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

Jillian A. Fontes[a], **Noel R. Rose**[a,b], and **Daniela Čiháková**[a,b]

[a]William H. Feinstone Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, 21205

[b]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD, 21205

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.

Keywords

IL6; gp130; trans-signaling; heart failure; myocarditis; CVD

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

Author correspondence: Daniela Čiháková, Johns Hopkins University School of Medicine, Ross 648, 720 Rutland Avenue, Baltimore, MD, 21205-2196. dcihako1@jhmi.edu.

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 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.

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.

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), cilliary 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.

4. IL-6 in mouse models of inflammatory disease

IL6 is pathogenic in a variety of inflammatory mouse models. IL6KO mice are resistant to experimentally induced RA [96], colitis [87], experimental autoimmune encephalitis (EAE) [97], experimental autoimmune myocarditis (EAM) [98] and autoimmune kidney disease [99]. Additionally, antibodies that target IL6 signaling block the development of many of these same diseases. IL6R blockade ameliorates colitis [87], inhibits the onset of autoimmune kidney disease [100] and inhibits the development of collagen induced arthritis [101]. How exactly IL6 is exerting its effects in each model may show a role for signaling both to the immune system as well as the local affected tissue.

Evidence for the role of local, tissue-specific IL6 signaling in the pathogenesis of chronic inflammatory diseases comes from mouse studies that specifically target IL6 trans-signaling. The argument can be made that whole-animal knockouts of IL6 or systemic blockade of IL6 have many effects and thus the specific role that IL6 is contributing cannot be teased away from these off-target effects. However, by targeting trans-signaling, classical IL6 signaling is preserved, therefore only cells that do not express the IL6R are impacted. In many studies this translates into the local blockage of IL6 signaling in the tissue by blocking IL-6 trans-signaling as immune cells have the IL6R. In one study of renal pathology in lupus-prone mice, an inhibitor of trans-signaling, sgp130Fc was overexpressed in Lyn-deficient mice and its effect on lupus-associated pathology was measured. IL6-deletion in Lyn-deficient mice leads to decreased inflammation, decreased autoantibodies and decreased nephritis [102]. In the sgp130Fc mice, that have classical IL6 signaling but lack trans-signaling, there was no

changes in immune cells, however, there was significantly attenuated glomerulonephritis and improved renal function and reduced complement fixation, showing a role for IL6 in the local kidney response [102]. Additional studies support these findings in other mouse models. It has long been known that IL6KO mice do not develop RA [103] but further studies have shown that targeting IL6 trans-signaling ameliorates RA [104]. Methods to target the local response to IL6 have been developed, such as tissue-restricted IL6 production where the whole animal is an IL6KO except for a tissue of interest. CNS-specific production of IL6 in a mouse model of EAE showed that IL6 production in the brain increases inflammatory cell infiltration impairs the blood-brain barrier and worsens disease outcome [105]. Collectively, these studies demonstrate a powerful, pathogenic role of IL6 in the local tissue that potentially can be therapeutically targeted through the sIL6R.

5. IL-6 in the Heart

The cellular response to IL6 in the heart has been well characterized. Cardiac tissue provides a revealing example where the duration of signaling, from acute to chronic, demonstrates the protective and pathogenic transition.

IL6 family signaling on cardiac myocytes is cardio protective during the acute response however, when remains elevated chronically, induces maladaptive hypertrophy and decreases contractile function [106, 107]. Myocytes themselves make IL6 in response to injury and in addition to increase Il6 signaling, increased IL6 production is associated with depressed cardiac function [108]. Acutely, IL6-family cytokines protect myocytes against oxidative stress and its signaling induces an anti-apoptotic program [107, 109, 110]. However, IL6-family signaling also depresses the basal contractility of the myocytes as well as the beta-adrenergic responsiveness of the cells leading to decreased function [111]. IL6 family signaling also induces gene expression in the myocytes that is associated with pathological hypertrophy [106]. In chronically exposed myocytes, the depressive effects on contractility of IL6 are mediated by enhancing de novo synthesis and activation of calcium-independent iNOS proteins [112]. Interestingly, the IL6-driven decrease in contractility was associated with JAK/STAT signaling but not the alternative downstream signaling, ERK pathway, suggesting that differential regulation of downstream signaling is a factor in fine-tuning the cellular response to IL6-family signaling [112].

The best characterized protective functions of IL-6 family signaling have been studied in ischemia-reperfusion injury and myocardial infarction which both induce IL6 production by cardiac myocytes [113–117]. Increased IL6 plays a role in late phase pre-conditioning that confers cardio protection [44, 45]. STAT3, the downstream signaling molecule of IL6, is also required for pre-conditioning [44]. However, chronic elevated myocardial production of IL6-family cytokines, which occurs post-MI and in HF, have been associated with worse heart outcomes [107, 109, 118]. IL6 is consistently upregulated in the infarct zone after experimental MI and is associated with left ventricle (LV) enlargement [115, 119, 120]. It is thought that the combined effects of IL6, anti-apoptosis, depressed contractility and hypertrophy, will lead to preserved myocardium in the infarct border zone [115]. Thus, the deleterious effects of IL6 chronically, serve a protective function in MI. Acutely, the combined effects of IL6 production and signaling by the myocytes leads to preserved

cardiac tissue, where damage is limited by reducing the contractility of the cells and inducing an anti-apoptotic program. In the short term these experiments have led to smaller infarct zones and thus acute IL6 is protective in MI. However, in both mice and human studies showed that when this elevated IL6 continues past the initial requirement to preserve the insulted tissue, these same effects become deleterious. By inducing an anti-apoptotic program and reducing contractility in the long-term, the tissue is less effective as a muscle and begins to induce a genetic program related to hypertrophy, which can ultimately result in heart failure. Thus continued of IL6 signaling is pathogenic.

IL6 signaling has also been studied from the perspective of limiting or terminating signaling. In cultured cardiac myocytes overexpression of SOCS3 (limiting IL6-family signaling) completely suppressed the ability of the IL6-family cytokines to be anti-apoptotic as well as inducing hypertrophy[121]. This is mirrored in human data where a decrease in myocardium SOCS3 protein expression, which would lead to continuous IL6 signaling, has also been found in the LV of patients with DCM[48]. Fine-tuning the signal cascade of IL6 may solve the apparent discrepancy of high IL6 levels associating with poor heart outcomes, but experimentally evidence showing gp130 signaling to be cardio protective. In a mouse model of MI, high levels of IL6 increased adverse LV remodeling and heart failure because of impaired regulation of the downstream signaling of IL6, leading to pathogenic, sustained gp-130 mediated STAT3 activation [122]. This study was particularly clarifying because the authors identified that signaling through the tyrosine-757 residue on the gp130 receptor mediated these outcomes and lead to prolonged and enhanced JAK/STAT activation, without ERK and Akt signaling, thus pinpointing a specific cascade [122]. The identification of a specific downstream signaling cascade is an important goal because it may identify how or why acute IL6 is not properly regulated and instead shifts to a chronic signal.

In the myocardium, both chronically elevated IL6 and increased IL6R expression lead to continuous activation of gp130, which results in hypertrophy [110, 123]. To identify the role that STAT3 signaling in particular plays in pathogenic IL6 signaling, mice were created that over-express STAT3 in the heart. Mice with a cardiac-specific increase in expression of STAT3, the downstream signaling target of the IL6 cytokines, develop hypertrophy without stimuli [124]. This demonstrates that uncontrolled, continuous STAT3 signaling causes pathogenic changes in the myocardium, independent of initial tissue insult. Alternatively, complete loss of the myocyte expression of gp130 through cardiac-specific knockout results in a heart with normal structure and function, although is susceptible to cardiac myocyte apoptosis and dilation in response to pressure-overload[125]. This illustrates the need for IL6 in the acute response to injury. IL6 signaling thus plays a role in both helpful and harmful effects in the myocardium as cardiac myocyte loss, which IL6 normally protects against, contributes to the progression of compensatory LV hypertrophy to heart failure [126].

Myocarditis provides a striking example of the dysregulation of protective IL6 responses leading to pathogenic IL6 outcomes. Acutely, IL6 is protective in the heart as it limits viral replication and thus cardiac damage[42]. However, once the virus has been cleared a subset of patients will eventually develop an autoimmune response to their heart and present with autoimmune myocarditis, independent of viral presence [127]. In these cases, continuous

IL6 signaling is no longer protective but contributes to heart failure. Over time, patients with autoimmune myocarditis may develop dilated cardiomyopathy, which at its end-stage can only be treated with a heart transplant [127]. Circulating levels of IL6 increase with the severity of heart failure[128, 129] and upon autopsy, IL6 has been found to be increased in the heart tissue of patients with DCM [43, 130] and end-stage heart failure [129, 131, 132]. Myocarditis is an extreme example of how limited acute IL6 signaling is protective for viral clearance but the chronic, long term exposure of the heart to IL6 signaling contributes to pathology and loss of cardiac function and remodeling.

6. Conclusions

Classically IL6 is considered to be a proinflammatory cytokine. When homeostasis is disturbed within a host IL6 is elevated and induces protective responses determined by the nature of the insult. IL6 can activate immune cells, direct immune cell trafficking, signal protective responses in local tissue, initiate the acute phase response or contribute to wound healing. In the acute response, these are all vital functions. However, beyond this temporally limited role, the proinflammatory nature of IL6 can become pathogenic. In the short term, what are protective responses, increased cell infiltration, increased wound repair, can turn deleterious in the long term leading to inflammatory and fibrotic disorders. The heart is a tissue where this duality is very apparent. Studies from MI 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.

The identification of the unique nature of IL6 signaling, which occurs through both classical, membrane-bound signaling and through signaling in trans, with a soluble form of the IL6R, has created the opportunity for therapeutic intervention. Blocking all IL6 signaling has severe consequences as IL6 serves many vital functions, although is only currently used for severe cases of RA. Having a method to only block the particularly pathogenic signals of IL6 is an exciting avenue of research. The current use of the available IL6R antibody, which targets both classical and trans signaling, is limited as tocilizumab is given monthly by intravenous (IV) infusion. However, many animal studies are aimed to design more specific inhibitors, through the use of a soluble gp130 decoy, sgp130Fc, which inhibits only trans-signaling.

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Highlights

- IL6 is cardio protective during acute insult to the myocardium
- IL6 transitions to a pathogenic factor when it remains elevated chronically
- The transition is associated with specific downstream signaling unique to IL6
- Chronic IL6 signaling is associated with heart failure
- In myocarditis chronic IL6 signaling contributes to progression to dilated cardiomyopathy

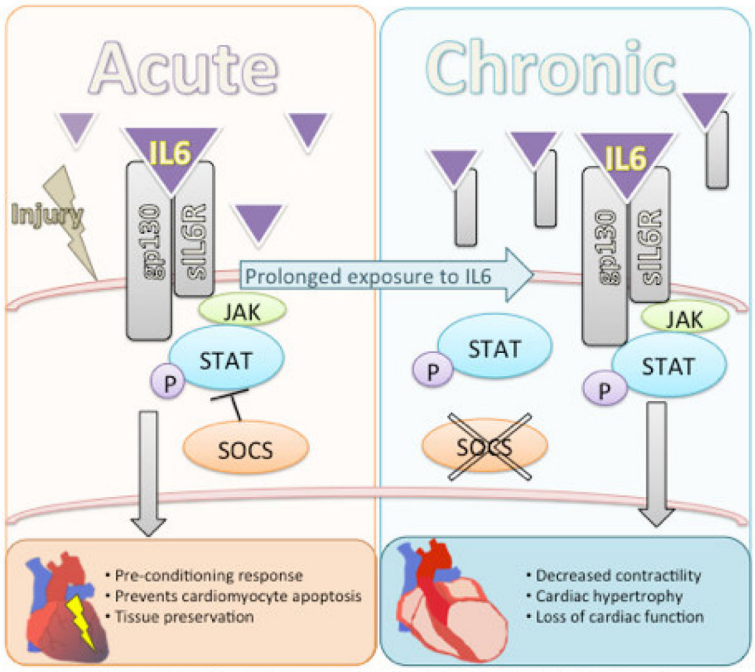

Figure 1.

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 pre-conditioning 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].

Table 1

The dual role of IL-6 in human studies

	Beneficial	**Harmful**
Acute signaling		
Elevated IL6 serum levels in patients with myocarditis	Limits viral infection [42]	Associated with DCM [43]
Elevated IL6 serum levels following myocardial infarction	Limits infarct size [44, 45]	Associated with HF and LVF[46]
Chronic signaling		
Long-term elevated IL6 serum levels		Two fold Increased life-time risk of CHD [4]
Long-term elevated sIL6R serum levels		Associated with severe RA [34, 35]
Polymorphism in IL6R leading to elevated IL6R protein expression in sera		Increased susceptibility to systemic juvenile idiopathic arthritis (SJIA) [14] Predictive of adverse outcomes in CVD [47]
Decreased myocardial SOCS3 protein expression		Found in myocardium of patients with DCM [48]

Table 2

The dual role of IL6 in mouse model studies

	Beneficial	**Harmful**
Acute signaling		
Increased myocyte production of IL6	Anti-apoptotic Protective against oxidative stress Pre-conditioning response [44, 45]	Depressed basal contractility Hypertrophic genes turned on Depressed b-adrenergic response LV enlargement [115, 119, 120]
IL6KO mice in experimental myocarditis	Resistant to experimental autoimmune myocarditis [98]	Increased susceptibility to viral-induced myocarditis mouse models [42]
Chronic signaling		
Myocyte-specific gp130 loss	No IL-6 signaling [125]	Susceptible to myocyte apoptosis in pressure-overload models [125]
Cardiac-specific increase in STAT3 expression	Increased IL6-family responsiveness [124]	Mice develop hypertrophy without stimuli [124]
IL6KO mice	Resistant to experimentally induced RA [96], colitis [87], EAE [97], EAM [98], autoimmune kidney disease [99]	Susceptible to infections [133, 134]