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Article title: Interleukin-6 in renal disease and therapy

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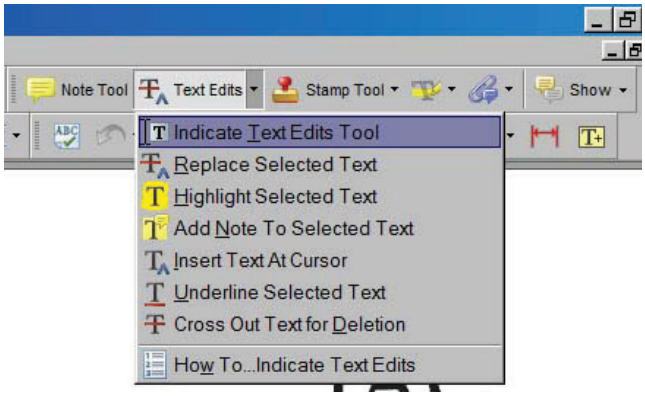

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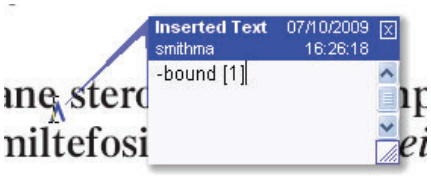

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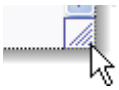

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Full Review

Interleukin-6 in renal disease and therapy

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ABSTRACT

Interleukin (IL)-6 has become a major target for clinical intervention in various autoimmune conditions. Here, drugs including the humanized anti-IL-6 receptor (IL-6R) antibody Tocilizumab emphasize the clinical importance of IL-6 in driving disease and poor patient outcomes. During the course of this review we will outline the biology surrounding IL-6 and will discuss the impact of IL-6 in renal disease and the clinical complications associated with renal replacement therapies and transplantation. We will also consider the merit of IL-6 measurement as a prognostic indicator and provide a clinical perspective on IL-6 blocking therapies in renal disease.

Keywords: cytokines, interleukin-6, renal disease, therapy

INTRODUCTION

Cytokines perform pivotal roles during infection, trauma, cancer and inflammation where they control cellular proliferation, differentiation, survival or death and cytokine specific gene expression. Here, cytokine-driven communication between immune cells and stromal non-haematopoietic cells enables resolution of the condition and is part of the healing process [1]. However during chronic inflammatory conditions, appropriate regulation of the immune response is lost and drives disease progression. Under these circumstances, cytokines affect the development of autoimmunity, chronic inflammation and deleterious tissue damage [1]. This has ultimately led to the design of biologic drug agents that target specific cytokines to prevent the rapid clinical progression of disease. For example, tumour necrosis factor-α (TNFα) blockers (e.g. the neutralizing anti-TNFα antibodies Infliximab, Adalimumab, Golimumab, Certolizumab or the soluble TNF-R2 Fc-fusion protein Etanercept) are broadly used to treat various autoimmune conditions, while interleukin (IL)-1β inhibitors (e.g. the IL-1 receptor antagonist, Anakinra) have shown robust efficacy in auto-inflammatory conditions [2]. Although these agents are effective treatments for many diseases, not all biologics work in all patients, and not all biologics work in all inflammatory conditions [1, 2]. Such observations are significantly influencing the way researchers consider cytokine involvement in disease. Emphasis is now placed on identifying alternative cytokine targets and strategies for therapeutic intervention, while a greater attention to cytokine biology and signalling is providing opportunities to stratify patients with chronic disease for more appropriate treatment. Here, research is leading to a detailed understanding of how the cytokine network becomes distorted to drive chronic inflammation instead of competent host defense. During the course of this review, we discuss the impact of IL-6 in renal disease and will describe aspects of its biology that affect disease onset and progression, prognosis and treatment decisions.

INTERLEUKIN-6 AS A CLINICAL TARGET

Interleukin-6 was first described as interferon β2, hepatocyte stimulating factor, cytotoxic T-cell differentiation factor, B-cell differentiation factor and B-cell stimulatory factor-2, which reflects its capacity to regulate lymphocyte activation and the acute phase response [3]. While these activities are markedly impaired in IL-6-deficient mice, it is important to remember that IL-6 also controls various homeostatic functions including glucose metabolism, the hypothalamic-pituitary-adrenal (HPA) axis, affecting mood, fatigue and depression and haematopoiesis [3,4]. In this regard, systemic elevations in IL-6 cause hyperthermia and leads to a general loss of activity and appetite [5]. As an inflammatory cytokine, IL-6 is one of the

most highly regulated mediators of inflammation (increasing from 1–5 pg/mL to several μg/mL in certain conditions) and performs central roles in infection, autoimmunity and cancer [6–9]. While traditionally viewed as a downstream target of TNFα and IL-1β activity, various other inflammatory stimuli induce IL-6 expression, and IL-6 forms part of an integrated cytokine network that controls innate and adaptive immunity [3, 8, 9]. As a consequence, IL-6 is a major target for therapeutic intervention and the complex nature of its biology has led to development of various therapies that target either the cytokine directly (e.g. Olokizumab, Clazakizumab) or the α-subunit of its receptor (e.g. Tocilizumab, Sarilumab) [9]. A full list of blocking IL-6 strategies and the current status of their clinical development is shown in Table 1. This information covers specific IL-6 targeting agents and small molecule inhibitors that block intracellular proteins associated with (but not necessary exclusive to) IL-6 receptor signalling. Given that cytokines, such as IL-6 contribute to the progression of renal disease and associated complications (e.g. vascular calcification, wasting, fatigue and cardiovascular risk), the potential applications of anti-cytokine targeted intervention deserves closer attention [16, 17]. For additional information on IL-6 targeted therapies the reader is directed elsewhere [2, 9, 18].

The IL-6 receptor complex consists of an 80 kDa cognate receptor (IL-6R, CD126) and a 130 kDa signal-transducing element (gp130, CD130) [8, 9]. Although IL-6R is largely confined to hepatocytes, certain leukocytes and some epithelial lining cells, IL-6 activity is also controlled by a naturally occurring soluble IL-6R (sIL-6R). The sIL-6R is a key regulator of IL-6 responses and forms a sIL-6R/IL-6 complex capable of activating cells via the ubiquitously expressed gp130 [3, 7–9, 19]. This process is called IL-6 trans-signalling, and activates IL-6-type responses in cells lacking IL-6R (e.g. vascular endothelial cells, peritoneal mesothelial cells and synovial fibroblasts). Interleukin-6 responses *in vivo* are therefore mediated by IL-6 activation of a membrane-bound IL-6R (classical IL-6R signalling) or via its soluble receptor (Figure 1). In both cases, IL-6 activates gp130 associated cytoplasmic tyrosine kinases (Janus kinases; Jak1, Jak2 and Tyk2), which control the latent transcription factors STAT1 and STAT3, and signalling through the Ras–Raf cascade. For a more detailed overview of IL-6 signalling the reader is directed elsewhere [20].

From a clinical perspective, measurements of IL-6, its soluble receptor and indices of IL-6 bioactivity (e.g. STAT3 responses) are increasingly viewed as surrogate markers of inflammation, disease severity and valuable predictors of disease progression. During the course of this review we will consider the impact of IL-6 biology in various aspects of renal disease, transplantation and therapy and detail potential avenues for future clinical translation (Table 1).

CONTROL OF IL-6 EXPRESSION BY INFLAMMATION, GENETIC VARIATION AND MICRORNAS

In chronic inflammation and autoimmunity IL-6 plays roles in both local (e.g. control of chemokine-directed leukocyte recruitment) and systemic inflammation (e.g. activation of the acute phase response). Here, IL-6 transcription is regulated by various pro-inflammatory cytokines and growth factors (e.g. IL-1, TNFα and platelet derived growth factor; PDGF), increases in intracellular cyclic AMP and certain pattern recognition receptors following activation by microbial or endogenous ligands [1]. Interleukin-6 is rapidly expressed in a highly transient manner during inflammation. Here, circulating sIL-6R concentrations act as a buffering system that helps to maintain the circulating half-life of IL-6. Thus, sIL-6R is a central regulator of IL-6 bioactivity and must be tightly controlled to limit overt IL-6 signalling (Figure 1). While circulating levels of soluble gp130 (sgp130) selectively antagonize IL-6 trans-signalling, intracellular regulators of IL-6R-gp130 signalling (e.g. suppressor of cytokine signalling; SOCS proteins) prevent a prolonged activation by IL-6. Of equal importance are genetic factors, which substantially influence *IL6* expression. This is best illustrated by the identification of functional polymorphisms within the *IL6* promoter. For example, a G > C (rs1800795) mutation found at position −174 bp upstream from the transcriptional start site leads to enhanced IL-6 expression [21]. Similar genetic variations up to 6 kb from the start of transcription also correlate with serum and constitutive IL-6 levels. Patients displaying the rs1800975 mutation often show increased susceptibility to coronary artery disease, juvenile idiopathic arthritis and many other conditions typified by chronic inflammation or autoimmunity. Similar genetic mutations also occur in the *IL6R* loci, with the rs2228145 variant affecting the proteolytic release of sIL-6R from cells. Significantly, the rs2228145 mutation in various ethnic populations has been linked to insulin resistance, an increase in body mass index, Type-II diabetes and diabetic nephropathy [22–28].

Recent data show that microRNAs also govern IL-6 expression and activity. MicroRNAs are short endogenous RNA regulators of gene expression, the first of which was identified in the nematode *Caenorhabditis elegans* in 1993 [29]. MicroRNAs are present in all human cells, and each represses the expression of a specific set of genes. The let-7 family contains the first microRNAs to be identified in mammals [30]. Let-7 microRNAs, most notably let-7a, target and repress synthesis of IL-6 [31]. Let-7 microRNAs are themselves down-regulated by Lin28B [31], which is induced following activation of nuclear factor-κB (NF-κB) to ensure optimal *Il6* expression and cellular transformation [32]. Also, microRNA-23a targets and represses *Il6r* [33], meaning that cellular capacity to respond to IL-6 is also microRNA-regulated. MicroRNAs are also important effectors of IL-6 responses. For example, microRNAs-21 and microRNAs-181b-1 are induced by IL-6 activation of Stat3. These increase NF-κB activity via repression of their targets phosphatase and tensin homologue (PTEN) and CYLD (the human gene associated with cylindromatosis) [34]. Finally, emerging data show that microRNAs may be released by cells, and serve as a mechanism for intercellular communication. A subset of these extracellular microRNAs can induce pro-inflammatory responses, including IL-6 secretion, by binding to and activating Toll-Like Receptors [35].

Table 1. Targeting IL-6 in disease

Targeting Strategy	Compound	Company	Specificity	Disease	Phase	ClinicalTrials.gov
Global IL-6 signaling Targeting soluble and membrane-bound Interleukin 6 receptor	Tocilizumab (ACTEMRA, RoACTEMRA)	Chugai, Roche	Humanized IL-6 receptor-specific mAb	Castleman's disease	2005, Japan	Approved
				Juvenile idiopathic arthritis	2008, Japan	Approved
				Systemic-onset juvenile idiopathic arthritis	2008, Japan 2009, EMEA; 2010, FDA	Approved Approved
				Rheumatoid Arthritis	Phase II; 2009–11	NCT01002781
				Adult's still disease	Phase III; 2011–13	NCT01297699
				Graves' ophthalmopathy	Phase II; 2010–12	NCT01104480
				Relapsing polychondritis	Phase III; 2010–14	NCT01209702
				Ankylosing spondylitis	2010–12	NCT01073826
				Type II diabetes and exercise		
	REGN88 (SAR153191)	Regeneron/ Sanofi-Aventis	Fully human IL-6 receptor-specific mAb	Rheumatoid arthritis	Phase II; 2010–12	NCT01217814
					Phase II + III; 2010–13	NCT01061736
					Phase III; 2010–15	NCT01146652
				Ankylosing spondylitis	Phase II; 2010–11	NCT01284569
					phase III; 2010–15	NCT01118728
	ALX-0061	Ablynx	IL-6 receptor-specific VHH	Rheumatoid arthritis	Phase I + II; 2011–12	NCT01242488
Global IL-6 signaling Targeting Interleukin 6	CDP6038 (Olokizumab)	UCB, Inc.,	IL-6 specific mAb	Rheumatoid arthritis	Phase I + II; 2009–10	NCT01009242
					Phase II; 2010–12	NCT01242488
					Phase II; 2011–14	NCT01296711
	CNTO136 (Sirukumab)	Centocor, Inc.,	Fully human IL-6-specific mAb	Rheumatoid arthritis	Phase II; 2008–11	NCT00718718
	CNTO328 (cCLB, Siltuximab)	Centocor, Inc.,	Chimeric IL-6-specific mAb	Castleman disease	Phase II; 2010–12	NCT01024036
				Multiple myeloma [125]	Phase II; 2006–12	NCT00402181
					Phase II; 2009–14	NCT00911859
					Phase III; 2010–14	NCT01266811
				Prostate cancer	Phase I; 2005–10	NCT00401765
					Phase II; 2006–008	NCT00385827
					Phase II; 2007–09	NCT00433446
				Solid tumors	Phase I + II; 2009–11	NCT00841191
				Metastatic renal cell carcinoma	Phase I + II; 2005–10	NCT00265135
				Metastatic kidney cancer	Phase II; 2006–10	NCT00311545
	ALD518 (BMS-945429)	Alder Biopharm./ Bristol-Myers Squibb	Humanized IL-6-specific mAb, aglycosylated	Rheumatoid arthritis	Phase II; 2008–09	NCT00867516
				Non-small cell lung-cancer related fatigue and cachexia	Phase II; 2008–09	NCT00866970
	C326	Avidia	anti-IL-6/anti-Fc avimer protein	Crohn's disease	Phase I; 2006–07	NCT00353756
IL-6 Trans-signaling Targeting IL-6/sIL-6R	FE301	Conaris/Ferring	Soluble gp130-Fc fusion protein	Crohn's disease	Preclinical	
Downstream signaling Targeting janus kinases (JAKs) downstream of gp130/IL6ST	Tofacitinib	Pfizer	JAK1 and 2	Rheumatoid arthritis	Phase III; 2013	NCT00661661
				Kidney transplant	Phase II; 2006	NCT00106639
				Psoriasis	Phase I-III; 2004–14	NCT01519089
				Rheumatoid arthritis	Phase I; 2012–13	NCT01741493
	Ruxolitinib	Incyte/Novartis	JAK1 and 2	Multiple myeloma	Phase II; 2010	NCT00639002
				Myelofibrosis	Phase II; 2012–13	NCT01340651
				Plaque psoriasis	Phase II; 2009	NCT00820950
	Baricitinib (INCB-28050)	Eli Lilly/Incyte	JAK1 and 2	Rheumatoid arthritis	Phase II; 2010	NCT00902486
	GLPG-0634	Abbot/Galapagos	JAK1	Rheumatoid arthritis	Phase I+ II; 2011–12	NCT01384422
						NCT01668641
	AC430	Ambit Biosciences	JAK2	Rheumatoid arthritis	Phase I, 2011	NCT01287858

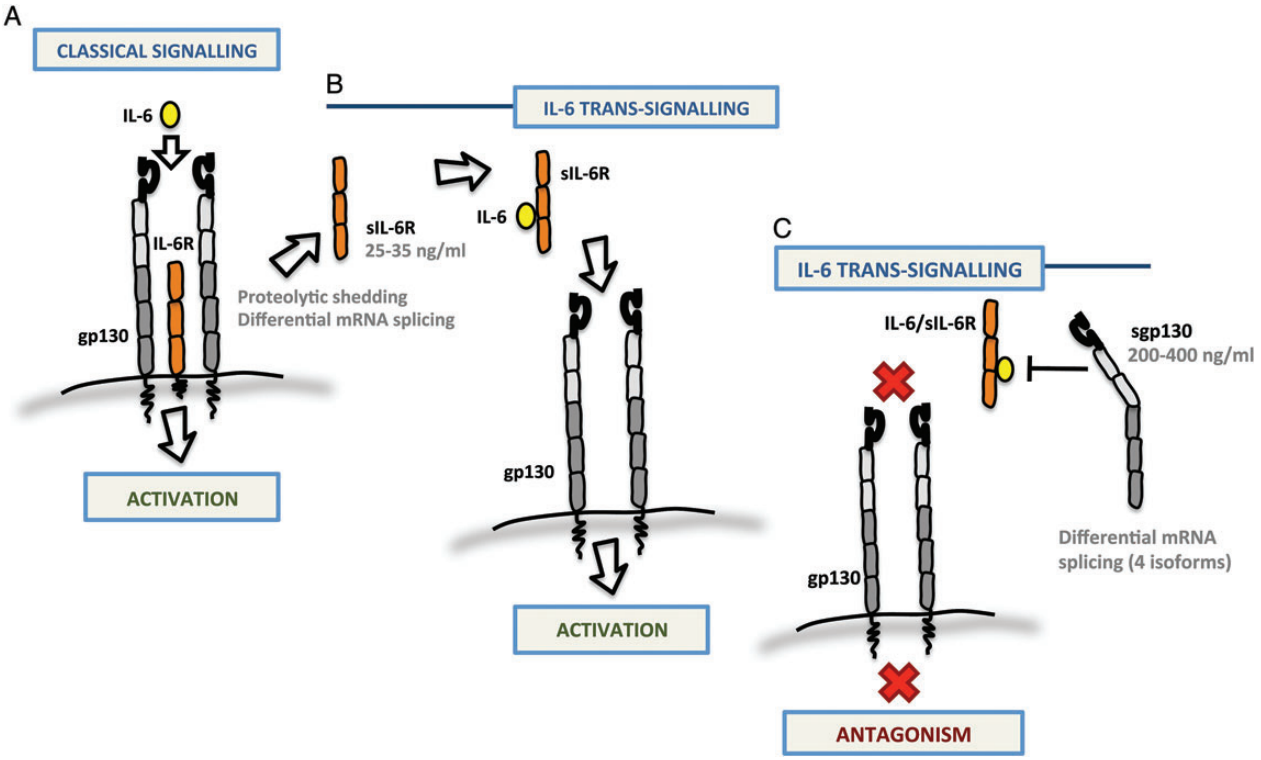

FIGURE 1: Interleukin-6 and mechanisms for receptor signalling. Interleukin-6 activates cells through two distinct mechanisms termed classical IL-6R signalling and IL-6 trans-signalling. The receptor complex responsible for regulating IL-6 responses consists of a non-signalling cognate receptor (IL-6R, CD126), which binds IL-6 and dimerizes with the signal-transducing receptor subunit gp130. (**A**) Classical IL-6R signalling occurs in cell types that inherently express both IL-6R and gp130. (**B**) While expression of IL-6R has a restricted cellular expression (hepatocytes, leukocytes and certain epithelial cells), these cells also generate a soluble form of the IL-6R (sIL-6R) that retains cytokine-binding properties and mediates IL-6 responses in cell types that lack IL-6R, but expression gp130 (IL-6 trans-signalling). (**C**) In many instances, IL-6 trans-signalling regulates various inflammatory activities and must be tightly regulated. Here, a soluble form of gp130, which circulates at high serum concentrations acts as an antagonist of IL-6 trans-signalling and binds IL-6 only when bound to sIL-6R.

FULL REVIEW

IL-6 IN GLOMERULONEPHRITIS, CHRONIC KIDNEY DISEASE AND ACUTE KIDNEY INJURY

Clinical and experimental studies suggest that IL-6 contribute to renal injury in glomerulonephritis and other forms of renal disease. For example, elevated IL-6 expression in kidneys and urine of patients with mesangial proliferative glomerulonephritis is often associated with poor outcome [36]. In this context, IL-6 induces mesangial cell proliferation [36]. In murine models of lupus nephritis IL-6 activities promote tissue damage and disease severity [37–39], while transgenic mice displaying elevated levels of circulating IL-6 develop proteinuric nephropathy that culminates in death from renal failure [40]. Ultimately, the role of IL-6 in these conditions may relate to IL-6 involvement in fibrosis and tissue damage. In models of angiotensin-II induced renal disease, infusion of angiotensin-II induces IL-6 expression and renal fibrosis. This response is IL-6 dependent and IL-6-deficient mice remain resistant to renal injury [41]. Mechanistically, IL-6 may contribute to renal disease by enhancing the signalling response of tubular epithelial cells to pro-fibrotic cytokines such as transforming growth factor-β (TGFβ) [42]. However, data from other experimental models of renal injury show that IL-6 is not always a key facet of progressive kidney damage [43–45]. What factors contribute to these differences in disease outcome remain to be established, but may reflect differences in disease induction methods or protocols using cytokine-deficient animals versus direct manipulation of cytokine activity in wild type strains.

In patients with acute kidney injury (AKI), high circulating levels of IL-6 are predictive of increased mortality [10]. This outcome is also seen in murine models of ischaemia reperfusion injury- and nephrotoxin-induced models of AKI [11, 46, 47]. In mercuric chloride-induced AKI, IL-6 deficient mice exhibit less kidney-associated inflammation, and have improved outcome [47]. In the same study, IL-6 trans-signalling in tubular epithelial cells ameliorated injury and led to preservation of renal function. This led the authors to conclude that IL-6 simultaneously promotes an injurious inflammatory response and, through a mechanism involving IL-6 trans-signalling, protects the kidney from further injury [47]. These studies are akin to the role of IL-6 and IL-6 trans-signalling in regulating homeostatic gut epithelia remodelling versus colitis-like inflammation [9]. Significantly, tocilizumab is not prescribed in patients with a history of diverticulitis [2, 9].

Biologics against IL-6 are highly effective in autoimmune conditions including rheumatoid arthritis [1, 2]. To date, there is little data relating to IL-6 blockade in patients with renal

disease. Case reports of tocilizumab use in patients with conditions where renal complications is an associated co-morbidity show promising improvements in urinary sediment, proteinuria and stabilization of renal function. These include the lymphoproliferative disorder multicentric Casteman's disease [48, 49], AA Amyloidosis [50, 51] and a subset of five patients with renal dysfunction in a Phase I study of SLE [52]. While these studies endorse the potential clinical application of IL-6 targeted interventions in acute or chronic renal disease, definitive randomized controlled trials are lacking.

INTERLEUKIN-6 IN RENAL TRANSPLANTATION

Renal transplantation is considered to be the 'gold standard' treatment for most patients with end stage renal failure. Benefits include improved patient survival, quality of life and healthcare cost [53]. Recent advances in treatment means that the rate of acute clinical rejection (AR) has fallen. However, AR remains a determining factor for the development of chronic rejection and long-term allograft survival [53, 54].

Interleukin-6 has long been highlighted as a pro-inflammatory cytokine associated with renal allograft rejection. While IL-6 levels are low in the serum and urine of healthy individuals, renal transplant recipients display high serum and urinary IL-6 levels immediately post transplantation and during AR [55, 56]. For example, increased IL-6 mRNA transcripts have been identified in renal biopsies from patients undergoing AR [57]. Notably, while AR episodes have been associated with increased serum and urine IL-6 levels, preventative rejection treatments stabilize IL-6 expression and return them to baseline [12, 58].

Most studies have underlined the greater sensitivity of urinary IL-6, over serum measurements, as potential indicators of rejection. For example urinary actin, IL-6 and CXC-chemokine ligand 8 (CXCL8) have been proposed as biomarkers of sustained acute renal failure in allograft recipients [59]. Kwon *et al.* [59] observed elevated urinary IL-6 excretion in patients displaying sustained acute renal failure compared with those that went on to recover. For patients showing sustained failure, urinary IL-6 was increased on the day of transplant and also remained higher at postoperative Day 5. In a recent analysis of 90 transplant patients, stable allograft recipients showed similar levels of serum IL-6 to healthy individuals. However patients undergoing allograft rejection displayed significant increases in circulating IL-6 [60]. Notably, higher IL-6 levels were observed in individuals undergoing chronic allograft rejection compared with patients in AR [60]. Interestingly, while increases in serum and urinary IL-6 are associated with AR, sIL-6R levels do not correlate with rejection [12]. While the mechanisms affecting these outcomes are far from clear, they may relate to associated genetic factors. Meta-analysis of transplant patients shows that alterations in AR risk are associated with individuals bearing the rs1800795 'high' IL-6 producing loci [61, 62]. Notably, in allogenic haematopoietic cell transplantation, the rs1800795 variant is linked with increased risk of developing acute graft-versus-host disease [62]. Therefore, IL-6 donor genotype may be more important in graft rejection than recipient genotype. Here, IL-6 may serve as an immune 'danger signal' thereby disrupting allograft tolerance.

Mechanisms underpinning the role of IL-6 in allograft transplant rejection may hinge on its partnership with TGFβ, which together balance the induction of T-cell tolerance versus pro-inflammatory effector responses. Regulatory T-cells (T_{reg}) provide tolerance by suppression of allo- and autoimmune responses [63–65]. These cells are defined by their expression of transcription factor FoxP3, and are either thymus derived (natural T_{reg}; nT_{reg}) or can differentiate from naïve $CD4^+$ T-cells activated in the presence of TGFβ (induced T_{reg}; iT_{reg}) [66]. Such has been the impact of T_{reg} cells on allograft tolerance in experimental animal models, that recent studies have proposed FoxP3 as a prognostic marker for renal allograft outcome (see review [67]). Interestingly, IL-6 inhibits the TGFβ-mediated differentiation of iT_{reg} cells, instead favouring the development of IL-17-producing $CD4^+$ T-cells (T_h17 cells) [68, 69]. While T_{reg} cells provide tolerance, there is mounting evidence of a role for T_h17 cells in allograft rejection. For example, allograft infiltrating T_h17 cells were associated with hallmarks of chronic rejection including exacerbated vasculopathy and fibrosis in models of cardiac allograft rejection [70, 71]. In renal allografts, elevated IL-17 mRNA and protein has been demonstrated during AR in both clinical patients and experimental models [72–74]. Owing to the bias of IL-6 for inducing effector T_h17 cells rather than regulatory T_{reg} populations with tolerogenic properties in allogenic grafts, therapeutically targeting the IL-6 signalling pathway may prove beneficial to renal transplant outcomes in patients undergoing acute and chronic rejection.

THE BIOLOGY OF INTERLEUKIN-6 IN RENAL REPLACEMENT THERAPY

Haemodialysis (HD) and peritoneal dialysis (PD) represent the two major renal replacement therapies available for patients with end-stage renal disease (ESRD). Both IL-6 and sIL-6R are considered important prognostic markers of clinical outcome in ESRD patients. ESRD patients have elevated serum IL-6 levels prior to treatment [75, 76]. Impaired excretion due to reduced kidney function has been suggested as one reason for this elevation [77], although IL-6 mRNA is increased in the peripheral blood mononuclear cells of ESRD patients [78]. PD treatment itself leads to increases in systemic and intraperitoneal IL-6 and sIL-6R levels [79]. Here, systemic elevations in circulating levels may reflect a consequence of persistent or episodic bouts of inflammation, patient co-morbidities, genetic factors, obesity, alterations in metabolism, infection incidence or other immunological events [80, 81]. However, raised serum IL-6 and sIL-6R levels at the beginning of treatment remain powerful predictors of mortality in both HD and PD patients [17, 75, 82, 83]. These changes may reflect the systemic inflammatory status of a patient, and often corresponds to elevations in C-reactive protein [83, 84]. For example, high IL-6 levels contribute to dialysis associated malnutrition [13, 14] and are prognostic of cardiovascular risk

[85], which is an adverse outcome of haemodialysis [15]. Here, systemic elevations in IL-6 likely arise from the liver, muscle and the inflammatory activation of stromal tissues or myeloid cells (Table 2).

Patients receiving PD often experience a number of clinical complications. These include: (i) susceptibility to recurrent episodes of peritonitis and (ii) changes in the structure of the peritoneal membrane resulting in loss of ultrafiltration capacity and treatment failure. PD-associated peritonitis is caused predominantly by Gram-positive *Staphylococcus* species (most commonly by *Staphylococcus epidermis* and *Staphylococcus aureus*), but also by Gram-negative bacteria (e.g. *Escherichia coli*) and fungi (e.g. *Candida albicans*) [86]. Here, IL-6 is essential for the appropriate control of acute inflammation and promotes bacterial clearance. Murine models of peritonitis have shown IL-6/sIL-6R signalling via STAT3 regulates leukocyte recruitment and activation [87–91], and IL-6-deficient mice are less able to clear a number of bacterial species [4, 92] ~~(unpublished data).~~ Interestingly, individuals with defects in IL-6 or STAT3 display an impaired immune defense against *Staphylococcal* infection [93, 94], implying IL-6 is an essential part of the immune response to *Staphylococcus* species. Under these conditions, IL-6 is highly expressed by resident peritoneal leukocytes and mesothelial cells following microbial sensing by pattern recognition receptors [95–98]. Indeed elevated concentrations of IL-6 and sIL-6R are present in peritoneal dialysis effluent of patients during acute episodes of bacterial peritonitis [88].

Extended PD therapy is associated with functional and morphologic alterations to the peritoneal membrane and result in PD treatment failure [99]. These changes may be induced by uraemia, hyperglycaemia, prolonged exposure to bio-incompatible peritoneal dialysis fluids, age and recurrent episodes of peritonitis. Here, vascular alterations contribute to increased peritoneal solute transport [100]. IL-6 levels are also an important determinate of solute transport in PD [101]. Intraperitoneal IL-6 and sIL-6R levels significantly correlate with the baseline peritoneal solute transport (PSTR) observed in PD patients and are predictive of pro-angiogenic factors present in the dialysate (CCL2; CC-chemokine ligand 2 and VEGF; vascular endothelial growth factor) [102]. In this regard, plasma levels of IL-6 and VEGF are associated with a high PSTR [17]. Again, the rs1800795 genetic loci relate to intraperitoneal IL-6 levels and baseline PSTR [103], and represent an independent risk factor for mortality and treatment failure [104]. Regarding the role of IL-6 in fibrotic changes, IL-6 plays a clear role in normal wound healing [105] and fibrogenesis in various organs (e.g. lung, skin and kidney) [41, 106,107]. Recently, we have found that IL-6 is essential for the development of peritoneal fibrosis following recurrent peritonitis in a murine model [108]. IL-6-dependent changes in peritoneal Th1 responses and IFN-γ and STAT1 activation within the peritoneal membrane lead to alterations in the balance of matrix metalloproteinase to tissue inhibitors of matrix metalloproteinases. Collectively, these studies demonstrate a fundamental aspect of IL-6 involvement in inflammation and specifically emphasize its importance in governing the balance between provision of competent host defense and inflammation-induced tissue injury.

INTERLEUKIN-6, COMORBIDITIES AND URAEMIA IN END-STAGE RENAL DISEASE

Considerable emphasis has been placed on the relationship between IL-6 (and to a lesser extent sIL-6R) and C-reactive protein, cardiovascular risk and patient outcomes such as fatigue. However IL-6 also functions as a homeostatic regulator of catabolism, iron uptake and muscle wasting. The IL-6 control of these processes has a major bearing on patients with ESRD and affects the incidence of anaemia, protein-energy wasting and muscle atrophy [16, 109–113]. For example, the hepatic control of hepcidin expression in response to systemic elevations in IL-6 disrupts iron homeostasis and leads to iron-restricted erythropoiesis and anaemia [114–116]. In patients with rheumatoid arthritis, treatment with the blocking anti-IL-6R monoclonal antibody tocilizumab rapidly improves anaemia by reducing serum hepcidin [117]. In ESRD many of these processes are ultimately influenced by underlining alterations in uraemia. Studies show that uraemia is a contributing factor in the control of increased plasma IL-6 concentrations [76, 118]. Thus, therapeutic control of IL-6 with selective anti-cytokine interventions in combination with a standard treatment for uraemia is likely to improve many compounding complications associated with the clinical management of ESRD [112, 119, 120].

INTERLEUKIN-6 AND CLINICAL OUTCOMES

It is widely acknowledged that cytokines play an integral role in determining the course of disease and IL-6 is increasing

Table 2. Role of the IL-6 pathway in renal disease, transplantation and renal replacement therapy

Factor	Condition	Associated outcome	Reference
IL-6	AKI	Mortality	[10]
	Ischaemia reperfusion injury	Unclear	[11]
	Chronic allograft rejection	Acute rejection	[12]
	Haemodialysis and peritoneal dialysis	Mortality	Pecoits-Filho *et al.* (2002) [17]
		Malnutrition	[13, 14]
		Vascular changes	[15]
IL-6R	Haemodialysis and peritoneal dialysis	Mortality	Pecoits-Filho *et al.* (2002) [17]

This table summarizes the published clinical and experimental studies linking the IL-6 pathway to renal disease, transplantation and renal replacement therapy, and its associated outcomes.

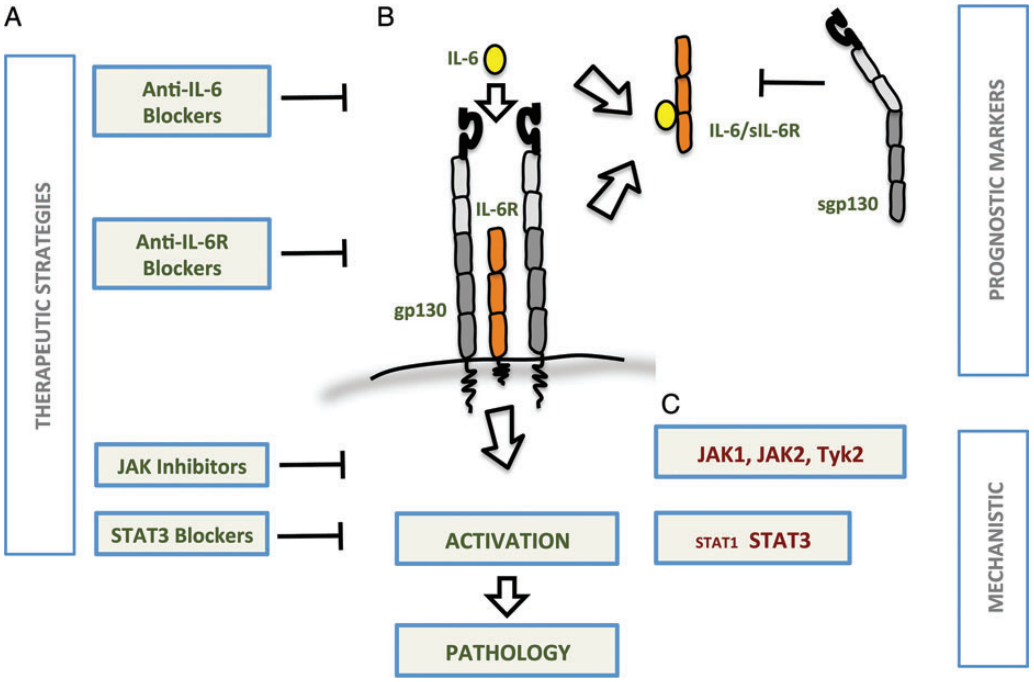

FIGURE 2: Clinical implications for IL-6 research. (**A**) Various therapeutic strategies are either in standard clinical practice or emerging through pre-clinical studies and early stage clinical trials. These include specific cytokine and cytokine receptor blockers and less selective inhibitors of signal transduction components. (**B**) Measurement of IL-6, sIL-6R and sgp130 are increasingly being viewed as prognostic indicators and inform clinical decisions ranging from the overall severity of inflammation to co-morbidities including cardiovascular risk. (**C**) An increased understanding of IL-6 signalling is identifying novel mechanisms for the involvement of IL-6 in autoimmunity, disease and cancer. Such research has also identified crosstalk between IL-6 signalling and other cytokines or immune sensing mechanisms.

viewed as major drug targets for therapy (Figure 2). The application of biologics in conditions such as rheumatoid arthritis emphasize that early therapeutic intervention is essential to ensure appropriate management of the condition and potential disease remission [2]. While certain biologics (e.g. bevacizumab, a humanized monoclonal antibody to VEGF-A) have shown therapeutic efficacy in forms kidney cancer, their application in chronic renal diseases appears to have minimal appeal. This in part may reflect the success of renal transplantation. Instead, clinical assessments of cytokine expression or activities may be considered important prognostic or predictive biomarkers that forecast the course of disease and aid treatment decisions. For example, the monitoring of IL-6 in PD patients is providing valuable information on the loss of ultrafiltration capacity, fibrosis onset, the control of infection and treatment failures [17, 77, 79, 82, 83, 102]. Here, IL-6 activities not only predict local disease processes, but also provide valuable information on systemic inflammatory events and patient co-morbidities (Figure 2). For example, detection of serum IL-6 in PD patients significantly increases with time on dialysis and, as seen in other chronic diseases, correlates with indices of cardiovascular risk [121]. Such findings offer a valuable addition to the standard measurement of C-reactive protein and provide additional information on the potential efficiency of treatment. While the clinical assessment of C-reactive protein is used to reflect the degree of systemic inflammation and potential cardiovascular risk associated with a patient's disease, the role of C-reactive protein in determining the underlining pathology is unclear [122]. Interleukin-6 is the principle driver of C-reactive protein expression and may be viewed as a surrogate marker of IL-6 bioactivity. In this context, the clinical assessment of IL-6 may provide a more powerful prediction of inflammation burden in ESRD [123, 124].

The impact of chronic kidney disease on healthcare systems around the world is increasing. In response, it is essential for new clinical assessments to be applied to provide a more personalized approach to patient stratification, and improvements in treatment decisions. Studies emphasize that IL-6 and associated downstream signalling events may represent one such marker (Figure 2). However to identify the pathways contributing to chronic disease progression in patients with varying degrees of renal disease, we must understand how cytokines like IL-6 govern acute resolving inflammation and how their activities become distorted to drive chronic inflammation.

FULL REVIEW

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