Emerging roles for IL-6 family cytokines as positive and negative regulators of ectopic lymphoid structures.

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ABSTRACT

IL-6 family cytokines display broad effects in haematopoietic and non-haematopoietic cells that regulate immune homeostasis, host defence, haematopoiesis, development, reproduction and wound healing. Dysregulation of these activities places this cytokine family as important mediators of autoimmunity, chronic inflammation and cancer. In this regard, ectopic lymphoid structures (ELS) are a pathological hallmark of many tissues affected by chronic disease. These inducible lymphoid aggregates form compartmentalised T cell and B cell zones, germinal centres, follicular dendritic cell networks and high endothelial venules, which are defining qualities of peripheral lymphoid organs. Accordingly, ELS can support local antigen-specific responses to self-antigens, alloantigens, pathogens and tumours. ELS often correlate with severe disease progression in autoimmune conditions, while tumour-associated ELS are associated with enhanced anti-tumour immunity and a favourable prognosis in cancer. Here, we discuss emerging roles for IL-6 family cytokines as regulators of ELS development, maintenance and activity and consider how modulation of these activities has the potential to aid the successful treatment of autoimmune conditions and cancers where ELS feature.

Keywords: Interleukin-6, interleukin-11, interleukin-27, oncostatin-M, leukaemia inhibitory factor, gp130, ectopic lymphoid structures, tertiary lymphoid structures, autoimmunity, cancer

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INTRODUCTION

Cytokines of the interleukin-(IL)-6 family are important orchestrators of the inflammatory response. In health, these soluble mediators balance responses that promote leukocyte activation and function required for host defence with regulatory mechanisms that support resolution of inflammation, immune tolerance and maintenance of tissue homeostasis. Dysregulation of IL-6 family cytokines is a key feature of chronic diseases involving autoimmunity, chronic inflammation, persistent infection and cancer. While biological drugs that target IL-6 signalling and downstream signalling events are used routinely in the clinic, strategies that modulate the activities of other family members remain at the pre-clinical stage of development [1]. These cytokines display overlapping as well as distinct biological functions and their contribution to disease is often disease- and context-dependent where genetic, environmental and prior immune activation determine how their signals are sensed and actioned. In many chronic inflammatory conditions, disease heterogeneity also gives rise to discrete clinical subtypes that presents an additional challenge to determine the most appropriate cytokines to target in different forms of the same disease. Here, we review emerging roles for IL-6 family cytokines in the development of ectopic lymphoid structures (ELS; also called tertiary lymphoid structures) that form in the inflamed tissues of some patients with autoimmunity and cancer, where they influence the progression of disease and the clinical response to drugs used in the management of these conditions [2-6].

IL-6 FAMILY CYTOKINES AND THEIR RECEPTORS

Members of the IL-6 family include IL-6, IL-11, IL-27, oncostatin-M (OSM), leukaemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1) and cardiotrophin-like cytokine factor 1 (CLCF1). All IL-6 family cytokines use a common 130 kDa β signalling receptor called glycoprotein 130 (gp130) that is ubiquitously expressed. Cytokine binding specificity is provided through unique α receptors (IL-6R, IL-11R, IL-27R, OSMRβ, LIFR, CNTFR) that display a more restricted cellular distribution and thus enable members of

this cytokine family to display distinct and diverse biological functions that span control of immune and tissue homeostasis, inflammation, infection, injury, cancer, haematopoiesis, pain, development and behaviour [1, 7]. While not formal members of the IL-6 cytokine family, IL-31 and IL-35 are also related by virtue of their use of gp130 or gp130-like receptors. IL-35 forms receptor complexes that comprise either a gp130 homodimer, gp130 and IL-12Rβ2, gp130 and IL-27Rα, or a homodimer of IL-12Rβ2 [8]. The cytokine IL-31 utilises a gp130-like receptor, IL-31RA, in combination with OSMRβ [9].

Formation of a functional receptor complex involves gp130 homodimers associating with a non-signalling α receptor (in the case of IL-6R and IL-11R), or heterodimers of gp130 partnering with another signalling receptor subunit that resembles gp130 (in the case of IL-27Rα, OSMR, LIFR) (**Figure 1**). Crystallography revealed that IL-6 forms a hexameric complex involving two molecules each of IL-6, IL-6R and gp130 [10]. While high-resolution structural data is not currently available for other IL-6 family members, comparable hexameric complexes have been proposed [11]. Cytokine binding and formation of the receptor complex initiates intracellular signalling cascades through Janus Kinase 1 (JAK1), JAK2 and non-receptor tyrosine-protein kinase 2 (TYK2)-mediated phosphorylation of tyrosine residues in the cytoplasmic domain of the receptors [12]. These tyrosine residues serve as binding sites for the activation of signal transducer and activator of transcription (STAT)-1, STAT3 and, to a lesser extent, STAT5 [1, 7, 13]. The SH2-containing protein tyrosine phosphatase-2 (SHP2) also engages these phosphorylated tyrosine residues resulting in activation of alternative signalling pathways, including the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)-AKT (also called protein kinase B) pathways [12].

Elegant alternative mechanisms of gp130 engagement have provided novel approaches to selectively target signalling mechanisms utilised by some IL-6 family members. For example, some family members signal through soluble forms of their receptors that are generated

through proteolytic cleavage of membrane-bound α receptors by the metalloproteases ADAM10 and ADAM17 (**Figure 1**) [14, 15]. As gp130 is ubiquitously expressed, this extends the cell types responsive to these cytokines and is best characterised for IL-6 signalling. The IL-6R is restricted predominantly to hepatocytes and some leukocyte populations, therefore relatively few cell types respond to IL-6 directly (termed 'classical' IL-6 signalling) [7, 16]. In inflamed tissues, an increase in soluble IL-6R (sIL-6R) levels, generated through mechanisms that include proteolytic cleavage of membrane IL-6R, results in a process called IL-6 trans-signalling [7, 16]. Here, agonistic IL-6:sIL-6R complexes engage with membrane gp130 enabling cells that lack a membrane-bound IL-6R to become IL-6 responsive. This represents the dominant form of IL-6 signalling that occurs within inflamed tissues [17]. Soluble forms of gp130 (sgp130) act as natural antagonists of IL-6 trans-signalling and engineered versions have been generated (e.g., Fc-conjugated sgp130 licenced as olamkicept) that show therapeutic benefit in pre-clinical disease models and early clinical trials [18-20]. IL-11 and CNTF can also trans-signal via sIL-11R and sCNTFR, while IL-6 and IL-11 bound to their cell surface receptors have further been shown to activate gp130 on neighbouring cells through a mechanism termed trans-presentation [21, 22].

The success of antibodies that target IL-6 signalling (e.g., tocilizumab, sarilumab, siltuximab) and JAK inhibitors (e.g., tofacitinib, baricitinib) in the clinic, and our understanding of the pathological roles played by other IL-6 family cytokines in pre-clinical disease models, underline the importance of regulatory mechanisms that limit excessive cytokine signalling. Mechanisms have evolved to negatively regulate intracellular signalling downstream of these cytokines. Protein inhibitor of activated STAT (PIAS) inhibits intracellular signalling through mechanisms that include interfering with STAT proteins binding to DNA in the nucleus [12, 23]. Suppressor of cytokine signalling (SOCS) family proteins are also induced by STAT proteins and contain SH2 domains that allow receptor binding and negative regulation of JAK proteins [23]. Here, SOCS3 is induced in response to IL-6 family cytokines and functions as a feedback mechanism by inhibiting JAK-STAT3 activation as well as targeting the receptor for

ubiquitination and proteasomal degradation [12, 23]. The biology of IL-6 family cytokines has been thoroughly reviewed elsewhere [1, 7, 12], therefore here we focus on the involvement of IL-6 family cytokines in the regulation of ELS.

ECTOPIC LYMPHOID STRUCTURES

Secondary lymphoid organs (SLOs) comprise highly organised cellular compartments that facilitate the interaction of immune cells for the generation of adaptive immune responses. The development of encapsulated SLOs follows a pre-programmed process that starts during embryogenesis and results in the formation of lymphoid organs that are permanent fixtures in our control of host defence and peripheral immune tolerance [24, 25]. ELS are SLO-like cellular formations that develop in tissues affected by chronic inflammation, autoimmunity, infection, cancer and allograft rejection [4-6, 26]. These non-encapsulated lymphoid structures are inducible sites that afford non-lymphoid tissues with functions that allow the development and maintenance of antigen-specific T cell and antibody responses, that can occur independently of those at SLOs [27-31]. Unlike SLOs, antigen clearance or resolution of tissue inflammation is associated with the disappearance of ELS, meaning that their presence is often transient. There is therefore interest in understanding the mechanisms that favour the development versus regression of ELS. Approaches that limit ELS development may have therapeutic benefit in autoimmune diseases where they are often associated with pathological outcomes, while encouraging the tumour-associated ELS formation may enhance anti-tumour immunity in certain cancers.

The development of ELS mirrors aspects of secondary lymphoid organogenesis, which is initiated through interactions between hematopoietic derived lymphoid tissue inducer (LTi) cells and mesenchymal derived lymphoid tissue organiser (LTo) cells. Here, the accumulation of LTi cells in response to IL-7, CXCL13 and RANKL leads to the expression of lymphotoxin (LT)α1β2, homeostatic chemokines (CXCL13, CCL19, CCL21, CXCL12), and adhesion molecules (ICAM-1, VCAM-1) that recruit lymphocytes and maintain their organisation within

SLOs [24, 25]. Triggered by inflammation, ELS formation instead involves complex interactions between tissue-resident stromal cells and tissue-infiltrating leukocytes, where inflammatory cytokines and lymphoid chemokines (e.g., CXCL13, CCL21, CCL19, CXCL12) coordinate the early recruitment of T and B cells into simple aggregates [2, 3]. Sustained inflammatory cues support the formation of more organised ELS that display T- and B-cell compartmentalisation, $CD21^+$ follicular dendritic cells (FDCs) networks, functional germinal centres (GCs) and peripheral lymph node addressin $(PNAd)^+$ high endothelial venules (HEVs) involved in the recruitment of $CD62L^+$ ($L\text{-selectin}^+$) lymphocytes that would typically home to SLOs. While ELS are often enriched in effector memory T cell populations, the presence of HEVs is associated with the recruitment and activation of naïve CD4 T cells supporting the concept that antigen-specific T cell responses can be generated locally within inflamed or cancerous tissues [32-36]. Similarly, mature ELS comprising GCs express activation-induced cytidine deaminase (AID, or AICDA) providing evidence that B cell affinity maturation and antibody class switching occurs at these sites [3, 27, 37, 38]. It should be noted, however, that ELS often fail to display the degree of cellular compartmentalisation seen in SLOs and can appear as dense lymphoid accumulations with varying degree of T/B cell segregation, stromal cell differentiation, GC activity and HEV involvement. As ELS are present in various conditions and at different stages of disease including after treatment, this presents a challenge to investigating ELS in the clinical setting [5, 6, 39-41]. The stage of disease at which tissue biopsy is performed may make it difficult to distinguish immature ELS from those in regression. Moreover, where biopsy sampling is not possible it may only be possible to characterise ELS in post-mortem tissues. Here, combining clinical studies with experimental models of disease provides important insight into the temporal relationship between ELS development and chronic disease progression.

ELS AS PROPOGATORS OF AUTOIMMUNITY AND ANTI-TUMOUR IMMUNITY

The formation of ELS is a clinical feature of many autoimmune conditions, chronic inflammatory diseases, solid tumours and tissue graft rejection. For a comprehensive review

of ELS in these conditions, the reader is directed elsewhere [4-6, 26]. In human autoimmunity, ELS are predominantly associated with pathogenic outcomes. Here, the ability to perform joint and salivary gland biopsies in patients with rheumatoid arthritis and Sjögren's syndrome has provided insight into ELS regulation at various stages of disease and treatment. In rheumatoid arthritis, synovial ELS are present in approximately 30-50% of patients and are associated with elevated systemic and synovial inflammation, increased disease activity, radiographic joint damage and an inferior response to biological drug treatment [5, 39, 40, 42, 43]. A similar proportion of patients with Sjögren's syndrome (~30-40%) develop ELS in inflamed salivary glands where they correlate with autoantibody (anti-Ro/SSA and anti-La/SSB) positivity, hypergammaglobulinemia and cryoglobulinemia, and are associated with progression to mucosa-associated lymphoid tissue (MALT) lymphoma [26, 44-47]. Post-mortem tissue from multiple sclerosis patients display meningeal ELS that are associated with increased inflammation, microglial cell activation and clonal B cell expansion suggesting an active role in immunopathogenesis [48-50]. Here, meningeal ELS were linked with a younger age of multiple sclerosis onset, more progressive demyelination, neurite loss in the cerebral cortex and irreversible disability [51].

The development of ELS in the above conditions is associated with the expression of homeostatic chemokines (CXCL13, CCL21, CCL19, CXCL12), $PNAd^{+}$ HEV and FDC, that may contribute cellular and molecular biomarkers with the potential to support the stratification of patients with ELS-rich tissue inflammation [40, 42, 43]. However, the prognostic significance of ELS is debated and while often associated with more severe pathology, a causative role for ELS in disease pathogenesis remains a controversial point for discussion. Nevertheless, several published studies support the idea that ELS actively contribute to disease pathogenesis. Following transplantation of rheumatoid arthritis synovial tissue or salivary glands from Sjögren's syndrome patients into mice with severe combined immunodeficiency (SCID), the tissue microenvironment supports the long term survival of ELS, maintains expression of AID and the secretion of autoantibodies (ACPA in rheumatoid arthritis; anti-

Ro/SSA and anti-La/SSB in Sjögren's syndrome) [27, 52]. Such persistence of ELS without contribution from the peripheral B cell pool is consistent with reports that ELS can survive B cell depletion therapy (Rituximab) [53-56]. Here, heightened expression of B cell activating factor (BAFF) at ELS provides a local survival signal for B cells. Additional studies describe the clonal expansion of B cells within ELS, where they undergo affinity maturation and the selection of antibodies against disease-specific tissue autoantigens [57-59]. Numerous studies in experimental models of autoimmunity similarly support pathogenic roles for ELS in immune-mediated pathology [27, 60-67]. Often the formation of ELS in these models is linked to recruitment of T helper (Th)17, Th22 and T follicular helper (Tfh) cells, or innate leukocyte populations (e.g., innate lymphoid cell 3, ILC3; γδ cells) that similarly secrete IL-17A, IL-17F and IL-22 [2, 3, 26, 68]. While the association between Th17-type responses and ELS development is often mechanistically attributed to IL-17, ELS can also form in the absence of the signature Th17 cytokine [69]. Interestingly, mice deficient in retinoic acid-related orphan receptor (ROR)γ and RORγt do not develop foetal LTi cells required for the development of Peyer's patches and lymph nodes, suggesting that effector mechanisms under the control of these transcription factors are critical to lymphoid neogenesis [70]. Here, it is notable that cells displaying Th17-type effector responses (Th17 cells, ILC3 and IL-17-producing γδ T cells) also express RORγt and share effector functions with LTi cells that may explain why Th17-rich inflammation often coincides with early ELS development [3, 31, 68]. In diseases like rheumatoid arthritis, loss of immune tolerance may take place at mucosal sites years before the onset of clinical symptoms. Interesting studies in the K/BxN model of rheumatoid arthritis suggest that gut commensals promote Th17 cell differentiation and the development of ELS in the lung (called inducible bronchus-associated lymphoid tissue; iBALT) that represent sites where autoantibody production in pre-arthritic disease is triggered [71]. ELS, therefore, contribute to disease-specific autoantibody production in established disease, and may also contribute to the loss of peripheral immune tolerance that triggers asymptomatic autoimmunity.

Despite evidence of pathogenic roles for ELS in chronic inflammatory conditions, there are notable exceptions. Studies in the apolipoprotein E-deficient *(Apoe*$^{-/-}$) mouse model of atherosclerosis reveal that aortic ELS maintain T cell homeostasis, promote Treg cell differentiation and provide atherosclerosis protection [32]. Here, the expression of LTβ receptor (LTβR) by vascular smooth muscle cells was required for the maintenance of ELS and atherosclerosis was exacerbated when LTβR signalling was ablated in *Apoe*$^{-/-}$*Ltbr*$^{-/-}$ mice. ELS can also harbour T and B cells displaying regulatory functions in allografts, where ELS may suppress otherwise destructive alloimmune responses that drive tissue rejection [72, 73]. Our recent studies describe CD21^{+}, CD23^{+}, Bcl-6^{+} and AID^{+} ELS as a feature of clinical disease in enucleated ocular tissue from patients with uveitis [74]. In a spontaneous autoimmune model of uveitis driven by a T cell receptor (TCR; the R161H TCR transgenic mouse) specific for the retinal antigen interphotoreceptor retinoid-binding protein, retinal lymphoid aggregates were detected in 40% of mice and displayed T/B cell segregation, HEV formation and the presence of FDC at GCs [75]. Surprisingly, mice with ELS showed improved visual activity compared to those lacking organised lymphoid accumulations, although this protective association was lost in aged mice with more advanced disease. Therefore, ELS formation is a feature of persistent inflammation in many tissues including sites of immune privilege and tissue rejection, and in some tissues are associated with beneficial outcomes.

The ability of ELS to generate antigen-specific immune responses at sites of infection and tumourigenesis is associated with enhanced anti-pathogen and anti-tumour immunity [6, 31]. Following viral or bacterial challenge ELS were shown to form in mucosal tissues including the salivary glands [65], lungs [76-78] and stomach [79, 80]. Several studies demonstrate that ELS can display functional anti-pathogen responses. For example, following influenza virus infection in mice, iBALT comprised plasma cells specific for influenza virus nucleoprotein [81]. In this model, ELS were maintained through secretion of pro-ELS factors (LTβ, CXCL13, CXCL12, CCL19, CCL21) by dendritic cells. Depletion of dendritic cells resulted in decreased levels of class-switched IgA suggesting that ELS actively contribute to local pathogen-specific

immune responses [81]. Indeed, anti-pathogen responses have also been observed at ELS independently of SLO involvement. When LTα-deficient mice that lack spleen, lymph nodes and Peyer's patches (SLP) were reconstituted with wild type bone marrow, mice were able to form iBALT and were effective in clearing influenza virus [29].

Despite the immunosuppressive microenvironment typical of tumours, ELS ranging from simple lymphoid aggregates to highly organised structures have been described in solid tumours. In the majority of cancers including colorectal [82, 83], pancreatic [84, 85], gastric [86], lung [87-89] and breast [90-92] cancers, ELS are prognostic of favourable clinical outcomes, that suggests an active role in enhancing anti-tumour immunity. Evidence for a role in generating anti-tumour responses includes the expression of AID, ongoing antibody class switching and somatic hypermutation at ELS in lung cancer, ovarian cancer and melanoma [87, 93, 94]. Notably, in non-small cell lung cancer (NSCLC) patients with tumour-associated ELS, intratumoral plasma cells secreted antibodies specific for tumour antigens (e.g., NY-ESO-1, TP53, LAGE-1) [87]. Studies in mouse models similarly support a role for ELS as sites for the clonal expansion for T cells that display reactivity to tumour antigens and suppress tumour growth [28, 34]. However, tumour-associated ELS are not universally associated with improved clinical outcomes. In hepatocellular carcinoma, ELS signify a poor prognosis and provide a protective microniche for the survival and growth of malignant progenitor cells before they egress and develop into tumours [95]. Therefore, while studies in cancer predominantly support the notion that tumour-associated ELS generate effective anti-tumour responses further studies are needed to determine which types of cancer may benefit from therapeutic approaches that encourage ELS formation.

In this regard, recent clinical investigations involving patients with soft-tissue sarcoma and melanoma have highlighted the prognostic value of B cells associated with ELS as indicators of improved responses to immune checkpoint blockade (anti-PD1, anti-CTLA4) [96-98]. Here, transcriptomic and mass cytometry revealed that hallmark ELS genes and class-switched

memory B cells were enriched in responding tumours and were associated with T cells displaying memory-like effector characteristics linked with improved responses to checkpoint immunotherapy. Therefore, tumour-associated ELS may represent anti-tumour powerhouses-in-waiting that can be activated in response to immune checkpoint blockade. Furthermore, strategies that encourage ELS development in tumours may present an opportunity to enhance anti-tumour immunity in patients that fail to respond to immune checkpoint inhibition alone.

IL-6 REGULATES BIDIRECTIONAL INTERPLAY BETWEEN T AND B CELLS

IL-6 is a highly pleiotropic cytokine with diverse actions across innate and adaptive immunity that determine the host response to infection, tissue injury, chronic inflammation, autoimmunity and cancer [1, 16]. In certain leukocyte and stromal cell populations, IL-6 secretion is triggered by microbial and danger sensing mechanisms that include pattern recognition receptors (e.g., toll-like receptors; TLRs), alarmins (e.g., uric acid, HMG-1) and inflammatory cytokines (e.g., TNF, IL-1β) [99]. IL-6-deficient (*Il6*$^{-/-}$) mice, therefore, show an impaired immune response to bacterial and viral challenge [100-103]. Studies also revealed that *Il6*$^{-/-}$ mice are protected from immune-mediated tissue damage in various models of autoimmunity and chronic inflammation, including experimental autoimmune encephalomyelitis (EAE), inflammatory arthritis, colitis and tissue fibrosis [104-108]. The recent recommendation by some governments that anti-IL-6R drugs (tocilizumab, sarilumab) be repurposed for the treatment of severe coronavirus disease 2019 (COVID-19) in the current pandemic highlights the diverse and important contribution of this cytokine to immune-mediated pathology.

While early studies defined IL-6 (originally named B cell stimulating factor-2) as a factor that promotes B cell proliferation and antibody production [109], its role in immune-mediated damage to tissues has largely been linked to dysregulation of CD4 T cells. Here, IL-6 in concert with either IL-12, IL-4 or TNF supports the expansion of Th1 cells, Th2 cells or IL-22-

producing Th22 cells respectively [108, 110, 111]. In autoimmunity, pathogenesis is often attributed to the ability of IL-6 together with transforming growth factor (TGF)β to favour the differentiation of pathogenic IL-17-producing Th17 cells [112-114], while also suppressing the development of FoxP3$^+$ regulatory T cells [115, 116]. Published studies highlight important roles in regulating the interplay between B cells and T cells in lymphoid tissues. For example, B cells are an essential source of IL-6 that support pathogenic Th17 cell responses in EAE [117]. The ability of IL-6 to promote the differentiation of CXCR5$^+$Bcl-6$^+$ICOS$^+$ and IL-21-producing T follicular helper (Tfh) cells that migrate to B cell follicles and support high-affinity antibody generation is also consistent with the early description of IL-6 as a B cell stimulating factor [103, 118]. More recent studies implicate the Th17 and Tfh cell-associated IL-21 and IL-22 in the post-translational modification of autoreactive antibodies at GCs that trigger a transition from asymptomatic autoimmunity to the clinical onset of rheumatoid arthritis [119]. Such observations underscore the importance of Th17 and Tfh cells in autoantibody-driven disease and highlight an important role for IL-6 in regulating the bi-directional relationship between B and T cells.

IL-6 SHAPES TISSUE INFLAMMATION AND ELS DEVELOPMENT

Given the roles described above for IL-6 in promoting Th17, Th22, Tfh and T cell-dependent antibody responses at GCs [110, 112-114, 117, 120, 121], it is perhaps unsurprising that IL-6 and other family members are linked with ELS development (**Figure 2** and **Table 1**). Studies have identified a role for IL-6 in the development of podoplanin-expressing Th17 cells that also acquire Tfh-like effector characteristics (expression of Bcl-6, ICOS and CXCR5) and drive the development of ELS within the CNS [67]. A similar phenotype was observed in Th17 cells that display Tfh-like functions and support IgA secretion at GCs in Peyer's patches [122]. While podoplanin has also been described as an inhibitory receptor on CD4 T cells [123, 124], these observations are consistent with its expression on stromal populations (e.g., lymphatic endothelial cells, fibroblastic reticular cells and FDCs) and the requirement for podoplanin in the development of peripheral lymph nodes in early life [67, 125]. Th17-, Tfh- and T peripheral

helper (Tph)-associated effector functions, including expression of IL-17, IL-22, IL-21 and ICOS are associated with the development of ELS in various models of autoimmunity, inflammation and infection that affect the lung (iBALT), salivary glands, retina, synovium and aorta [3, 44, 68]. In Sjögren's syndrome, salivary gland epithelial cells produce IL-6 and drive Tfh cell differentiation [126]. Notably, the expansion of IL-21-producing Tfh and Tph cells in salivary glands was recently shown to identify Sjögren's syndrome patients with ELS and parotid B cell MALT lymphomas [44]. Other published studies show that podoplanin expression on synovial fibroblasts is associated with ELS- and autoantibody-positive RA, where these cells represent a stromal source of IL-6 in the joint [127].

A direct role for IL-6 in ELS development was demonstrated in double transgenic mice overexpressing human IL-6 and IL-6R [128]. These mice display leukocyte infiltrates in the lung that form organised lymphoid follicles comprising CD4 T cells, B cells, plasma cells, FDCs and HEVs by 20 weeks of age. Here, lymphocyte recruitment was associated with the localised induction of CXCL13 in ELS. In these transgenic mice, the development of ELS is likely mediated through the increase in cell types able to respond to IL-6 directly and thus, as gp130 is ubiquitously expressed, may more accurately reflect a model of exaggerated gp130 activation. While these mice overexpressed the transmembrane form of IL-6R, the transgene also resulted in high levels of circulating sIL-6R. Thus, IL-6 trans-signalling via the sIL-6R may also be at play during ELS formation in inflamed tissues.

ELS have been extensively studied in rheumatoid arthritis, offering insight into the potential of targeting IL-6 signalling in conditions where ELS are considered pathogenic. Histological and transcriptomic studies of synovitis have identified clinical subtypes where the local inflammatory response can be classed into three pathotypes: ‘Lymphoid’ featuring synovial ELS, ‘diffuse’ synovitis enriched in myeloid cell infiltrates, and fibroblastic-rich ‘pauci-immune’ pathology [40, 42, 43]. While it remains controversial whether ELS actively participate in the pathogenies of rheumatoid arthritis or are bystanders that mark a particular disease state,

their presence is associated with increased systemic inflammation (e.g., CRP), local T and B cell activation and autoantibody production, higher disease severity, erosive joint pathology and inferior responses to conventional and biological drugs [5, 26, 39, 40, 42, 43].

Consistent with studies that describe a role for exaggerated gp130-signalling in the development of systemic and local Th17 cell responses [129, 130], lymphoid neogenesis in rheumatoid arthritis has been associated with Th17/IL-23 gene signatures [131]. Recent studies reveal the importance of negative feedback mechanisms downstream of TCR activation and gp130 signalling as determinants of CD4 T cell and ELS responses [132, 133]. Genetic polymorphisms that result in reduced expression of the *PTPN2* gene are associated with RA, which encodes for a negative regulator of TCR and cytokine receptor signalling in T cells called protein tyrosine phosphatase nonreceptor type 2 (PTPN2). Consistent with this, mice with a haploinsufficiency in the *Ptpn2* gene develop exacerbated T cell-driven inflammatory arthritis involving synovial Th17 cell infiltration and ELS formation [133]. Here, negative regulation of IL-6-STAT3 signalling by PTPN2 was critical in preventing the conversion of FoxP3 Tregs into pathogenic RORγt- and IL-17-positive CD4 T cells. Accumulations resembling ELS were similarly observed in diabetic NOD mice with a T cell specific deletion of *Ptpn2,* and were associated with exaggerated Tfh cell responses and other autoimmune comorbidities [134]. Other studies in inflammatory arthritis also revealed an important role for PTPN2 in limiting IL-6-driven STAT1 signalling, which shaped the transcriptional output of effector CD4 T cells [132]. Here, activated murine CD4 T cells show preferential activation of STAT3 over STAT1 in response to IL-6, resulting in elevated expression of effector cytokines (e.g., *Il17a, Il21*), transcriptional regulators (e.g., Bcl6) and homeostatic chemokines involved in lymphoid neogenesis (e.g., *Cxcr4, Cxcr5*). Notably, *PTPN2* expression was increased in the synovial tissue of patients with ELS and correlated with the expression of *IL21* and *IL17A* [132]. Thus, studies spanning basic and clinical investigations of ELS highlight key roles for IL-6 in shaping the CD4 T cell effector response and lymphoid neogenesis.

Interestingly, synovial ELS have been proposed as predictors of a negative response to anti-TNF treatment [39]. A study by Dennis *et al.* used synovial gene expression to correlate synovial pathotypes with responses to anti-TNF and anti-IL-6R treatment [42]. A molecular signature of the lymphoid phenotype was associated with increased serum levels of CXCL13 while diffuse synovitis was linked with circulating soluble intercellular adhesion molecule 1 (sICAM1) [42]. Patients with high serum CXCL13 displayed an inferior response to anti-TNF (adalimumab) compared to those with high sICAM levels but showed a favourable response (American College of Rheumatology response criteria ACR50) to tocilizumab suggesting that targeting IL-6 signalling may be particularly effective in patients with the lymphoid pathotype of RA. However, a recent clinical trial in patients displaying an inadequate response to anti-TNF revealed that rituximab and tocilizumab showed comparable clinical responses in patients with B cell-rich synovitis, while tocilizumab was more effective in patients classed as having low B cell involvement [135]. Therefore, further studies are needed to determine whether ELS and other molecular signatures of joint inflammation can be harnessed for the effective stratification of patients and the targeted deployment of biological therapies for improved patient treatment.

IL-27 CONTROLS ADAPTIVE IMMUNITY AND IMMUNOPATHOLOGY

Owing to an ability to promote IFNγ secretion in CD4 T cells, IL-27 was initially described as a pro-inflammatory cytokine [136-138]. Subsequent studies, however, identified protective roles for IL-27 in models of immune-mediated pathology that collectively revealed important roles in the negative regulation of CD4 T cell responses. Early work showed that when IL-27R-deficient (*Il27ra*$^{-/-}$) mice were challenged with *Toxoplasma gondii,* they displayed effective anti-parasite Th1 cell responses but a failure to downregulate this response caused lethal T cell-mediated pathology [139]. Studies in models of autoimmunity similarly outlined important roles for IL-27. Through inhibition of pathological Th17 cell responses, IL-27 limited the severity of EAE, inflammatory arthritis, experimental autoimmune uveitis and colitis [140-146].

Further anti-inflammatory activities were later described that include inhibition of granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion [147, 148], the ability to induce IL-10 [149-151] and to promote the differentiation of regulatory T cells that traffic to inflamed tissues [152, 153]. Consistent with a role for IL-27 in regulating peripheral immune tolerance, IL-27 has also emerged as an important regulator of immune checkpoints. Several studies have shown that IL-27 promotes T cell expression of programmed death-ligand 1 (PD-L1), programmed cell death protein 1 (PD-1), lymphocyte-activation gene 3 (LAG-3), T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) [154-157]. Indeed, a recent single-cell RNA-sequencing and mass cytometry analysis of tumour-infiltrating T cells highlighted a key role for IL-27 as an inducer of a co-inhibitory gene module that comprised PD-1, TIM-3, LAG-3, TIGIT, activated protein C receptor (PROCR) and podoplanin (PDPN) [124]. While the above studies outline anti-inflammatory roles for IL-27, some pro-inflammatory activities have also been described. These include an ability to increase cytokine secretion downstream of pattern recognition receptor engagement, induce IFNγ secretion and the survival of CD4 T cells, enhance cytotoxic T cell and NK cell responses, and inhibit inducible Treg development through negative regulation of IL-2 [158, 159]. These observations are consistent with studies that demonstrate less severe disease when *Il27ra*$^{-/-}$ mice are exposed to certain experimental models associated with Th1-driven pathology [160, 161], and the spontaneous development of systemic inflammation in mice overexpressing IL-27 [162]. Therefore, translational studies that investigate the therapeutic potential of IL-27 delivery must also consider its potential to increase the number of IFNγ-secreting CD4 T cells and limit certain Treg populations.

IL-27: A NEGATIVE REGULATOR OF THE ELS RESPONSE

Recent studies in autoimmunity identify a role for IL-27 in regulating ELS. Consistent with previous reports that described roles for IL-27 in limiting the severity of inflammatory arthritis [142, 143], our group found that *Il27ra*$^{-/-}$ mice with antigen-induced arthritis develop more

severe joint inflammation and an increase in Th17 cell numbers in draining lymph nodes [61]. Exacerbated arthritis was associated with the development of T cell-rich synovial ELS and the expression of genes encoding IL-17A, IL-21, lymphotoxin (LT)α, LTβ and B lymphocyte-induced maturation protein-1 (Blimp-1). Interestingly, while wild type mice do not typically develop ELS in the antigen-induced arthritis model, a modified immunisation protocol that promotes recurrent arthritic flares (designed to model a late chronic phase of disease) also results in synovial ELS formation that is CXCR5- and CCR7-dependent [60]. Thus, synovial ELS development in *Il27ra*$^{-/-}$ may be driven by an increase in pathogenic Th17 cells, but may also reflect the more persistent synovitis observed in these mice. Synovial lymphoid neogenesis is also associated with elevated expression of Th17-type cytokines (e.g., *IL17A*, *IL17F*, *IL21, IL22, IL23*) in clinical rheumatoid arthritis [61, 163]. Analysis of synovial tissue from patients with ELS revealed increased expression of the IL-27R and the presence of IL-27R-expressing lymphocytes within ELS. The expression of IL-27 also decreased in the joints of patients with ELS and showed a negative correlation with histological scores for CD3$^+$ and CD20$^+$ infiltrating cells [61]. Thus, therapeutic strategies that aim to exploit the anti-inflammatory characteristics of IL-27 may provide therapeutic benefit in rheumatoid arthritis and other autoimmune and inflammatory diseases where ELS are linked with pathology.

Two studies in experimental models that display Sjögren's syndrome-like pathology further underline a role for IL-27 in ELS regulation. First, mice treated with an adeno-associated viral vector expressing IL-27 showed reduced clinical disease, lower levels of serum IL-17 and splenic Th17 cells, fewer lymphocytic aggregates in lacrimal glands and a reduction in anti-nuclear antibody IgG titres [164]. Similarly, in collaboration with the Bombardieri and Pitzalis groups, our studies revealed that salivary gland cannulation with a replication-deficient adenovirus resulted in exaggerated lymphoid chemokine expression (e.g., *Cxcl13*, *Ccl19*) and ELS formation in the salivary glands of *Il27ra*$^{-/-}$ mice [38]. In the absence of IL-27 signalling, ELS showed enhanced levels of GC activity, with increased CD21$^+$ follicular dendritic cell networks, GL7$^+$ GC B cells and AID expression. While ELS development in this model is

dependent on IL-22 [64], the exaggerated ELS response observed in *Il27ra*$^{-/-}$ mice was driven by IL-17. Notably, when translating these observations into human disease, the ability of IL-27 to suppress IL-17-secretion in circulating CD4 T cells was impaired in Sjögren's syndrome patients compared to healthy individuals. Therefore, IL-27 represents an important immunoregulatory checkpoint for the control of CD4 T cell responses, and disruption to the physiological suppression of Th17-driven outcomes may influence the course of disease and development of ELS. Interestingly, in a recent study involving patients with spondyloarthritis, anti-IL-17 (secukinumab) treatment reduced the number of synovial HEV and lymphoid aggregates providing further evidence of a role for the Th17/IL-17 axis in propagating ELS [165].

In contrast to the inhibitory actions outlined above, several studies describe roles for IL-27 in promoting Tfh cell responses and GC activity [166-168]. These apparent contradictions may be due to site- and disease-specific differences in how IL-27 controls effector CD4 T cell responses. For example, the ability of IL-27 to support Tfh and GC responses in SLOs as shown in models of lupus (pristane-induced and Roquin$^{san/san}$ lupus models) contrasts with the inhibition of these responses in inflammatory lesions where IL-27 can also limit lymphocyte recruitment [166, 168]. Thus, approaches that aim to exploit the ability of IL-27 to inhibit ectopic GC responses may need to consider innovative drug delivery platforms that target cytokines to inflamed tissues [169-172].

OSM, IL-11 AND LIF: STROMAL REGULATORS OF IMMUNE-MEDIATED PATHOLOGY

As critical mediators of leukocyte and stromal cell interactions, IL-6 family cytokines coordinate distinct and overlapping functions that determine various aspects of host defence, immune-mediated pathology and cancer [1, 99]. While the IL-6R and IL-27R are highly expressed in leukocyte populations, OSM, LIF and IL-11 mostly regulate non-hematopoietic cells.

The OSMR is expressed by fibroblasts, epithelial cells, endothelial cells, adipocytes and neurons [9, 99]. OSM maintains haematopoiesis, promotes leukocyte recruitment, adipocyte differentiation, the release of inflammatory mediators by fibroblasts (e.g., IL-6, CCL2, CXCL1, ICAM-1, MMP) and has pro-tumorigenic activities [173-177]. OSM is, therefore, implicated in the pathogenesis of various inflammatory conditions including tissue fibrosis, inflammatory bowel disease, rheumatoid arthritis, psoriasis and asthma. Reflecting a similar contribution made by IL-6 to inflammation-driven tissue fibrosis, intranasal administration of OSM promotes inflammation and pulmonary fibrosis independently of the classical pro-fibrotic mediators IL-4, IL-13 and TGFβ [108, 178]. Overexpression of OSM or IL-6 through adenoviral delivery similarly exacerbates bleomycin-induced lung fibrosis [179]. While the functional significance of a single nucleotide polymorphism in *OSMR* in inflammatory bowel disease is currently unknown [180], OSM promotes intestinal inflammation in experimental colitis and its expression is predictive of non-responsiveness to anti-TNF treatment in patients [177]. Studies have also investigated the potential of neutralising OSM in inflammatory arthritis. Despite encouraging results in pre-clinical models of rheumatoid arthritis [181], a humanised anti-OSM monoclonal antibody (GSK315234) showed little efficacy in a phase II trial in patients with active disease, possibly due to the lower binding affinity of the OSM/antibody interaction compared to that of the OSM/OSMR complex [182]. Further clinical trials are underway using a high-affinity OSM-specific antibody (GSK2330811) in systemic sclerosis (ClinicalTrials.gov identifier NTC03041025) [183].

In contrast to pro-inflammatory roles described for OSM, anti-inflammatory actions for IL-11 led to phase-I/II clinical trials of recombinant IL-11 in rheumatoid arthritis, albeit without significant benefit [184]. In acute inflammation as a consequence of lipopolysaccharide-induced endotoxemia, animals treated with IL-11 also showed reduced mortality, lower systemic pro-inflammatory cytokine release and were protected from hepatic injury [185, 186]. However, both pro- and anti-inflammatory outcomes are associated with activities of IL-6 family cytokines. In the case of IL-11, immunopathology has been linked with Th2-type

immune responses. Owing to the ability of Th2-type cytokines to promote IL-11 and IL-11R expression, endogenous IL-11 contributes to IL-13-driven allergen-induced airway inflammation resulting in increased eosinophilic infiltration, mucus production and airway remodelling in mouse models [187, 188]. As described for IL-6 and OSM, roles in tissue fibrosis are also apparent for IL-11. Pro-fibrotic factors including TGFβ, IL-13 and OSM are potent inducers of IL-11 in fibroblasts and genetic ablation of *Il11ra* protects mice from cardiac and kidney fibrosis [189]. A neutralising IL-11-specific antibody similarly prevented fibroblast activation and reversed pathology in a model of pulmonary fibrosis [190]. A stromal IL-11 response is also a key mediator of inflammation-associated cancer. Here, IL-11-mediated STAT3 signalling results in pro-tumorigenic responses in cancers of the gastrointestinal tract and breast [191-194]. In gastric tumours, IL-11 promotes the expression of TLR2 on the gastric epithelium that enables innate sensing mechanisms to promote hyperproliferation and increased epithelial cell survival resulting in tumour growth [195]. Similarly, in endometrial cancer, blockade of IL-11 signalling reduced primary tumour growth, epithelial-to-mesenchymal transition and metastasis [196]. Together, the above studies suggest that IL-11 may represent a therapeutic target for the treatment of tissue fibrosis, certain cancers and conditions such as asthma where Th2-polarized responses promote immunopathology. Hematopoietic activities, including the maturation of megakaryocytes which form platelets, resulted in the approval of recombinant IL-11 (oprelvekin) for the treatment of thrombocytopenia in patients following myelosuppressive chemotherapy [197].

The ability of LIF to display either pro- or anti-inflammatory activities is similarly highly context-dependent. Like IL-11, LIF curtails systemic inflammatory cytokine release and protects from lethal septic shock following endotoxin challenge [198, 199]. However, in synovial fibroblasts recovered from the synovium of rheumatoid arthritis patients, an autocrine loop that maintains LIF responsiveness promotes a STAT4-mediated secretion of inflammatory cytokines including IL-6, IL-8, G-CSF, IL-33 and IL-1β [200]. LIF, and OSM acting through either an

OSMR-gp130 heterodimer or LIFR-gp130 heterodimer, also regulate bone turnover through control of osteoblast differentiation and RANKL-mediated osteoclastogenesis [201, 202]. Within tumours, various cytokines activate cancer-associated fibroblasts resulting in an invasive tumour microenvironment. LIF in concert with TGFβ promotes the activation of stromal fibroblasts, extracellular matrix remodelling and drives an epigenetic programme resulting in constitutive JAK1/STAT3 activity that maintains a pro-invasive tumour state [203, 204]. Here, LIF expression correlated with poor clinical outcome in lung tumours and head and neck carcinoma, and JAK1/2 inhibition (Ruxolitinib) blocked fibroblast-driven carcinoma cell invasiveness. Despite these pro-inflammatory and tumour invasive properties, LIF displays neuro-immune modulatory effects that may offer therapeutic application in diseases such as multiple sclerosis. For example, in contrast to IL-6, LIF favours the expansion of FoxP3$^+$ Treg cells while inhibiting the differentiation of IFNγ- and IL-17-secreting CD4 T cells [205, 206]. Indeed, the ability of neural progenitor cell therapy to alleviate CNS pathology in a pre-clinical model of multiple sclerosis was shown to be mediated via LIF secretion, which inhibited the differentiation of pathogenic Th17 cells [207]. Thus, alongside prominent actions for LIF in stromal cell regulation, a role in the control of CD4 T cells is consistent with that of IL-6 and IL-27 as critical regulators of adaptive immunity. Furthermore, IL-11 and OSM have also emerged as positive and negative regulators of the Th17 cell response respectively [208, 209].

OSM, IL-11 AND LIF AS REGULATORS OF INDUCIBLE LYMPHOID COMPARTMENTS

Transgenic mice overexpressing OSM or LIF highlight a role for these cytokines in the organisation and cellular composition of lymphoid organs. The overexpression of OSM in early T cell lineages, or the administration of recombinant OSM in non-transgenic mice, was shown to promote lymphopoiesis. In these studies, OSM caused an expansion in the number of immature and mature T cells in lymph nodes, without the need for a functional thymus (in NU/NU nude mice) [210, 211]. Here, expression of the OSMR on HEVs was associated with

cyclooxygenase-2-dependent neoangiogenesis, enhanced expression of CCL20 by the stromal compartment and the accumulation of memory ($CD62L^{lo}$) CD4 T cells in SLOs. Peripheral lymph nodes in LIF transgenic mice similarly showed a pronounced expansion of $CD4^+CD8^+$ lymphocytes, thought to be mediated by disruption of stromal-lymphocyte crosstalk due to a disorganisation of the thymic epithelium [212]. OSM and LIF, therefore, shape the composition of lymphoid organs, a function that extends to the control of ectopic gremial centres in inflamed tissues. When OSM was overexpressed in the lung through administration of an adenovirus vector, lymphoid (CXCL13, CCL21) and inflammatory chemokines (CCL2, CCL20, CCL24, CXCL1) promoted the accumulation of activated B cells, T cells and dendritic cells, and formed iBALT [213]. IL-6 signalling has similarly been shown to drive lymphoid follicle formation in the lung [128]. However, while the recruitment of neutrophils and eosinophils was impaired in *Il6*$^{-/-}$ mice administered with the OSM-expressing adenovirus, the formation of B cell follicles comprising FDCs networks was independent of IL-6 [213]. Overexpression of LIF in mice also caused a phenotype resulting in early mortality associated with respiratory distress and the presence of perivascular lymphoid-like accumulations in the lung [212]. These mice also displayed ectopic formation of B cell follicles in the thymus, which was driven by transgene expression in the non-hematopoietic compartment. Therefore, IL-6, OSM and LIF all promote ectopic lymphoid neogenesis highlighting a functional redundancy for IL-6 family cytokines in ELS control.

Our group recently characterised the development of tumour-associated ELS in an experimental model of gastric cancer (the $gp130^{F/F}$ mouse) that recapitulates the presence of submucosal lymphoid aggregates, high IL-11 expression and STAT3 hyperactivation observed in clinical disease [80]. These mice feature a knock-in tyrosine-to-phenylalanine mutation at residue 757 in the cytoplasmic domain of gp130. As a result, negative feedback imposed by SOCS3 on gp130 signalling is impaired, which promotes the spontaneous development of gastric adenomas that is both IL-11 and STAT3 dependant [191, 214, 215]. The development of tumours coincided with the local expression of *Ccl19*, *Cxcl13* and *Ccl21*

and the formation of extra-tumoral ELS displaying peanut agglutinin$^+$, Bcl-6$^+$ and Ki67$^+$ GCs, CD21$^+$ FDCs and T/B-cell segregation [80]. Both tumorigenesis and early lymphoid neogenesis were independent of IL-17, a potent driver of ELS formation in models of autoimmunity and infection, but were dependent on hyperactive STAT3 signalling. Notably, gastric tumours and submucosal leukocyte clusters also form in *gp130$^{F/F}$:Il6$^{-/-}$* mice suggesting the IL-6 is not required for ELS development in this model [191]. Tumour-associated ELS feature in relatively few experimental models of cancer [6, 80, 216]. Such models provide an opportunity to understand an important feature of clinical disease and to temporally track coincident lymphoid neogenesis and tumorigenesis, which is difficult to achieve in humans. The presence of ELS is associated with a favourable prognosis in many types of cancer and recent studies associate ELS with improved clinical responses to immune checkpoint blockade [6, 96-98]. Consistent with the role of exaggerated STAT3 signalling in gastric tumorigenesis, increased expression of the STAT3 target gene *SOCS3* correlated with the expression of lymphoid chemokines in patients [80]. While an ELS chemokine gene signature (*CXCL13, CCL21, CCL19*) lacked prognostic significance in our analysis of patients with intestinal-type gastric cancer, the signature was associated with advanced stages of disease. Independent studies revealed that the histological presence of ELS was associated with improved relapse-free and disease-free survival in gastric cancer patients [86, 217]. Further studies are required to determine whether submucosal ELS contribute to the transition from chronic gastritis to gastric tumorigenesis or whether ELS may support anti-tumour immunity. Here, modulation of the gp130 signalling axis may provide an opportunity to reduce gastric cancer progression.

CONCLUDING REMARKS

Dysregulation of the IL-6 cytokine family places these cytokines as key mediators of autoimmunity, autoinflammation, persistent infection and cancer. In particular, IL-6 signalling has emerged as an important target for the treatment of chronic inflammatory conditions. Recent studies have highlighted overlapping and sometimes opposing roles for IL-6 family

cytokines in the development of ELS. While the contribution of ELS to immune-mediated damage to tissues remains a divisive subject, their ability to form functional GCs and promote antigen-driven autoreactive B cell responses provides a strong rationale for further investigations into the mechanisms that drive ELS activities. Moreover, as their presence in autoimmunity is often associated with severe disease and poor prognosis, approaches that interfere with ELS development, persistence or activity have the potential to address unmet clinical needs. For example, the presence of ELS marks discrete clinical subtypes in certain autoimmune conditions that may benefit from a pathotype-specific approach to treatment [40, 42]. Here, IL-6 family cytokines and molecular pathways linked with their activities may contribute biomarkers capable of stratifying patients with ELS-rich tissue inflammation [61, 80, 132, 133]. Given strong associations between Th17-, Tfh-, Tph cells and ELS formation, it is tempting to speculate that biological agents that target these effector responses present an attractive opportunity to curtail ELS responses. Some studies suggest that targeting the IL-6R, an important contributor to Th17 and Tfh cell responses, may yield improved outcomes in rheumatoid arthritis patients that display ELS-rich synovitis [42]. Modalities that block alternative signalling mechanisms employed by IL-6 in inflamed tissues (e.g., trans-signalling via the sIL-6R) are also an exciting prospect. An improved understanding of the contribution made by IL-11, LIF and OSM to ELS development in experimental models of disease will also be key in determining whether these cytokines hold translational potential either as drug targets or biomarkers. In this regard, the effect of small molecule inhibitors (e.g., JAK inhibitors) that target signalling mechanisms downstream of IL-6 family cytokines (and other cytokines that utilise the JAK-STAT pathway) remain untested in experimental models focused on tracking ELS, or in clinical trials that monitor ELS presence before and after treatment. Notably, IL-27 remains unique as a negative regulator of ELS formation in experimental models of disease [38, 61, 164]. In this regard, recombinant IL-27 supplementation may limit immunopathology in chronic inflammatory conditions [140-146] and for control of ELS-associated pathologies may have potential either as a stand-alone therapy or as adjunct therapy alongside other drugs (e.g., that target IL-6, TNF, IL-17 or IL-23). Notably, the p28

subunit of IL-27 (IL-27p28) antagonises gp130 signalling and inhibits GC formation in SLOs [218]. Whether IL-27p28 also interferes with ectopic GC responses remains to be determined. Synthetic cytokines that combine the cytokine and receptor subunits of IL-6 family members with members of other families may also have the potential to modulate ELS activity. For example, a recombinant heterodimer combining the IL-27p28 subunit with the p40 subunit of IL-12 inhibits Th1 and Th17 cell responses in autoimmune uveitis [219].

Given that tumour-associated ELS are predictive of improved responses to immune checkpoint blockade [96-98], the targeted delivery of cytokines or other approaches that drive ELS formation in 'cold' immune-low tumours has the potential to reduce tumour growth and improve responsiveness to immunotherapy [169, 171, 216, 220, 221]. Whether IL-6 family cytokines have the potential to modulate ELS development or activity in tumours remains to be determined. However, combined roles for IL-27 in the control of ELS and co-inhibitory receptor expression may be particularly relevant when considering approaches to enhance anti-tumour responses [38, 61, 124, 222]. In the coming years, systems immunology approaches that combine bulk and single-cell multi-omic analysis offers an exciting opportunity to determine how IL-6 family cytokines regulate ELS in experimental models and patient cohorts. This knowledge will be key in determining how ELS can be exploited as a source of molecular markers that aid patient stratification, and inform how drugs that modulate cytokine activity can be used in the clinical management of ELS-rich pathologies in autoimmunity and cancer.

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DECLARATION OF INTEREST STATEMENT

The authors declare no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

FIGURES

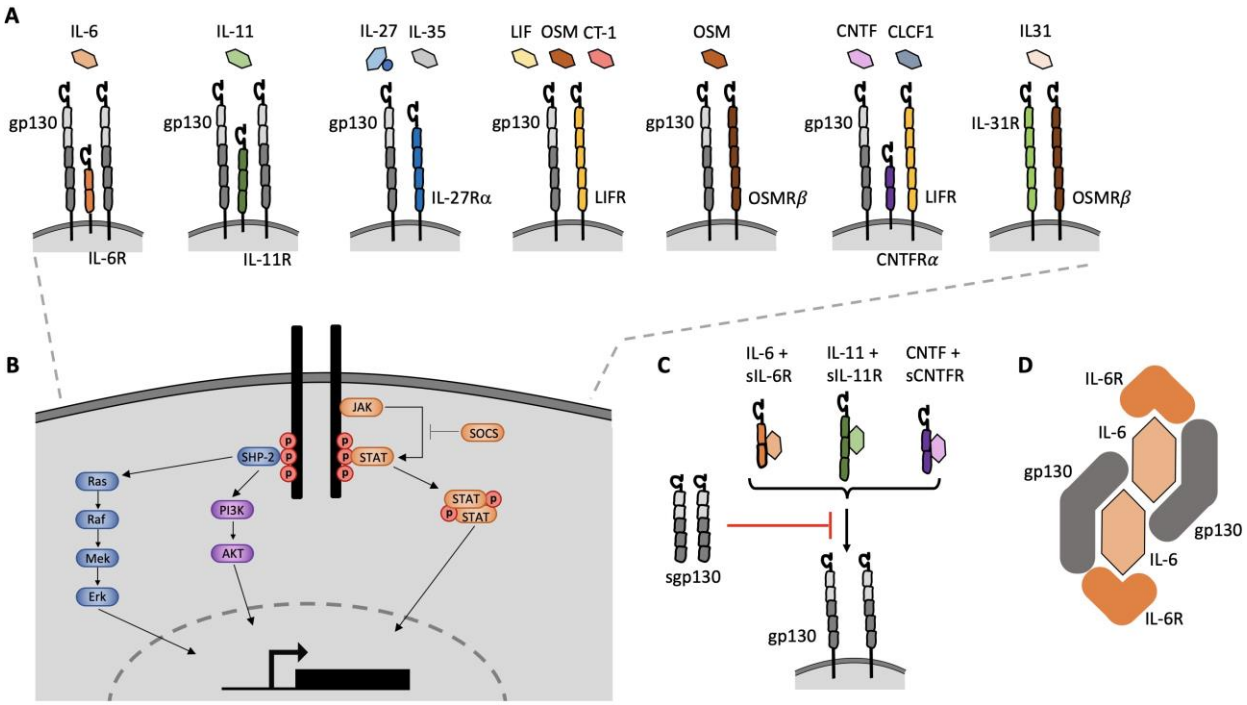

Figure 1. Signalling by IL-6 family cytokines. (**A**) IL-6 family cytokines use a common 130 kDa beta signalling receptor called glycoprotein 130 (gp130). For the IL-6R and IL-11R, signalling involves a gp130 homodimer. For the IL-27R, LIFR and OSMR a heterodimeric signalling complex with gp130 is formed. The receptor for CNTF and CLCF1 is composed of the CNTFR, LIFR and gp130. While not formally a member of the IL-6 family, the receptor for IL-31 is composed of a gp130-like receptor, IL-31RA in combination with OSMR. (**B**) The binding of IL-6 family cytokines to their cognate receptors activates JAK1, JAK2, TYK2-mediated phosphorylation of tyrosine residues in the cytoplasmic domain of the receptors. Phosphorylated residues serve as binding sites for STAT1, STAT3 and STAT5, which themselves are phosphorylated. Upon phosphorylation, STATs form dimers and translocate to the nucleus to regulate gene transcription. SOCS proteins are induced by STATs and act as negative feedback regulators to inhibit signalling. Although IL-6 family cytokines primarily activate the JAK-STAT pathway, they also activate alternative pathways including the MAPK and PI3K-AKT pathways. (**C**) The IL-6R, IL-11R and CNTFR also exist as soluble receptors. Signalling through the soluble receptor is known as trans-signalling, which can be blocked by

a soluble form of gp130. **D)** IL-6 forms a hexameric signalling complex comprising two molecules each of gp130, IL-6 and IL-6R. Similar hexameric complexes are proposed for IL-11 and CNTF, the latter composed of two molecules each of CNTF and CNTFR and one each of gp130 and LIFR.

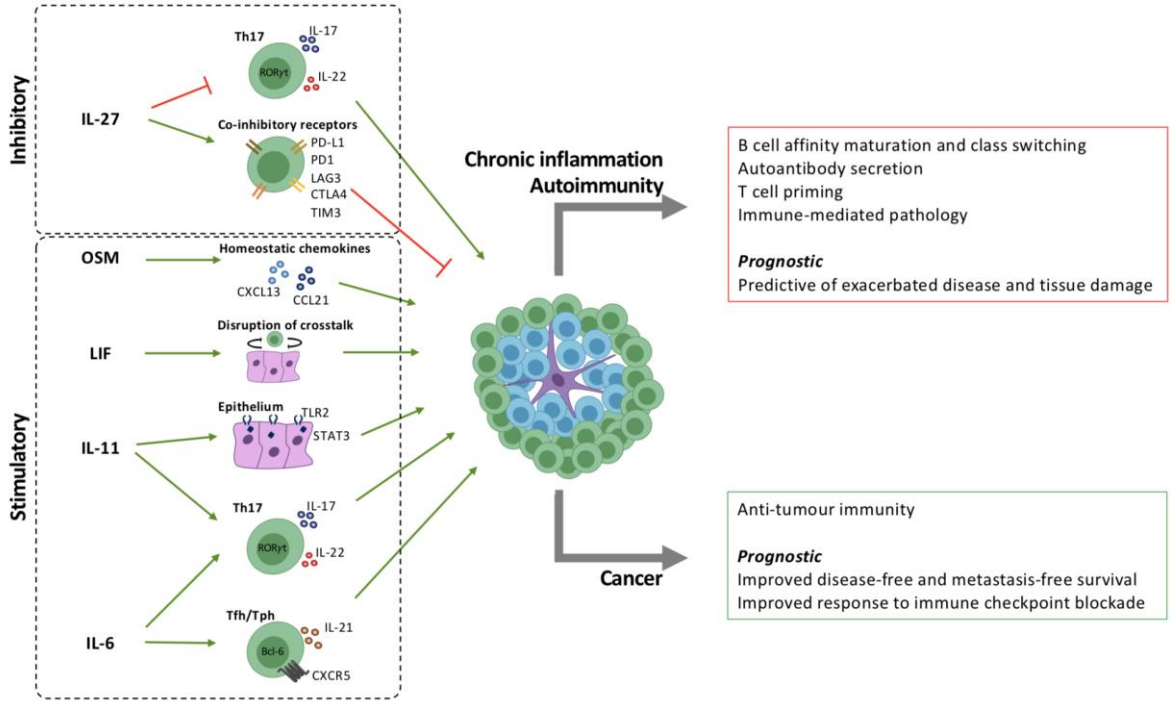

Figure 2 Control of ELS development by IL-6 family cytokines. The IL-6 family cytokines IL-6, IL-11, OSM and LIF have all been shown to promote the development of ELS, whereas IL-27 inhibits ELS development. In inflamed arthritic joints and salivary glands, the inhibitory action of IL-27 involves inhibition of Th17 cells. IL-27 also promotes immunosuppression through the induction of co-inhibitory receptors. In the lung, overexpression of OSM led to the induction of homeostatic and inflammatory chemokines leading to ELS formation. Similarly, overexpression of LIF in the lung resulted in immune cell aggregates that may be mediated by disrupting crosstalk between immune and stromal populations. In a model of gastric cancer IL-11 and STAT3 activation promotes tumorigenesis and associated submucosal ELS. IL-11 and OSM have both recently been shown to promote Th17 cells, which may provide a mechanism through which they contribute to ELS development. In the lung, overexpression of IL-6 and IL-6R leads to iBALT development. The IL-6 driven development of Th17 and Tfh-like populations has also been linked with ELS development in the CNS. While the contribution of ELS formation to tissue pathology is highly disease- and context-dependent, in chronic inflammation and autoimmunity ELS are associated with local immune cell priming, autoantibody generation and a poor prognosis. In cancer, tumour-associated ELS are linked with enhanced anti-tumour responses, favourable outcomes and increased responsiveness to immune checkpoint blockade.

Table 1. Roles for IL-6 family cytokines in ELS regulation.

IL-6 family Cytokine	Positive or Negative regulation of ELS	Disease or experimental model	Location	Mouse or Human	References
IL-6	Positive	Transgenic mice overexpressing IL-6 and IL-6R	Lungs	Mouse	[128]
		RA (Tocilizumab treatment)	Synovium	Human	[42]
		SKG arthritis	Synovium	Mouse	[133]
		EAE	CNS	Mouse	[67]
IL-27	Negative	RA/AIA	Synovium	Human/Mouse	[61]
		Sjögren's Syndrome	Salivary glands	Mouse	[164]
		Sjögren's Syndrome	Salivary glands	Human/Mouse	[38]
OSM	Positive	Adenoviral vector expressing OSM	Lung	Mouse	[213]
LIF	Positive	LIF-expressing transgenic mice	Lung	Mouse	[212]
IL-11	Positive	Gastric Cancer	Gastric antrum	Human/Mouse	[80, 191]

IL-6, Interleukin-6; IL-6R, IL-6 receptor; EAE, Experimental Autoimmune Encephalitis; CNS, Central Nervous System; RA, Rheumatoid Arthritis; AIA, Antigen Induced Arthritis; IL-27, Interleukin-27; LIF, Leukaemia Inhibitory Factor; IL-11, Interleukin-11; OSM, Oncostatin-M

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