

IL-6 in inflammation, autoimmunity and cancer

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IL-6 is involved both in immune responses and in inflammation, hematopoiesis, bone metabolism and embryonic development. IL-6 plays roles in chronic inflammation (closely related to chronic inflammatory diseases, autoimmune diseases and cancer) and even in the cytokine storm of corona virus disease 2019 (COVID-19). Acute inflammation during the immune response and wound healing is a well-controlled response, whereas chronic inflammation and the cytokine storm are uncontrolled inflammatory responses. Non-immune and immune cells, cytokines such as IL-1 β , IL-6 and tumor necrosis factor alpha (TNF α) and transcription factors nuclear factor-kappa B (NF- κ B) and signal transducer and activator of transcription 3 (STAT3) play central roles in inflammation. Synergistic interactions between NF- κ B and STAT3 induce the hyper-activation of NF- κ B followed by the production of various inflammatory cytokines. Because IL-6 is an NF- κ B target, simultaneous activation of NF- κ B and STAT3 in non-immune cells triggers a positive feedback loop of NF- κ B activation by the IL-6–STAT3 axis. This positive feedback loop is called the IL-6 amplifier (IL-6 Amp) and is a key player in the local initiation model, which states that local initiators, such as senescence, obesity, stressors, infection, injury and smoking, trigger diseases by promoting interactions between non-immune cells and immune cells. This model counters dogma that holds that autoimmunity and oncogenesis are triggered by the breakdown of tissue-specific immune tolerance and oncogenic mutations, respectively. The IL-6 Amp is activated by a variety of local initiators, demonstrating that the IL-6–STAT3 axis is a critical target for treating diseases.

Keywords: cytokine storm of COVID-19, IL-6 amplifier, local initiation model, NF- κ B, STAT3

Introduction

Cytokines function in many fundamental processes for life and disease including immunity, inflammation, embryonic development, regeneration, angiogenesis, metabolism, obesity, aging and so on. Among these diverse functions, their roles in inflammation have attracted attention in relation to disease development and treatment.

Inflammation is involved in homeostasis and regenerative processes such as wound healing. It is also involved in acute-phase reactions and immune responses against pathogens. In these cases, inflammation is well controlled. On the other hand, chronic inflammation and cytokine storm are uncontrolled forms of inflammation. The former plays crucial roles in the development of many complex diseases and disorders such as chronic inflammatory diseases, including metabolic syndrome, neurodegenerative diseases and cardiovascular diseases, along with autoimmune diseases and cancer (1–11). Cytokine storm has received a great deal of attention in connection with the pathology of corona virus disease 2019 (COVID-19) (12–17). Cytokine storm is considered a type of inflammation where the massive production of inflammatory cytokines is acutely induced in a dysregulated manner

in response to infection, trauma, chimeric antigen-receptor T-cell (CAR-T) therapy and so on. In this regard, inflammation is a double-edged sword in that it is dependent on the context, location and timing, making it difficult to develop therapeutics.

Inflammation is a complex process in which a variety of cells, including B lymphocytes, T lymphocytes, myeloid cells, epithelial cells, fibroblasts, endothelial cells, muscle cells and adipocytes, interact with each other through membrane-associated molecules, matrix metalloproteases (MMPs) and soluble factors, such as cytokines, chemokines and growth factors. Pro-inflammatory cytokines such as IL-1 β , tumor necrosis factor alpha (TNF α) and IL-6 play crucial roles in inflammation. Among them, IL-6 is a major player in chronic inflammatory diseases, autoimmune diseases, cancer and cytokine storm (1, 3, 10–26).

IL-6, which was discovered in 1986 (27), is a pleiotropic cytokine involved not only in immune responses but also in inflammation, hematopoiesis, bone metabolism, embryonic development and other fundamental processes (1, 21, 28–32). IL-6 is a prototypical member of the IL-6 family of cytokines,

which is composed of 10 members including IL-6, IL-11, IL-27, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine factor 1 (CLCF1), IL-35 and IL-39 (33). It was originally identified as B-cell stimulating factor-2 (BSF-2), an inducer of immunoglobulin production (27). Several other proteins including IFN β 2 (34), IL-1-induced 26-kDa protein (35), plasmacytoma/hybridoma/myeloma growth factor (36–38) and hepatocyte-stimulating factor (39, 40) were found to be identical to BSF-2 and thus IL-6 (41). These studies indicated that IL-6 has a variety of functions not only in health but also in diseases, such as plasmacytoma and myeloma.

Studies in the 1980s also showed that IL-6 is produced by cardiac myxoma cells (42) and Castleman's germinal center cells (43) and is present at high amounts in the synovial fluid of rheumatoid arthritis (RA) patients (44, 45), suggesting its role in autoimmune diseases and chronic inflammatory diseases (1). Accordingly, a working hypothesis explaining the possible mechanisms of chronic inflammatory diseases and autoimmune diseases was proposed (1, 46). The original hypothesis has since been updated and is here called the local initiation model, which emphasizes the importance of local initiators, such as infection, injury and stress in the promotion of interactions between non-immune cells and immune cells in disease. A similar hypothesis was proposed for local lesions triggering these interactions rather than the breakdown of tissue-specific immune tolerance (47, 48). Consistently, evidence has indicated that interactions between immune cells and non-immune tissues play critical roles in chronic inflammatory diseases and autoimmune diseases (3, 41, 49–51). Furthermore, tissue property-dependent events (49), microbleeding (52, 53), neural stimulation (54, 55), cell senescence (56, 57) and oncogenic mutations in pre-neoplastic cells have been shown to trigger these interactions.

Additionally, interactions between a tumor and its micro-environment through the immune system are critical for tumor development and progression (2, 6, 9, 58–60), and aging is related with cancer progression as well as inflammation and autoimmunity. Notably, IL-6 is involved in cell senescence, is produced by senescent cells and is critically involved in senescence-induced inflammation and age-dependent pathologies and cancer (7). IL-6 is also a key factor in inflammation, autoimmunity and cancer, with its effect mainly exerted through the IL-6–signal transducer and activator of transcription 3 (STAT3) pathway (18–26, 61–65).

The IL-6 amplifier (IL-6 Amp) is an amplification mechanism for the production of IL-6 and a variety of other cytokines and chemokines through a synergic interaction between STAT3 and nuclear factor-kappa B (NF- κ B). It too plays a key role in inflammatory diseases including cytokine storm syndromes, autoimmune diseases and cancer (10, 11, 15, 41, 66–68), providing a link for STAT3 and NF- κ B in these disorders (67).

Considering the properties of IL-6, an anti-IL-6 therapy against multiple myeloma was tried in the 1990s (69). Although anti-IL-6 murine monoclonal antibody (MoAb) inhibited the proliferation of myeloma cells and production of C-reactive protein (CRP), the effect was limited, most likely because of the increase of the IL-6 half-life (70). Instead of murine MoAb against IL-6, a humanized MoAb against IL-6 receptor

(IL-6R), tocilizumab, has proven successful for treating RA and Castleman's disease (71–75). The IL-6–STAT3 pathway is now considered a major target for the treatment of inflammatory diseases (15, 19, 21, 24–26, 76).

In this review, the central roles of IL-6 and the local initiation model in inflammation, autoimmunity and cancer are summarized and discussed.

IL-6 expression, IL-6 receptor and its mode of action and signaling

The IL-6 gene contains several elements for transcription factor binding, including NF- κ B, activator protein 1 (AP-1), CCAAT/enhancer-binding protein beta (C/EBP β), cyclic adenosine monophosphate (cAMP)-responsive elements and STAT3 (77–84). IL-6 transcription is induced by a variety of stimuli, such as Toll-like receptor (TLR) ligands, IL-1, TNF α , reactive oxygen species (ROS) and zinc (Zn) and also depends on epigenetic regulation (33, 82, 84–86). Post-transcriptional control of IL-6 mRNA affects the IL-6 expression level. Regnase-1 degrades IL-6 mRNA (87), while Arid5a protects IL-6 mRNA from Regnase-1-mediated degradation (88). Lin 28 induced by NF- κ B activation prevents IL-6 mRNA degradation by inhibiting microRNA let-7 (89). STAT3-induced microRNA (miR)-21 and miR-181b-1 activate NF- κ B, resulting in the induction of IL-6 gene expression (90). Finally, MiR-26a inhibits hepatocellular carcinoma growth and metastasis by inhibiting IL-6 expression (91).

The IL-6R is composed of an IL-6-binding receptor molecule (IL-6R α) and a signal transducer, gp130, which is shared among the IL-6 family of cytokines (Fig. 1A) (33). For IL-6 activity, the expression of both IL-6R α and gp130 on the cell surface is required, which limits the number of target cells on which IL-6 acts to lymphocytes, myeloid cells and hepatocytes (33). However, IL-6 complexed with the soluble form of IL-6R α (sIL-6R α) can act on cells expressing only gp130, such as heart muscle cells. Double transgenic mice expressing both IL-6 and IL-6R α , but not transgenic mice expressing either IL-6 or IL-6R α alone, show myocardial hypertrophy (92). In the early 1990s, it was found that IL-12 is composed of a disulfide heterodimer that included p40 and p35 subunits, resembling IL-6 and sIL-6R α , respectively (93). Additionally, IL-12 acts through IL-12R, which is closely related to gp130 (94). The complex of CNTF and the soluble form of CNTF receptor alpha acts on cells expressing LIFR β and gp130 (95). These early studies show that there is a mechanism by which a cytokine acquires different target specificity through complex formation with the ligand and the soluble form of the cytokine receptor subunit. Through this mechanism, a cytokine acquires a novel function, namely cytokine-soluble receptor complex function, to act as a novel cytokine on target cells (1). This mode of IL-6 action is now called the trans-signaling mode, while the original membrane type is called the classic mode (Fig. 1B) (96). The trans-signaling mode expands the range of cells that respond to IL-6, because gp130 is expressed in a wide range of cells, including endothelial cells and fibroblasts, explaining one of the mechanisms by which IL-6 acts on a wide range of cells and tissues to exert a pleiotropic function. Indeed, this mode plays crucial roles in chronic inflammation (33, 96).

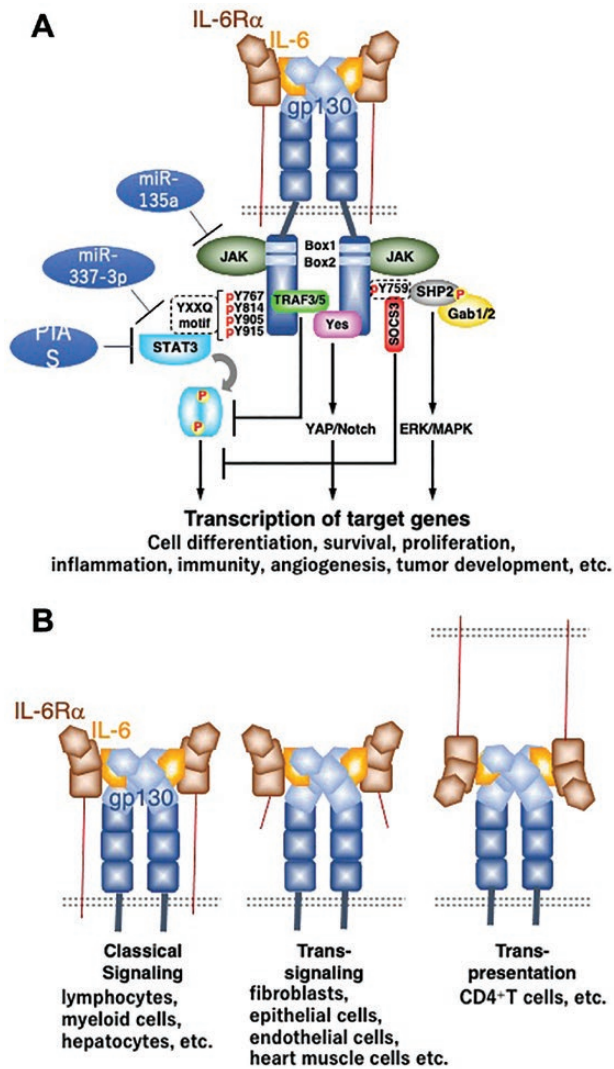


Fig. 1. IL-6 receptor and signaling. (A) IL-6 binding induces a hexameric complex composed of two molecules of IL-6, IL-6R α and gp130 each, leading to the activation of JAKs associated with gp130 at Box1 and Box2. The phosphorylation of tyrosine 759 of gp130 is required for the gp130-mediated ERK–MAPK pathway via SHP2 and GAB adaptor molecules and essential for the SOCS3-mediated negative feedback loop. The distal four tyrosine residues of gp130 (Y767, Y814, Y905 and Y915) form a YXXQ motif, which is required for STAT3 activation. The YAP–Notch pathway is triggered by Yes. TRAF is associated with gp130 and inhibits the STAT3 signaling pathway. MiR-135a and miR-337-3p down-regulate JAK2 and STAT3, respectively. PIAS directly inhibits STAT3. All amino acid positions are of human gp130. (B) Three modes of gp130-mediated signaling. IL-6 acts on cells expressing both IL-6R α and gp130 (classical signaling). The complex of IL-6 and sIL-6R α acts like a novel cytokine on cells expressing only gp130 (trans-signaling). In the trans-presentation mode, IL-6 bound to IL-6R α expressed on one type of cell acts on another cell type expressing gp130.

One example has IL-6 together with sIL-6R α acting on endothelial cells that express only gp130 to induce STAT3 activation, chemokine expression and the augmentation of ICAM-1, thus contributing to local inflammation by activating leukocyte recruitment (97). In addition, IL-6 and sIL-6R α induce a

transition between the early predominantly neutrophilic stage of an infection and the more sustained mononuclear cell influx, contributing to the switch from acute to chronic inflammation (98). Further, they act on fibroblasts and endothelial cells to recruit T helper 17 (T_h17) cells, leading to an RA-like joint disease (F759 arthritis) and experimental autoimmune encephalomyelitis (EAE) (54, 66, 99).

sIL-6R α is generated mainly by proteolysis by ADAM17 and to a minor extent by alternative splicing in humans. Notably, sIL-6R α is increased in several diseases, indicating that trans-signaling plays important roles in the progression of inflammation in many diseases including severe COVID-19 (15, 96).

In certain cases, IL-6 bound to cell surface IL-6R α can act on another cell that expresses gp130 in a manner consistent with the IL-6–sIL-6R α complex. For example, IL-6 bound to IL-6R α expressed on dendritic cells (DCs) directly acts on CD4(+) T cells through gp130 to induce T_h17 cells (100). The signal transduction by this trans-presentation (Fig. 1B) might differ from trans-signaling, since the soluble form of gp130 efficiently inhibits trans-signaling, but not trans-presentation or classical signaling (101).

IL-6 activates Janus kinase (JAK) family tyrosine kinases through gp130, leading to the activation of STAT family transcription factors, mainly STAT3, as well as src homology region 2 domain-containing phosphatase 2 (SHP-2), GRB2-associated-binding protein (GAB), extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) signaling pathways (Fig. 1A). Activated JAK phosphorylates tyrosine residues in the cytoplasmic domain of gp130 (30, 31, 61, 62, 102, 103).

Utilizing chimeric receptors carrying the intracellular region of human gp130, it was shown that Y767, Y814, Y905 and Y915, which all have YXXQ moieties, are required for STAT3 activation *in vitro*, and that Y759 is an SHP-2-binding site (104, 105). The binding of SHP-2 to Y759 mediates activation of the ERK–MAPK cascade via the adaptor molecules GAB1 and GAB2 (106, 107). Gp130 signaling is also mediated by the Src family kinase, Yes, which directly associates with gp130 via amino acid residues 812–827 (108). IL-6 activates the Yes-associated protein (YAP)–Notch pathway through Yes, stimulates epithelial cell proliferation and confers regeneration capacity in injured intestinal epithelia. The IL-6–Notch-3 pathway is also involved in cell growth and the promotion of a hypoxia-resistant/invasive phenotype in breast cancer development (109).

These pathways affect each other and are negatively regulated by several molecules. The gp130-mediated activation of STAT3 is involved in the cell-cycle transition through the up-regulation of cyclins D2, D3 and A, and cdc25A, and the concomitant down-regulation of p21 and p27, while p21 is induced when STAT3 activation is suppressed, indicating the balance of contradictory signals determines the final output (110). Similarly, defective STAT3 activation enhances SHP-2–ERK–MAPK activation pathways, most likely through an impaired STAT3-mediated induction of suppressor of cytokine signaling 3 (SOCS3) (111, 112). Phosphorylated Y759 (human gp130) or Y757 (murine gp130) serves as a binding site for SOCS3 and SHP-2. In fact, knock-in mice expressing human gp130

with Y759F mutation (F759 mice) (113) or mice expressing murine gp130 with Y757F mutation (64) display splenomegaly, lymphadenopathy, an enhanced acute-phase reaction and prolonged STAT3 activation. The enhanced STAT3 activation was initially considered the result of an inability to recruit SHP-2, a negative regulator having tyrosine phosphatase activity (113–115). However, this site is also a recruitment motif for SOCS3, and it was found that the F759/F757-dependent negative regulation is mainly dependent on the recruitment of SOCS3 (116, 117). SOCS3 is induced by STAT3 and considered to regulate a major negative feedback loop of a gp130-mediated signaling pathway (118–120). In addition, TNF receptor-associated factor 5 (TRAF5) negatively regulates IL-6–gp130-mediated STAT3 activation in naive CD4(+) T cells to suppress the T_h17 differentiation (121), while TRAF3 facilitates the association of protein tyrosine phosphatase non-receptor type 2 (PTPN22), inhibiting STAT3 activation in B cells (122). MiR-135a and miR-337-3p down-regulate JAK2 and STAT3, respectively (123, 124). A protein inhibitor of activated STAT (PIAS) is also known to be a direct inhibitor of STAT3 (125).

These multiple signal transduction pathways intimately regulate cell survival, proliferation, inflammation, immunity, angiogenesis, and tumor development and progression through the expression of several genes (1, 19, 21, 26, 31).

IL-6 signaling in cell survival, proliferation, metastasis and angiogenesis

Concerning cell survival and proliferation, two signals through gp130 are involved. One is the SHP-2–ERK–MAPK pathway and the other is STAT3–bcl-2-mediated cell survival (104). STAT3 is involved not only in bcl-2 induction, but also in the induction of c-myc, cyclins and Pim1/2 kinase to regulate cell survival and cell cycle progression in a pre-B-cell line (110, 126, 127). STAT3 activation by IL-6 is required for intestinal epithelial cell survival and cell-cycle progression during colitis-induced tumorigenesis (20).

The proto-oncogene serine/threonine-protein (Pim) kinases, Pim-1 and Pim-2, are targets of STAT3 and involved in cell proliferation and cell survival together with c-myc (127). The IL-6–STAT3–Pim kinase axis is involved in the development and cell growth of pancreatic cancer (128, 129). In fact, Pim-1 expression in pancreatic cancer tissues and plasma Pim-1 levels are increased, and a high expression level is negatively associated with prognosis. Furthermore, high plasma Pim-1 expression is an independent adverse prognostic factor for pancreatic cancer (129) and also for breast cancer (130). The IL-6–STAT3 pathway is involved in the epithelial–mesenchymal transition (EMT) (131, 132), tumor migration (133), cancer stemness (130, 134, 135) and the induction of hypoxia-inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF), two key players for angiogenesis (136–140). Furthermore, oncogenic miR-21 and miR-181b are targets of IL-6–STAT3, leading to the activation of NF- κ B (90, 141). An increased expression of miR-200 family members is associated with both tumor initiation in STAT3-dependent murine gastric cancer and early-stage gastric cancer in patient cohorts (142).

IL-6–STAT3 signaling in immunity

IL-6 was originally cloned as a factor acting on B cells to induce immunoglobulin production (27) and having a role in B-cell abnormality (42). Indeed, IL-6 promotes antibody production by directly acting on plasma cells and by indirectly promoting Bcl6-dependent follicular CD4(+) T (T_{fh}) cell differentiation together with IL-21 (Fig. 2) (143–146). IL-6 transgenic mice show severe plasmacytosis with hypergammaglobulinemia (147), while IL-6-deficient mice are defective in immunoglobulin production (148, 149). Moreover, mice reconstituted with hematopoietic stem cells carrying mutant gp130 lacking STAT3-binding sites show lower serum immunoglobulin levels (113), and conditional knockout of Stat3 in mouse B cells results in a loss of T-cell-dependent plasma cells (150). STAT3 is also required for human plasma cell differentiation by up-regulating BLIMP1 and down-regulating BCL6 (151). STAT3 loss-of-function (LOF) patients have impaired antigen-specific antibody responses (152, 153). IL-6-induced STAT3 activation is critical for *in vivo* plasma cell survival and immunoglobulin secretion in humans (154). Consistently, TRAF3 inhibits IL-6–STAT3 signaling in B cells and reduces plasma cell development (122). In addition to the aforementioned role of IL-6 on T_{fh} cells, IL-6 is known to direct the differentiation of IL-4-producing T helper type 2 (T_h2) cells, while it inhibits the differentiation of IFN γ -producing T_h1 cells (155). T-cell responses against tumors are mediated by CD8(+) effector T cells (T_{eff}), of which differentiation is dependent on IFN γ -secreting T_h1 cells. It was shown that myeloid-derived sIL-6R complexed with IL-6 inhibits T_h1 responses through STAT3-induced c-Maf. This is considered to be one of mechanisms by which IL-6 inhibits T-cell immunity against tumors (156). However, the effect of IL-6 on the diversity of T_h1 and T_h2 cells is not simple: IL-6 induced by repeated inflammation is responsible for T_h1 cell responses in peritoneal fibrosis (157).

IL-17-producing T_h17 cells have been shown to have a crucial role in autoimmunity and a still-controversial role in cancer (pro-tumorigenic or anti-tumorigenic), whereas regulatory T (T_{reg}) cells inhibit autoimmunity and tumor immunity (158–163). IL-6 together with TGF β induces T_h17 cells (Fig. 2) (164). RAR-related orphan receptor gamma t (ROR γ t) is the key transcription factor for IL-6 and TGF β -induced T_h17 cell differentiation (165). On the other hand, IL-6 inhibits the TGF β -induced generation of T_{reg} cells (166). This inhibition by IL-6 is a direct action on naive T cells (167). However, IL-6-mediated inhibition is restricted to inducible T_{reg} cells and has no effect on natural T_{reg} cells (168).

The requirement for human naive T cells in T_h17 cell differentiation differs from that of mice, since human T cells in the presence of IL-1 β with IL-6 or IL-23 can differentiate to T_h17 cells without TGF β (169, 170). However, even in the absence of TGF β , the combination of IL-1 β , IL-6 and IL-23 induces pathogenic T_h17 cells from mouse naive T cells *in vitro* and *in vivo*, suggesting an alternate mode of T_h17 cell differentiation (171). T_h17 cells generated without TGF β express both ROR γ t and T-bet, while T_h17 cells generated in the presence of TGF β express only ROR γ t. IL-6 up-regulates IL-23R expression in a manner dependent on STAT3, and IL-23 further enhances its own receptor expression to increase the pathogenic potential of T_h17 cells

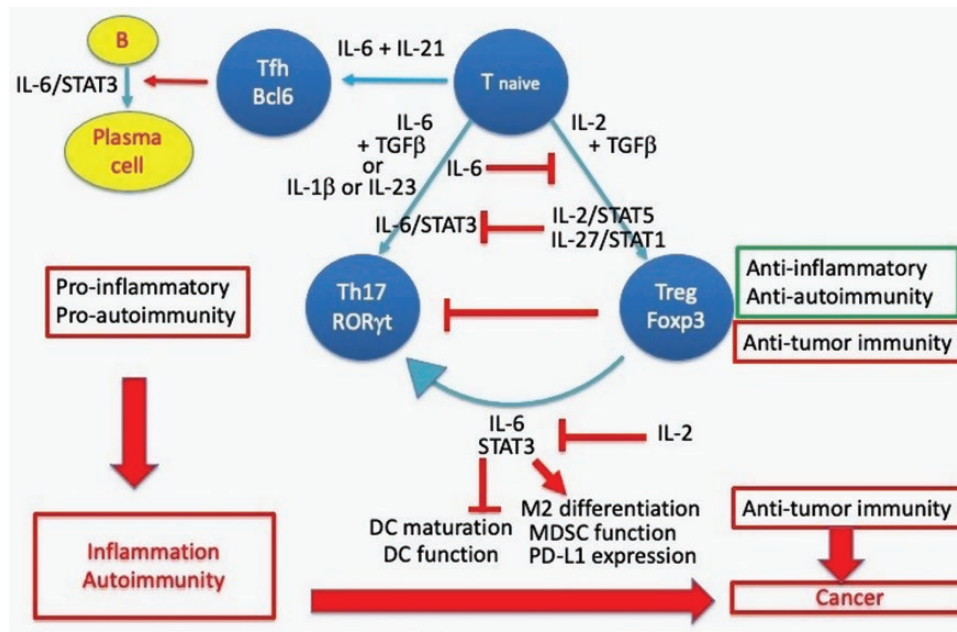


Fig. 2. IL-6/STAT3 in immunity. IL-6 promotes antibody production by either directly acting on plasma cells or indirectly promoting Tfh cell differentiation. IL-6/STAT3 together with TGF β or IL-1 β and IL-23 induces T_h17 cells, while IL-6 inhibits the TGF β /IL-2-induced generation of T_{reg} cells. IL-2/STAT5 or IL-27/STAT1 inhibits the IL-6/STAT3-induced differentiation of T_h17 cells. IL-6/STAT3 induces the conversion of T_{reg} cells to T_h17 cells, and this process is inhibited by IL-2. The IL-6/TGF β and IL-2/TGF β axes regulate the balance of T_h17 and T_{reg} cells; the former is pro-inflammatory and the latter anti-inflammatory. IL-6/STAT3 induces the differentiation of M2 macrophages and activates MDSCs, both of which have anti-tumor immunity effects. In addition, IL-6/STAT3 inhibits DC maturation and function. Finally, IL-6/STAT3 induces PD-L1 expression.

(171). Consistently, IL-23R is essential for the terminal differentiation of T_h17 cells that are capable of inducing EAE *in vivo* (172). IL-6-activated STAT3 promotes T_h17 cell pathogenicity by up-regulating IL-1R through miR-183c induction (173).

The IL-6–STAT3 pathway in CD4(+) T cells is essential for T_h17 cell development and for the expression of ROR γ t (174, 175), while IL-27, a member of the IL-6 family of cytokines and activator of STAT3, inhibits T_h17 cell differentiation in a manner dependent on STAT1 (Fig. 2) (176, 177). This effect suggests that STAT1 inhibits STAT3-induced T_h17 cell differentiation. In fact, it was shown that IL-27 induces T_h17 cell differentiation in the absence of STAT1 and that T_h17 cell differentiation is dependent on the ratio of activated STAT3 and STAT1. The ratio induced by IL-6 is more than 1, whereas that induced by IL-27 is less than 1 (178). Of note is that both STAT3 LOF and STAT1 gain-of-function (GOF) mutations in patients show defects in T_h17 cell differentiation (179, 180). Hyperactivated STAT1-mediated inhibition of T_h17 cell differentiation is most likely due to a STAT1-induced up-regulation of PD-L1 in naive T cells (181), since the PD-L1–PD-1 interaction in naive T cells impairs T_h17 cell differentiation (182). The critical role of STAT3 for T_h17 cell differentiation is also supported by the fact that *n*-3 fatty acid docosahexaenoic acid and platelet factor 4, both of which induce SOCS3, inhibit T_h17 cell differentiation and tumor growth (183, 184). Further, Zn, which is an essential trace element and affects the immune response and oncogenesis by either pro-inflammatory or anti-inflammatory effects in a context dependent manner (185), inhibits T_h17 cell differentiation through the inhibition of IL-6-induced STAT3 activation (186).

TGF β and IL-6 together induce T_h17 cells, while TGF β together with IL-2 induces T_{reg} cells. IL-2-activated STAT5 inhibits T_h17 cell differentiation (187), while IL-6 reduces Foxp3 expression, which inhibits ROR γ t-mediated IL-17A promoter activation (188). Furthermore, opposing regulation of the locus encoding IL-17 through the reciprocal actions of STAT3 and STAT5 suggest the balance between IL-6–STAT3 and IL-2–STAT5 regulates the development of T_h17 cells and T_{reg} cells from naive CD4(+)T cells (189).

Furthermore, there is T_h17/T_{reg} cell plasticity (Fig. 2). T_{reg} cells when stimulated with IL-6 differentiate into T_h17 cells (190). IL-6 down-regulates Foxp3 expression through STAT3 and together with IL-1 induces the genetic reprogramming of T_{reg} cells to express T_h17 cell function (191). Such a conversion of T_{reg} to IL-17-producing T_h17 cells is induced by IL-6 derived from synovial fibroblasts in mice suffering collagen-induced arthritis. T_h17 cells converted from T_{reg} cells are more potently osteoclastogenic than conventional T_h17 cells (192). The IL-6-induced conversion of T_{reg} cells to T_h17 cells is inhibited by miR-125a-5p, which is induced by IL-2 and down-regulates the expression of IL-6R and STAT3 in T_{reg} cells (193). IL-6 further inhibits the suppressive activity of T_{reg} cells. The microbial induction of IL-6 through TLRs inhibits T_{reg} cell activity (194). IL-6–STAT3 signaling prevents the T_{reg} cell-mediated suppression of T_{eff} cells in patients with psoriasis and multiple sclerosis (MS) (195, 196).

All evidence supports the idea that the immune system tightly regulates T_h17/T_{reg} cell homeostasis through the IL-6–IL-2 axis, and the disturbance of this balance in the presence of TGF β causes inflammation and autoimmunity (Fig. 2). T_{reg} cell dysfunction due to Foxp3 mutation causes

a lethal autoimmunity known as immunodysregulation, polyendocrinopathy, enteropathy and X-linked (IPEX) syndrome (197), and defects of IL-2 signaling induce severe autoimmunity (198). Accordingly, low-dose IL-2 therapy for autoimmune and inflammatory diseases is under development (199). On the other hand, the enhancement of IL-6–STAT3 signaling causes IL-17A-dependent autoimmune arthritis in mice (41, 63, 66). In line with these findings, several inflammatory and autoimmune diseases, including RA, MS and inflammatory bowel disease show a bias for T_{h17} cells over T_{reg} cells (163). Anti-IL-6R therapy in RA restores the homeostasis, suggesting one of possible mechanisms by which the therapy functions (200).

DCs present antigens to T cells to initiate immune responses and inflammation against infectious pathogens, organ transplants and tumors (201). Much evidence has accumulated to show that STAT3 functions as an inhibitor for DC differentiation, maturation and antigen-presenting ability, and therefore STAT3 inhibits tumor immunity by interfering with DC functions (Fig. 2) (25). The requirement for STAT3 in hematopoietic stem cell commitment to the DC lineage has also been shown (202), but TLR4-induced DC maturation is inhibited by IL-6 (203). Further, IL-6–STAT3 signaling inhibits the LPS-induced maturation of DCs and DC-mediated activation of T cells *in vivo* (204). In line with this observation, IL-6–STAT3 signaling reduces intracellular MHC class II levels in DCs by increasing cathepsin S activity (205). STAT3 activated through TLR9 in myeloid cells inhibits DC maturation and tumor immunity (206). The enhanced expression of IL-6 in tumor-infiltrating DCs from colorectal cancer patients correlates with a decrease in the expression of HLA-DR and CD86 on DCs and attenuation of DCs' T-cell-stimulating ability (207). Accordingly, mammary tumor-derived exosomes block the differentiation of DCs *in vitro* through IL-6 (208). Versican is a soluble tumor-derived factor that induces DC dysfunction by up-regulating IL-6 and IL-10 receptor signaling (209).

Classically activated M1 macrophages produce nitric oxide synthase, IL-12 and TNF α and promote T_{h1} cell responses, while activated M2 macrophages produce arginase-1, IL-10 and TGF β and relate with the T_{h2} cell response. M1 macrophages are pro-inflammatory, while M2 macrophages are anti-inflammatory (210). Tumor-associated M2 macrophages not only promote tumor progression and metastasis by producing tumor growth factor and angiogenic factors, such as epidermal growth factor (EGF), VEGF and IL-6, but also inhibit tumor immunity by arginase-1, IL-10 and TGF β (211–214). IL-6 and IL-10 are abundant in tumor microenvironments originated from myeloid cells, fibroblasts and tumor cells, and they further induce M2 macrophage differentiation through STAT3 (215, 216). Breast cancer-derived exosomes that contain gp130 induce IL-6 production and activate gp130–STAT3 signaling to induce phenotypic changes in bone marrow-derived macrophages toward M2 macrophages (217).

Myeloid-derived suppressor cells (MDSCs), which are abundant in tumor microenvironments, inhibit T-cell activation to suppress tumor immunity by producing IL-10 and TGF β (218). MDSC function is dependent on STAT3 (25). Tumor-derived Hsp72 mediates the MDSC suppressive activity of tumor growth in a manner dependent on STAT3 activation through the autocrine production of IL-6 (Fig. 2) (219).

Inhibitors of immune checkpoints, such as inhibitors of CTLA-4 and PD-1 and their ligands, have been shown to be effective to treat several cancers such as melanoma (25, 220). PD-L1, which is a ligand of PD-1, is expressed in tumor microenvironments and tumors in a manner dependent on STAT3. For example, the STAT3-dependent expression of PD-L1 in pancreatic carcinoma and head and neck squamous carcinoma was reported (221, 222). The direct binding of STAT3 to the PD-L1 promoter was also shown (223). PD-L1 is expressed in non-small-cell lung cancer cells through EGF receptor (EGFR)-mediated IL-6–STAT3 activation (224). Cancer-associated fibroblasts induce PD-L1 in neutrophils in an IL-6–STAT3-dependent manner (225). In addition, glioblastoma and tumor-associated stromal myofibroblasts induce PD-L1 expression in DCs through IL-6–STAT3 signaling (Fig. 2) (226, 227).

All evidence indicates that IL-6–STAT3 signaling determines the homeostasis of T_{h17} cells and T_{reg} cells. T_{h17} cells are favored for inflammation and autoimmunity, while T_{reg} cells suppress these responses. Interestingly, the suppressive activity of T_{reg} cells is observed in several autoimmune diseases (163, 228). IL-6 makes T_{reg} cells resistant to the suppressive effect of T_{reg} cells (195, 196). In addition, IL-6–STAT3 signaling induces the conversion of T_{reg} cells to T_{h17} cells, which are pro-inflammatory, and induces the differentiation of M2 macrophages and MDSCs, both of which suppress tumor immunity. IL-6 further inhibits DC maturation and up-regulates PD-L1 through STAT3 to suppress T-cell activation against tumors. Moreover, IL-6 itself is an autocrine and paracrine growth factor as well as a survival factor for a variety of cancers and promotes cancer development and progression by inducing angiogenesis and metastasis. Overall, accumulating evidence supports the intimate relationship of IL-6 with inflammation, autoimmunity and cancer (Fig. 2).

Involvement of IL-6 in chronic inflammation, autoimmune diseases and cancer

Chronic inflammation is often accompanied with autoimmune disease and cancer (2, 4, 9). Autoimmune diseases are thought to result from a breakdown in self-tolerance and/or dysregulation of immune responses. However, true pathogenic antigens causing the breakdown have not been identified for many autoimmune diseases, including RA and other tissue-specific disorders (229–231). This raises the possibility that a breakdown in tolerance to a tissue-specific antigen is not always required for localized autoimmune diseases. Instead, hyper-activation of the immune system to the target tissue may be a consequent event that is initiated by local initiators in non-immune target tissue in a manner dependent on genetic and/or environmental factors (1, 47, 48, 50). This view highlights the importance of local initiators in the target tissue as a trigger of autoimmunity (49, 51, 52, 57, 232). Even in cancer development, it is now known that only 5–10% of all cancers are due to an inherited gene defect, and the remaining 90–95% have their roots in an environment and lifestyle that are intimately related with chronic inflammation (233). Therefore, rather than the dogma that oncogenesis is intrinsically triggered in pre-neoplastic cells, environmental factors, such

as infection, stress, obesity, aging and smoking, each of which can induce chronic inflammation, could be a major cause of oncogenesis (4, 6, 9, 233).

Just after the molecular cloning of IL-6, cardiac myxoma cells were found to produce IL-6 (42). Patients with cardiac myxoma show a variety of autoimmune symptoms, including hypergammaglobulinemia, auto-antibodies and increased acute-phase proteins. These symptoms disappear after surgical resection of the tumor, suggesting the intimate relationship between cardiac myxoma cells and autoimmune symptoms. In addition, it was found that synovial fluid obtained from patients with RA contains high amounts of IL-6 (44, 45), and serum IL-6 levels in RA patients correlate with clinical and laboratory indices of the disease (234). In addition, serum IL-6 levels are increased and correlate with the poor prognosis of multiple myeloma patients (235). Taking the above together with the fact that IL-6 is a growth factor for plasmacytoma and myeloma (28, 37) and the production of IL-6 in Castleman's germinal center (43) suggests that IL-6 is involved in inflammation, autoimmunity and B-cell malignancies. Of note is that the pleural effusion cells of patients with pulmonary tuberculosis produce a large amount of factors inducing immunoglobulin production (236); one of the factors was partially purified as a TRF-like factor with similar properties to IL-6 (237). Importantly, an intimate relationship between tuberculosis and autoimmunity and B-cell malignancies was reported (238–240). Furthermore, pristane and mineral oil, strong inducers of chronic inflammation and later found to induce IL-6 production, develop plasmacytoma, arthritis and auto-antibody production in mice (241–245). Accordingly, IL-6 transgenic mice develop polyclonal plasmacytosis and monoclonal plasmacytoma in C57BL/6 and BALB/c genetic backgrounds, respectively (147, 246). Moreover, IL-6 induces CRP and fever (247, 248). All these early studies more than 25 years ago support the idea that IL-6 is involved in diseases (1, 80). In 1994, Kopf *et al.* showed that IL-6-deficient mice have impaired immune responses against vaccinia virus and *Listeria monocytogenes*, T-cell-dependent antibody responses against vesicular stomatitis virus and inflammatory acute-phase responses after tissue damage or infection (148), confirming the pleiotropic function of IL-6 and its role in immune responses as well as inflammation. By utilizing IL-6-deficient mice, it was shown that IL-6 is required for type II collagen-induced arthritis (249), antigen-induced arthritis (AIA) (250), EAE (251, 252), pristane-induced autoantibody production (253) and plasmacytoma (254), further showing that IL-6 is involved in experimental autoimmune diseases and B-cell malignancies. However, experimental autoimmune disease models usually utilize autoantigens in the presence of adjuvants as an inducer of the disease, making it difficult to interpret the results obtained from these experiments in relation to naturally occurring diseases. From this point of view, F759 mice are an ideal murine model of RA, which show an increased activation of STAT3 through gp130 because of the lack of negative regulation exerted by SOCS3 (63, 113). Of note is that F759 mice spontaneously develop IL-6-dependent and CD4(+) T-cell-dependent F759 arthritis in a manner dependent on

age, supporting the idea that enhanced but dysregulated IL-6–STAT3 signaling is involved in age-related inflammatory autoimmune diseases, such as RA. Furthermore, F759 arthritis is enhanced by human T-cell lymphotropic virus 1 (HTLV-1) pX gene, which encodes Tax, a transcriptional trans-activator of NF- κ B, showing the synergistic effect of STAT3 and NF- κ B (255).

Another knock-in mouse strain (gp130^{Y757F/Y757F} mice) having the point mutation Y759F in murine gp130 also shows the hyper-activation of STAT3 and develops gastric hyperplasia resembling human early-stage gastric cancer (64, 256). Further, the mice show a similar expression pattern of STAT3-dependent miR-200 family members with that of early stage gastric cancer patients (142). Gp130^{Y757F/Y757F} mice show enhanced colitis-associated tumorigenesis in a manner dependent on the enhanced activation of STAT3 (20). The requirement of IL-6 and STAT3 for activated mutant EGFR-induced lung cancer and colitis-associated cancer has also been demonstrated (18, 257). Taken together with the fact that the development of pristane or mineral oil-induced plasmacytoma and obesity-related hepatocellular carcinoma (HCC), both of which are related to inflammation, are dependent on IL-6 (254, 258), all studies indicate the intimate link between inflammation and tumorigenesis via IL-6–STAT3 signaling.

The reason why different phenotypes are observed between F759 mice and gp130^{Y757F/Y757F} mice is not known, but the reason could be due to the difference of gp130; the former is human gp130 and the latter is mouse gp130. In fact, it takes about 1 year for F759 mice to develop arthritis, while gp130^{Y757F/Y757F} mice show hyperproliferative lesions in the stomach mucosa as early as 6 weeks (256). It has not yet been reported whether gp130^{Y757F/Y757F} mice spontaneously develop arthritis as F759 mice do, but AIA, which is also IL-6-dependent, is enhanced in gp130^{Y757F/Y757F} mice in a manner dependent on STAT3 (259). Thus, it seems the IL-6–STAT3 axis is involved in inflammation, autoimmunity and cancer and that they are all intimately related to each other.

In line with this notion, there is a correlation between IL-6 and the severity of RA and other inflammatory and autoimmune diseases (3, 260, 261). In addition, the correlation between IL-6 and the prognosis of 23 different cancer types was demonstrated (262). Genome-wide association studies (GWAS), meta-analysis, exome analysis and single nucleotide polymorphism (SNP) mapping have associated IL-6, IL-6R and gp130 with inflammatory diseases such as RA and coronary artery disease (263–269). It was also reported that IL-6R is associated with asthma and atopic dermatitis (270, 271). Somatic GOF mutations in gp130 that activate gp130–STAT3 signaling lead to inflammatory hepatocellular tumors (272). LOF mutations of TRAF3, a negative regulator of IL-6–STAT3 signaling, are observed in B-cell lymphoma and multiple myeloma patients (122, 273, 274). On the other hand, the frequency of a polymorphism at the 5' flanking region of the IL-6 gene that is correlated with lower levels of plasma IL-6 is reduced in systemic-onset juvenile chronic arthritis (275). Further, a non-conservative SNP in the gp130, Gly148Arg, which has low IL-6 responsiveness, is associated with a decreased risk of myocardial infarction in a hypertensive population (276).

Cross-talk between non-immune cells and immune cells through the IL-6 Amp

Although the development of F759 arthritis is dependent on T_H17 cells, the F759 mutation is required in non-immune cells but not immune cells, clearly indicating that the interaction between non-immune cells and immune cells is crucial for arthritis development in F759 mice (66, 99). In fact, a mutated gp130-mediated excessive production of cytokines and chemokines in non-immune cells in F759 mice is necessary for CD4(+) T-cell proliferation, T_H17 cell accumulation in the lesion and the arthritis development (66, 99). The effects of non-immune cells in F759 arthritis is explained by the capability of these cells to produce large amounts of chemokines, growth factors and IL-6 under the situation where gp130-mediated STAT3 activation is enhanced. Furthermore, IL-6 and IL-17 or TNF α synergistically enhance the production of various pro-inflammatory mediators including IL-6 from non-immune cells in a manner dependent on STAT3 and NF- κ B (66). The produced IL-6 further induces T_H17 cell differentiation through STAT3 in the presence of TGF β , IL-1 β and IL-23, all of which are rich in inflammatory lesions and tumor microenvironments (164, 166, 169–171, 174, 175). Therefore, there is an *in vivo* positive-feedback amplification loop of IL-6 production via T_H17 cell differentiation and their interaction with non-immune cells, such as fibroblasts (41). In addition, the enhanced production of epiregulin and TNF α is induced by the activation of the IL-6 Amp, and these molecules further activate NF- κ B alone or STAT3 as well (10). Therefore, amplification of the IL-6–STAT3 axis is augmented by several pathways after the induction of other STAT3 and NF- κ B activators during inflammation processes (Fig. 3) (41, 66). Of note is that the IL-6 Amp

enhances NF- κ B activity by STAT3 through the interaction of these two molecules. Therefore, the IL-6 Amp amplifies not only IL-6 but also a variety of pro-inflammatory cytokines and growth factors that are targets and/or activators of the NF- κ B pathway. STAT3 activation is also augmented through enhanced IL-6 production. Consistent with the concept that IL-6 Amp activation in non-immune cells plays a pivotal role in the development of autoimmune diseases, mice devoid of STAT3 or gp130 in non-immune cells like type-1 collagen positive cells are highly resistant to F759 arthritis and EAE (54, 66).

The IL-6 Amp could be exerted by several mechanisms. For example, STAT3 prolongs NF- κ B nuclear retention through acetyltransferase p300-mediated RelA acetylation, thereby interfering with NF- κ B nuclear export in both cancer cells and tumor-associated hematopoietic cells (277). The cooperative role of NF- κ B and STAT3 recruitment to ICAM-1 intronic consensus elements in the invasion and migration of radiation-induced glioma was also reported (278). STAT3 directly binds to the IL-6 promoter to induce IL-6 gene expression (82, 83). In addition, STAT3 activates NF- κ B through the direct induction of miR-21 and miR-181b-1, leading to IL-6 gene expression (90). NF- κ B also increases IL-6 levels by inhibiting let-7 expression (89).

As described above, the IL-6 Amp is a mechanism by which the regional production of a variety of cytokines and growth factors is augmented through the interaction between NF- κ B and STAT3, both of which are activated not only in inflammatory lesions but also in tumor microenvironments and neoplastic tumor cells. Furthermore, NF- κ B and STAT3 play crucial roles in cancer development and progression (19, 25, 67, 279). Thus, the IL-6 Amp plays a crucial role in not

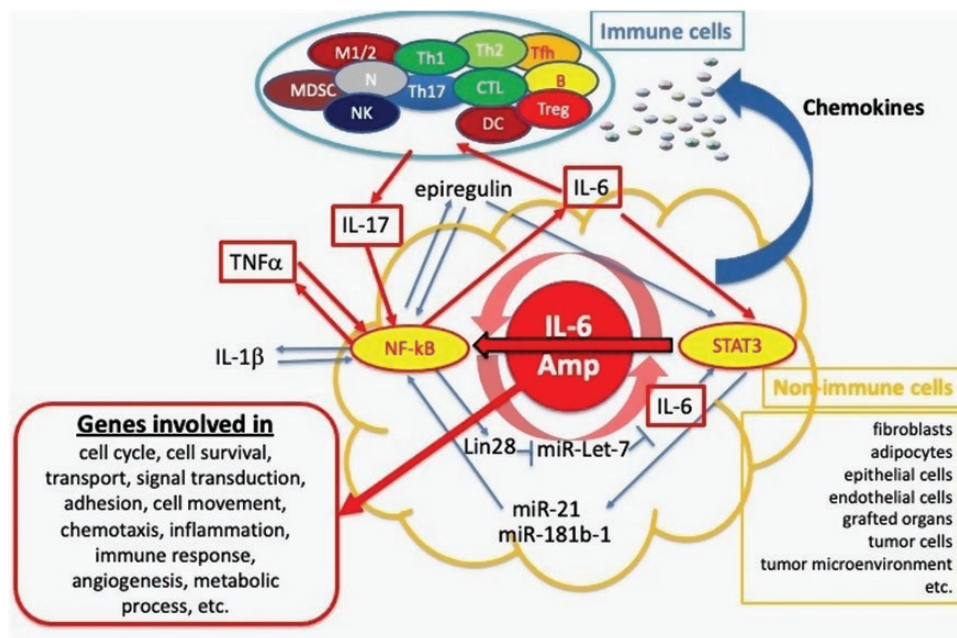


Fig. 3. The IL-6 Amp. STAT3 activators (e.g. IL-6) and NF- κ B activators (e.g. IL-17 or TNF α) synergistically enhance the production of various pro-inflammatory mediators including IL-6 from non-immune cells in a manner dependent on STAT3 and NF- κ B. This amplification mechanism is called the IL-6 amplifier (IL-6 Amp). The IL-6 Amp recruits immune cells such as activated T cells into the lesion by chemokines. The interaction between immune cells and non-immune cells further strengthens the IL-6 Amp. The IL-6 Amp enhances the expression of many genes involved in cell proliferation, survival, movement, inflammation, angiogenesis and so on.

only chronic inflammatory and autoimmune diseases but also cancer. In fact, a comparative analysis between GWAS data and the targets or regulatory genes of the IL-6 Amp revealed that 202 out of 1700 screened genes show over 490 indications of association not only with autoimmune diseases but also with metabolic syndromes, neurodegenerative diseases and other chronic inflammatory diseases, including RA, lupus, pancreatitis, thyroiditis/Graves' diseases, type 1 diabetes (T1D) and type 2 diabetes (T2D), MS, cardiovascular diseases/atherosclerosis/systemic sclerosis, Alzheimer's disease/hippocampal atrophy, pulmonary disease/asthma/cystic fibrosis, hepatitis, inflammatory bowel disease/colitis, stroke and nephropathy/glomerulonephritis (10). Furthermore, many cancer-associated genes were identified as regulators or target genes of the IL-6 Amp (11). Ingenuity Pathways Analysis (IPA) showed that these genes are related with multiple biologic processes, such as cell development, cell cycle, transport, signal transduction, adhesion, cell movement, chemotaxis, immune response, angiogenesis and metabolic process. Moreover, the IL-6 Amp is related with various types of cancer, including hematologic malignancies, tumors in lung, and colorectal/intestinal, urinary/bladder/vulvar, breast, stomach and liver cancers (11).

The IL-6 Amp, which is activated not only in non-immune cells such as fibroblasts and endothelial cells but also in grafted organs and tumor cells, acts as a linker between these cells and immune cells by attracting immune cells through the production of a variety of chemokines. Accumulated immune cells interact with non-immune cells in inflammatory lesions and tumor microenvironments as well as with tumor cells to further enhance the IL-6 Amp by producing not only IL-6 but also a variety of IL-6 Amp stimulators such as IL-17, TNF α , IL-1 and epi-regulin. Target molecules of the IL-6 Amp include EGFR, c-Myc, Pim1, VEGF α , hypoxia-inducible factor 1-alpha (HIF1- α), MMPs and many pro-inflammatory cytokines and growth factors involved in cell survival, proliferation, angiogenesis and metastasis (Fig. 3) (10, 11).

The local initiation model

In 1964, Boyden pointed out the importance of local initiators such as injury or infection as triggers of inflammation followed by the destruction of the target tissues (47). Decades later, Wilkin proposed the primary lesion theory, in which a primary lesion triggers autoimmunity, rather than the popular view, which held the primary cause of autoimmunity was the breakdown of self-tolerance (48).

Patients with RA show a variety of symptoms, including polyclonal plasmacytosis accompanied by the production of rheumatoid factor, enhanced bone resorption and increases in the amount of acute-phase proteins, agalactosyl IgG and platelet numbers. None of these phenotypes at first glance appear related to each other, suggesting that complex factors are involved in RA. However, the pleiotropic nature of IL-6, which induces B-cell differentiation with immunoglobulin production (27), osteoclast activation (280, 281), the production of acute-phase proteins (39, 40), the increase of agalactosyl immunoglobulin (282) and megakaryocyte differentiation (281, 283, 284), suggested an intimate relationship between IL-6 and RA. Assuming that the same cause can

induce both RA and IL-6 expression, such an intimate relationship could be explained. This possibility led to a working hypothesis (1, 46), the updated version of which is called the local initiation model (Fig. 4). In this model, NF- κ B and STAT3 are activated by a variety of local initiators, including injury, infection, stressors, age-related events in senescent cells and oncogenic mutation in pre-neoplastic cells, leading to the activation of the IL-6 Amp in non-immune cells, such as fibroblasts, epithelial cells, endothelial cells and adipocytes. The IL-6 Amp enhances the production of a variety of pro-inflammatory cytokines and chemokines, resulting in the recruitment of immune cells, such as activated T cells into the lesion. The interaction between immune cells, in particularly activated T cells, further strengthens the IL-6 Amp. The IL-6 Amp can become dysregulated depending on the genetic background and other factors including local initiators, leading to inflammatory diseases and autoimmune diseases. Because initial events occur in non-immune cells or tissues, this model strengthens the importance of both local initiators in the target tissue and the interaction between non-immune and immune systems in the disease onset and progression. The local initiation model is similar to the primary lesion theory proposed by Wilkin (48), but the former clearly shows the key role of transcription factors, such as NF- κ B and STAT3, which can simultaneously induce multiple actions and be activated by a variety of local initiators. Therefore, the local initiation model could be applied not only to chronic inflammatory diseases and autoimmune diseases, but also to age-related diseases and cancer (Fig. 4).

One clear piece of evidence supporting the local initiation model has been obtained from F759 mice. F759 mice bred by mating T-cell antigen-receptor transgenic mice and Rag2-KO mice to express only one T-cell antigen-receptor on CD4(+) T cells still develop arthritis. These results suggest even T-cell-dependent tissue-specific autoimmune diseases do not necessarily require antigen-specific T cells (52). The question is, what determines the tissue specificity of the autoimmune disease without tissue-specific CD4(+) T cells? Murakami *et al.* demonstrated that local initiators such as microbleeding induce the accumulation of T cells in the joints through CCL20 production (52). The disease induction requires IL-17A production by transferred T cells, IL-6 and CCL20 expression and STAT3 signaling in type I collagen-expressing cells. This is consistent with the IL-6 Amp being involved in the disease.

Persistent local initiator activity, such as chronic infections, with or without genetic factors leads to chronic activation of the IL-6 Amp. This effect induces the manifestation of inflammatory diseases and autoimmune diseases (232). This scenario highlights the importance of local initiators and supports the local initiation model (Fig. 4). It is also consistent with the fact that many chronic inflammatory diseases are dependent on aging and accompanied by the activation of polyclonal T cells and an increase of IL-6 (285).

Local initiators activating the IL-6 Amp in chronic inflammation

A variety of stressors, such as pain, light and gravity are sensed by a sensory-sympathetic neural network. Neuroinflammation is associated with the invasion of various

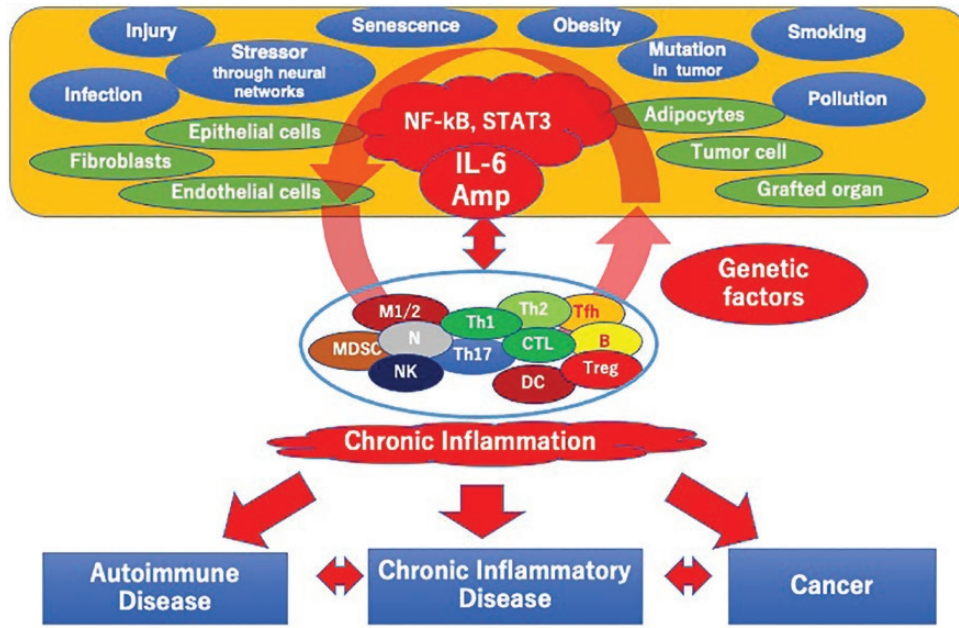


Fig. 4. Local initiation model. A variety of local initiators, such as infection, injury, stressors acting through neural networks, senescence, obesity, smoking and oncogenic mutations, activate both STAT3 and NF- κ B, leading to activation of the IL-6 Amp in non-immune cells such as fibroblasts, epithelial cells, endothelial cells and adipocytes. The IL-6 Amp amplifies the production of IL-6 and other pro-inflammatory cytokines and growth factors. Chemokines produced by the IL-6 Amp recruit immune cells such as activated T cells to the lesion to interact with non-immune cells, leading to further activation of the IL-6 Amp. The IL-6 Amp becomes dysregulated depending on the genetic background and or other factors including the properties of local initiators, leading to chronic inflammatory diseases, autoimmune diseases and cancer.

immune cells in the central nervous system (CNS) followed by the dysregulation of homeostasis in the brain and spinal cord. However, the CNS is protected by the blood–brain barrier, which tightly limits the traffic of substances and immune cells from the blood. In an adoptive transfer model of EAE using myelin-specific autoreactive CD4(+) T cells, it was found that the initial invasion site of these cells is determined by specific neural activation through the sensory–sympathetic pathway stimulated by gravity (54). This neural pathway, which is now called the gateway reflex (286, 287), activates the IL-6 Amp through beta-adrenergic receptors in the dorsal vessels of the fifth lumbar cord, allowing for autoreactive T-cell accumulation and disease onset (54). Further, pain sensation induces a relapse of EAE by activating the IL-6 Amp through another sensory–sympathetic neural network (55). Consistent with this, it was reported that adrenergic receptor stimulation not only activates STAT3 in an ovarian cancer cell line (288) but also enhances the IL-6 production that is induced by IL-1 β , an NF- κ B activator in cardiomyocytes, to induce cardiac hypertrophy (289). Additionally, it was shown that acute stress induces a systemic increase of IL-6 secreted from brown adipocytes in a beta-3-adrenergic-receptor-dependent manner in mouse models (290).

These studies provide evidence supporting the claim that a variety of stressors, such as gravity and pain, act as local initiators through specific neural pathways, resulting in activation of the IL-6 Amp, linking inflammation and autoimmunity and possibly affecting cancer development and progression.

Age-related changes in senescent cells also act as local initiators. Senescent fibroblasts secrete high levels of several

MMPs, EGF and inflammatory cytokines, resembling fibroblasts undergoing a wound response or associations with cancer. Of note, the local low-grade inflammation that characterizes aging is triggered by senescent cells and is intimately related to age-related diseases such as cardiovascular diseases and cancer (5, 291, 292). It might also be associated with the cytokine storm in COVID-19 (293, 294). These mediators maintain and propagate the senescence process to neighboring cells and then recruit immune cells to clear the senescent cells. In this scenario, Campisi proposed a model in which senescent cells by themselves contribute to the disruption of normal tissues through the production of degradative enzymes as well as inflammatory cytokines, while senescent cells help pre-neoplastic mutated cells to proliferate by producing inflammatory cytokines (5). NF- κ B-regulated and C/EBP β -regulated cytokines such as IL-6 and CXCR2-binding chemokines including IL-8, which are produced by senescent cells, play crucial roles in the senescence process (7, 8). IL-6–STAT3–PIM-1 signaling is involved in cytokine-induced senescence (295). Importantly, senescent cells and tissues contribute to age-related pathologies including cancer by producing inflammatory cytokines such as IL-6, which act as autocrine and paracrine factors (7). Consistently, IL-6 levels increase with age (296, 297). Concerning age-related diseases, senescent cells themselves are critically involved in T1D and T2D, and the deletion of senescent beta cells prevents diabetes (57, 298), indicating that even in T1D in which tissue-specific T cells are involved (299–301), local initiators originating from senescent beta cells play critical roles. This process is consistent with the idea that the primary cause of T1D may be a senescence-induced local initiator

that can activate the IL-6 Amp rather than the breakdown of self-tolerance.

Obesity causes chronic low-grade inflammation and is closely related with chronic inflammatory diseases, such as cardiovascular diseases and T2D and some cancers, such as breast, liver and colon cancers (233, 302–304). The enlargement of adipose tissue in obesity induces mechanical stress, ER stress and hypoxia in adipocytes, resulting in the release of free fatty acids (FFAs) and inflammatory cytokines such as IL-6 and TNF α and chemokines (303–305), suggesting activation of the IL-6 Amp. Consistently, these events recruit macrophages, which further produce IL-6 and TNF α , major players involved in obesity-induced low-grade inflammation and cancer development (303, 304). Shi *et al.* showed that FFA activates TLR4 signaling and that mice lacking TLR4 are partially protected against high fat diet-induced insulin resistance (306). In line with these findings, FFA activates NF- κ B through TLR4, leading to the expression of monocyte chemoattractant protein-1 (MCP-1) to recruit macrophages, which further produce IL-6 and TNF α (307, 308). IL-6–STAT3 signaling in adipocytes is known to be involved in adipocyte-induced EMT in breast cancer cells (23) and obesity-promoted HCC (258). Lysophospholipid sphingosine-1-phosphate (S1P), a lipid metabolite, activates STAT3 through its G protein-coupled receptor, S1P receptor-1 (309). Intracellular S1P induces IL-6 production through NF- κ B activation, resulting in the activation of both STAT3 and NF- κ B, major players of the IL-6 Amp. This process is critically involved in colitis-associated cancer (310). These findings support the idea that obesity-induced mechanical and/or ER stress and lipid metabolites act as local initiators in the target tissue to trigger chronic activation of the IL-6 Amp.

Pre-neoplastic cells or cancer cells by themselves act as local initiators much like senescent cells do. Either or both of STAT3 and NF- κ B are activated in a variety of tumors, including lung, breast, pancreatic and prostate cancers (67). Additionally, either or both are activated in cells transformed with HTLV-1 (311), v-src (312), abl (313), bcr-abl or v-eyk (314). K-RAS mutation is often observed in many cancers, such as lung cancer and pancreatic cancer. Mutated K-RAS activates NF- κ B in a mouse model of lung cancer (315), and the K-RAS-induced activation of NF- κ B is required for pancreatic cancer development (316), which depends on IL-6 trans-signaling-mediated STAT3 activation (317). Mesothelin (MSLN) is up-regulated following K-RAS, p53 and p16 mutations in pancreatic cancer (318). MSLN is also suggested to be involved in the progression of breast cancer, ovarian cancer and pancreatic cancer. It confers pancreatic cancer cell resistance to TNF α -induced apoptosis through NF- κ B activation and the enhanced expression of IL-6 (319). MSLN also promotes pancreatic cancer cell proliferation through autocrine IL-6 trans-signaling (320). Similarly, activated mutant EGFR in lung cancer induces IL-6 gene expression to activate constitutive IL-6–STAT3 signaling in a paracrine and autocrine manner (257). HER2 overexpression occurs in approximately 25% of breast cancers. Its expression in breast cancer activates an IL-6 autocrine signaling loop to activate STAT3, which is critical for tumorigenesis (321). The loss of p53 alone is insufficient to initiate intestinal tumorigenesis but markedly enhances carcinogen-induced tumor incidence, the

progression of which is associated with increased intestinal permeability, causing the formation of a NF- κ B-dependent inflammatory microenvironment (322). Another oncogenic molecule, BRAF^{E600}, induces IL-6 and IL-1, a NF- κ B activator, through C/EBP β (7).

All the above results are in line with cancer cells activating the IL-6 Amp through the direct or indirect activation of NF- κ B and STAT3, likely resulting in the recruitment of T_h17 cells and/or myeloid cells to further enhance the IL-6 Amp. RANTES and MCP-1 secreted by tumor cells and tumor-derived fibroblasts mediate the recruitment of T_h17 cells (159). Exosomal miR-1247-3p secreted by hepatocellular carcinoma activates beta1-integrin–NF- κ B signaling in fibroblasts, resulting in the production of pro-inflammatory cytokines, including IL-6 and IL-8 (323). The IL-6 Amp at the leading edge could play a critical role in tumor progression. Indeed, Chang *et al.* showed that IL-6–STAT3 signaling is increased at the leading edge of breast tumors to promote MDSC recruitment, angiogenesis, fibroblast infiltration and metastases (83).

Infection is a local initiator that triggers and maintains inflammation, leading to chronic inflammatory diseases and cancer. For the initial detection of microbes, the immune system utilizes pattern-recognition receptors (PRRs), such as TLRs to activate MyD88-dependent signaling and ultimately activate NF- κ B (324). In addition to NF- κ B activation, TLRs such as TLR2, TLR4, TLR7 and TLR9 activate STAT3 (206, 325). TLR stimulation also induces IL-6 production and other pro-inflammatory cytokines through NF- κ B, leading to activation of the IL-6 Amp. Therefore, infection is one trigger of the IL-6 Amp. Indeed, a human colonic bacterium, enterotoxigenic *Bacteroides fragilis* (ETBF)-derived toxin, which triggers colitis and induces colonic tumors in mice, activates the STAT3 and T_h17 response (326). *Helicobacter pylori*, which induces gastritis and is related to gastric cancer, activates STAT3 in epithelial cells (327). Both hepatitis B and hepatitis C viruses, which induce hepatitis and cause hepatocellular carcinoma, activate STAT3 (328–330), while HTLV-I, Epstein–Barr virus and papilloma virus activate STAT3 and NF- κ B (311, 331, 332).

Cytokine storm, uncontrolled acute inflammation

COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is now a pandemic. The life-threatening phenotype of COVID-19 is severe acute respiratory distress syndrome (ARDS) (333). ARDS is a lethal syndrome induced by mechanical injury and infection such as pneumonia, sepsis and trauma (334). ARDS in COVID-19 is considered the result of cytokine storm (12–17), resembling the disease caused by SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) (335). Cytokine storm is uncontrolled and rapidly progressing inflammation accompanied by the massive production of pro-inflammatory cytokines, chemokines and growth factors. Consistent with the notion that severe COVID-19 is a cytokine storm syndrome (12–17, 336), the severity of COVID-19 is associated with an increased level of inflammatory cytokines, such as IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF) and TNF α (333, 337). Among the elevated inflammatory mediators, the blood IL-6 level is highly

correlated with the disease mortality (293, 338) and predicts the need for mechanical ventilation (339). Notably, IL-6 and TNF α serum levels are known to be significant predictors of disease severity and death (340).

SARS-CoV-1 and MERS-CoV activate NF- κ B in a manner dependent on MyD88 through PRRs, such as retinoic acid-inducible gene I protein (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), leading to the activation of a variety of pro-inflammatory cytokines, including IL-6, TNF α , IL-8 and CC-chemokine ligand 2 (CCL2) (335). In addition to this PRR-mediated activation of NF- κ B, the nucleocapsid protein of SARS-CoV-1 activates IL-6 expression through NF- κ B by facilitating the translocation of NF- κ B from the cytosol to the nucleus (341). Since SARS-CoV-2 uses angiotensin-converting enzyme (ACE) 2 as a receptor (342, 343), it is speculated that SARS-CoV-2 induces pro-inflammatory cytokines through angiotensin II (AngII)/angiotensin type 1 receptor (AT1R) (15) as SARS-CoV-1 does (344–346).

The AngII–AT1R axis activates the NF- κ B pathway through various growth factors and pro-inflammatory cytokines (347, 348). This axis activates ADAM17, which generates the mature form of EGFR ligand and TNF α , two NF- κ B stimulators (346). Furthermore, ADAM17 increases sIL-6R α , which activates STAT3 through gp130 on a variety of non-immune cells including fibroblasts, endothelial cells and epithelial cells (33, 96). Therefore, it is likely that the AngII–AT1R axis is involved in the ARDS induced by SARS-CoV-2 infection (15), which is like SARS-CoV-1-induced ARDS in a mouse model (344).

Therefore, SARS-CoV-1 and SARS-CoV-2 infection activate both NF- κ B and STAT3, key elements of the IL-6 Amp, to cause cytokine storm (12, 13, 15, 349, 350). Since an activated IL-6 Amp enhances the production of chemokines to recruit lymphoid cells and myeloid cells including T_H17 cells in the lesion, the IL-6 Amp could be further enhanced (66).

Cytokine storm also occurs in CAR-T treatment, which is used to treat leukemia. It is triggered by the activation of CAR-T cells that recognize cognate antigens expressed by tumor cells, leading to the release of cytokines and chemokines, including IL-6 in parallel with the release of pro-inflammatory cytokines and chemokines by monocytes and/or macrophages (351, 352). IL-1 and IL-6 are involved in the lethal cytokine storm sometimes seen in CAR-T treatment (353, 354).

The massive cell death commonly observed in cytokine storm, regardless of the inducer type, activates damage-associated molecular pattern (DAMP) receptor-mediated signaling pathways and/or TLR-mediated ones. These events further induce pro-inflammatory cytokines including IL-6 through NF- κ B activation.

Taking together all the evidence described above, a possible mechanism of SARS-CoV-1-induced and SARS-CoV-2-induced cytokine storm is illustrated in Fig. 5. This model could be applied to ARDS induced by other causes. ARDS with a cytokine storm occurs in viral infections such as MERS-CoV, influenza virus and sepsis. Furthermore, it also occurs due to lung damage caused by gastric acid or inappropriate operation of a ventilator, like aspiration pneumonia (334). The

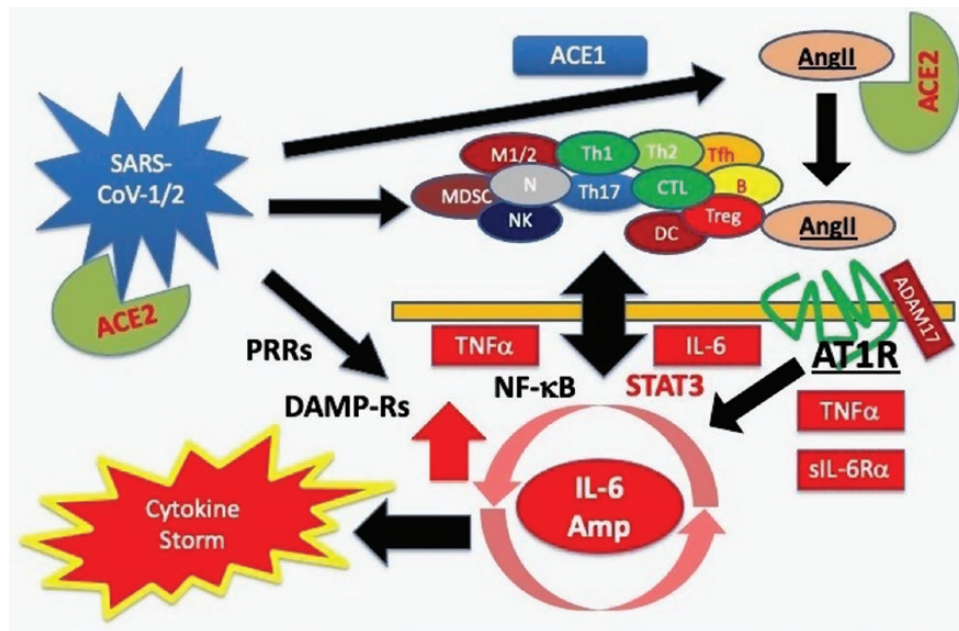


Fig. 5. A possible mechanism of SARS-CoV-1/2-induced cytokine storm. Because SARS-CoV-1/2 utilizes ACE2 as a receptor, virus infection decreases the cell surface expression of ACE2, which is a peptidase of angiotensin II (AngII), resulting in an increase of AngII. In addition, virus-induced lung injury activates ACE1, further increasing serum AngII levels. As a result, AT1R-mediated signaling is enhanced. In turn, so too is the inflammatory response, including TNF α and sIL-6R α via ADAM17 activation. Virus infection itself activates signaling through pattern-recognition receptors (PRRs). Furthermore, virus-induced massive cell death can activate DAMP receptor-mediated signaling pathways. Moreover, virus infection activates and/or recruits lymphoid cells and myeloid cells in the lesion. All these events synergistically activate the IL-6 Amp through the interaction of STAT3 and NF- κ B, leading to cytokine storm.

AngII–AT1R signaling system plays an important role not only in pneumonia but also in ARDS model mice (345), indicating that lung injury itself activates the AngII–AT1R signaling. Macrophage activation via TLR4, a type of PRR, is also involved in gastric acid-induced ARDS and mouse ARDS models induced by SARS-CoV-1 or influenza virus H5N1 (355). Furthermore, it has been shown that ARDS and renal dysfunction induced in a sepsis rat model are suppressed by anti-IL-6R antibody through the suppression of NF- κ B activation (356). Interestingly, *ACE1* gene polymorphisms are involved in the development and severity of ARDS (357). Furthermore, the *ACE1* II genotype is protective against COVID-19 as compared to the *ACE1* DD genotype (358), and serum levels of ACE1 are higher in the DD genotype compared with the II genotype (359).

Consistent with animal models, it was reported that AngII–AT1R axis inhibitors may be beneficial for COVID-19 patients (360–363) to decrease serum IL-6 levels (360). The anti-IL-6R antibody tocilizumab is effective at treating patients with CAR-T-induced cytokine release syndrome (CRS) (352, 364) and is being considered for treating ARDS in COVID-19 patients (365–368). Baricitinib, an inhibitor of JAK1 and JAK2, is reported to prevent COVID-19 severity followed by lowering IL-6 and TNF α levels (369). In addition, dexamethasone reduces the death rate of patients with severe COVID-19 (370).

Of note, aging, obesity and inflammation-related diseases such as diabetes and cardiovascular diseases have been shown to be risk factors for the severity of COVID-19 (293, 371–373). As discussed in this manuscript, these risk factors are all associated with chronic inflammation, which could decrease the threshold of the activation of the IL-6 Amp to induce cytokine storm.

Conclusion and perspectives

At the time of its discovery in 1986, IL-6 was considered just one of many cytokines. It has since been clarified that IL-6 is a critical factor in inflammation, autoimmunity and cancer, and its inhibitors are used as therapeutic agents for several diseases already, with the potential of being expanded to more in the future. The anti-IL-6R antibodies tocilizumab and sarilumab are used to treat RA, Castleman's disease and CAR-T-induced CRS (71–75, 352, 364) and have promise for treating the severe form of COVID-19 (365–367). Other inhibitors against the IL-6–STAT3 signaling pathway are under development (19, 21, 24–26, 76, 374).

One possible explanation for why inhibiting IL-6 activity is effective against inflammation-related diseases, in spite of the many cytokines involved, is that in inflammation IL-6 is the major stimulator of STAT3, which plays important roles in inflammation and oncogenesis together with NF- κ B, which expresses IL-6 as a target. Therefore, NF- κ B and STAT3 are the basis of the IL-6 Amp which is the amplification mechanism of IL-6 itself and other pro-inflammatory molecules, such as cytokines, chemokines and growth factors. A variety of local initiators, such as infection, stressors, injury, senescence, obesity, pre-neoplastic mutation, cell death and smoking can activate the IL-6 Amp, which mediates the interaction between non-immune cells and immune cells, leading to the manifestation of inflammatory and autoimmune diseases and

cancer. These observations have led to a strategy targeting the IL-6–STAT3 signaling axis to treat related diseases.

However, many questions remain. One of the reasons why IL-6 is a key cytokine in inflammation is that it has a wide range of target cells because of its trans-signaling mechanism. IL-6 usually acts on lymphoid and myeloid immune cells expressing both IL-6R α and gp130, but it acts on a wide range of non-immune cells as well, including fibroblasts and endothelial cells that express gp130 during inflammation. For this action, sIL-6R α is required. Therefore, more study of the mechanism by which sIL-6R α is generated is required to understand inflammation and develop therapeutics (96). Another question concerns the mechanism of the synergistic action of STAT3 and NF- κ B. STAT3 and NF- κ B are involved in a wide range of inflammatory diseases and cancer development and, more importantly, their interaction is central to activation of the IL-6 Amp. More study on the synergistic activation would also open the way to new therapeutics.

Since the IL-6 Amp is deeply involved in uncontrolled inflammation, it is critical to elucidate the genetic and environmental factors that destabilize it. Defects in the negative feedback mechanism mediated by SOCS3 observed in F759 mice is one factor worth investigating. So too are the transcriptional factors and microRNAs that cause STAT3 and NF- κ B to indirectly interact.

To realize a healthy aging society, it is crucial to prevent and cure age-related diseases. The list of diseases is long and includes autoimmune diseases, diabetes, cardiovascular diseases, dementia, pneumonia and cancer, all of which are related to uncontrolled inflammation. Uncontrolled inflammation is triggered by a variety of local initiators, including senescence, obesity, stressors through regional neural pathways, and infection through activation of the IL-6 Amp. More research on the effects of each initiator, either individually or synergistically with other initiators, on the inflammatory process and the IL-6 Amp would give deeper insights on inflammation, its prevention and cures.

Inflammatory diseases, autoimmune diseases and cancer are induced by complex interactions between non-immune cells and immune cells via the IL-6 Amp. Therefore, the expression and/or functions of IL-6 Amp-related molecules could be used to predict diseases initiated by local initiators. However, current knowledge is insufficient for predicting the end stage or detailed process of the disease. Furthermore, there are many pro-inflammatory molecules that determine the state of the IL-6 Amp as well as inflammation. The modes of interactions between these molecules too require more study. Improvements in detection technology and systems biology research for age- and inflammation-related diseases driven by artificial intelligence (AI) would be helpful (375).

Several inhibitors of IL-6 are now clinically used, but in order to develop small peptides or compounds with higher specificity and efficacy against diseases, high-resolution structural analysis of the ligand–receptor complex is needed. We can study the steady state of molecular interactions at the molecular level, but it is difficult to analyze in real time the dynamic changes of the molecular state of the receptor complexes and signaling molecules. Here, quantum life sciences in the field of inflammation will be helpful (376, 377).

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