importantly, gp130 is expressed on nearly all cells in the body. Therefore what gives IL-6 family cytokines tissue-specificity is the cellular expression of the co-receptor for each family member cytokine.

The IL6R is mainly expressed on hepatocytes and immune cells. However, IL6 is unique in the IL6-family because it has a soluble form of its receptor. Therefore, cells lacking the IL6R can still respond to IL6 because the naturally occurring soluble form of the IL6R exists and can create a complex with IL6. IL6 first binds to the IL6R and this complex of IL6 and IL6R then binds with gp130 [79,80]. The soluble IL6R (sIL6R) is generated either by cleavage of the membrane-associated receptor or, independently, by translation of an alternatively spliced mRNA [81–83]. This signaling of the sIL6R and the membrane bound gp130 is referred to as IL6 trans-signaling [84]. Trans-signaling has been shown to be active in many systems where cells only become responsive to IL6 in the presence of the sIL6R, such as in hematopoietic progenitor cells [85,86], T cells [87,88], and endothelial cells [89].

Downstream signaling of the IL6R combined with gp130, whether soluble or membrane bound, signals through either JAK-STAT, Ras-MAPK, or PI3K, pathways [90,91]. Within the JAK-STAT pathway, IL6 specifically signals through STAT3, which dimerizes and then translocates to the nucleus [92]. Regulation and termination of downstream IL6 signaling is mediated through suppressor of cytokine signaling (SOCS) proteins [93–95]. The negative regulator of IL6-STAT3 activation, SOCS3, may in part regulate the protective versus pathogenic affects of IL6.