# The Role of Interleukin (IL)-6/IL-6 Receptor Axis in Cancer

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**Abstract**

As a pleiotropic cytokine, interleukin (IL)-6 plays a key role in mediating the host's immune defense. Multiple cell types are involved in IL-6 production, including macrophages, dendritic cells, fibroblasts, mast cells, vascular endothelial cells, monocytes, dendritic cells, T cells, B cells, etc. Furthermore, stromal cells, immune cells that infiltrate tumors, and cancer cells present in the tumor microenvironment are also in charge of producing IL-6. Although the blood levels of IL-6 are barely noticeable at physiological levels (1–5 pg/ml), they have been observed to increase by more than 100,000 times during an immediate inflammatory reaction. Elevated intensities of IL-6 have been identified in almost all human cancers. Overexpression of IL-6 in the tumor microenvironment stimulates carcinogenesis by controlling all the pathways that lead to cancer. There are two categories of interleukin-6 receptors: the first one comprises the cell membrane-bound receptor of IL-6 (IL-6R). Upon binding with IL-6R, IL-6 forms a complex with glycoprotein 130 (gp130) (a signal transducer), and, thus, the classical signaling pathway that exhibits anti-inflammatory activity gets activated. The second category comprises a soluble derivative of the interleukin-6 receptor, i.e., soluble IL-6R (sIL-6R). Upon IL-6 binding to sIL-6R, a membrane-associated signal transducer (gp130) complex is formed and trans-signaling gets activated. Signaling pathways, for instance, Ras/Raf/mitogen-activated protein kinase (MAPK), Janus kinase/signal transducer and activator of transcription (JAK/STAT), phosphatidylinositol-3 kinase (PI3K), or Src/yes-associated protein (Src/YAP), exhibit inflammatory activity, as a result of which they get activated. Almost all human malignancies are related to higher IL-6 levels in the

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blood. In this chapter we have summarized the function of interleukin-6 and its associated signaling pathways that promote cancer progression via various processes such as angiogenesis and increased expression of antiapoptotic genes known to promote cancer. Moreover, we have discussed the potential agents targeting IL-6R/IL-6/JAK/STAT3 that restores the anti-tumor activity by inhibiting IL-6/JAK/STAT3 axis.

**Keywords**

Interleukin-6 · Glycoprotein 130 · mbIL-6Rα · sIL-6R · IL-6/JAK/STAT3 signaling · ADAM17 · Tumorigenesis · Tumor microenvironment · Angiogenesis · Metastasis · Invasiveness · Chronic inflammation

## 5.1 Introduction

Interleukins are a type of cytokines, which are cellular messengers with a low molecular weight of about 15–20 kDa, produced by both immune and nonimmune cells in response to pathogens and other antigens that mediate communication between cells as they bind to their receptors and trigger a cellular response in a target cell (Schafer and Brugge 2007; Gandhi et al. 2016; Takeuchi and Akira 2010). In 1979, the term "interleukin" was initially coined and used for several proteins secreted by leukocytes, which primarily act as a mediator between leukocytes, and were thus named "interleukins," meaning "between leukocytes." It is known that IL is also secreted by a variety of body cells (Brocker et al. 2010; Mir 2015a, b). The human genome encodes more than 50 different interleukins; they vary significantly in terms of structure and tend to overlap when it comes to their functions. Interleukins play a part in the differentiation, proliferation, and activation of immune cells (T and B lymphocytes) during inflammatory and immune responses. They exhibit properties of both anti- and pro-inflammatory cytokines (Scheller et al. 2011; Mir 2015a, b, c). Interleukin signaling mainly occurs through autocrine and paracrine mechanisms. Interleukins are not stockpiled within cells; rather, in response to a stimulus, they are rapidly secreted as they move toward their intended cell targets and elicit many cellular responses by binding to high-affinity receptor molecules on the cell surface. This interaction initiates a series of signal transduction pathways within the target cell that eventually change the cellular response (Vaillant and Qurie 2021).

A family of signaling molecules known as the cytokine family of interleukin-6 (IL-6)/glycoprotein 130 (gp130) came about as a consequence of infections and tissue injuries (Tanaka et al. 2014; Rose-John et al. 2015). IL-6 family members exhibit functional pleiotropy as well as redundancy. In their receptor complex, they have a core structure in common (Taga and Kishimoto 1997) and a signal transducer known as gp130 that performs a variety of functions in the body. Moreover, several molecules, such as tyrosine kinases of the JAK family and a STAT family member that communicates directly with the cytoplasmic domains of these receptors, have

been identified. Amongst the members of this family, IL-6 deregulation is responsible for many diseases. Inhibiting IL-6 signaling is extremely effective against diseases like cytokine release syndrome, Castleman disease, and rheumatoid arthritis (RA). The axis of IL-6/IL-6R is known to contribute to the growth of a number of autoimmune disorders and cancer as well (Hirano et al. 1988; Hodge et al. 2005; Hirano et al. 1987; Schafer and Brugge 2007). Undoubtedly, inhibitors of IL-6, IL-6R, or JAK family proteins are useful in the treatment of various immunological conditions. Several cell types are linked to the secretion of the cytokine interleukin-6, including keratinocytes, mesangial cells, fibroblasts, mast cells, macrophages, vascular endothelial cells, monocytes, dendritic cells, B cells, and T cells (Mir 2015a, b, c). Furthermore, stromal cells, tumor-infiltrating immune cells, and the tumor cells located in the tumor niche are also responsible for IL-6 production (Fig. 5.1).

As a pleiotropic cytokine, interleukin-6 has many different names depending on the type of biological activity it carries out. It was discovered nearly 50 years ago in 1973 and was originally identified as a T-cell-derived soluble mediator essential for B cells to produce antibodies (Kishimoto et al. 1978). IL-6 was first identified as a B-cell differentiation factor or a B-cell stimulatory factor 2 (BSF-2) (Howard et al. 1982). It was formerly referred to as interferon-2 (IFN-2) due to its antiviral interferon-like action (Zilberstein et al. 1986). Because of its capacity to encourage the generation of acute-phase proteins like fibrinogen, serum amyloid A (SAA), and C-reactive protein (CRP), interleukin-6 became characterized as a hepatocyte-stimulating factor shortly after (Gauldie et al. 1987). Furthermore, it was reported to

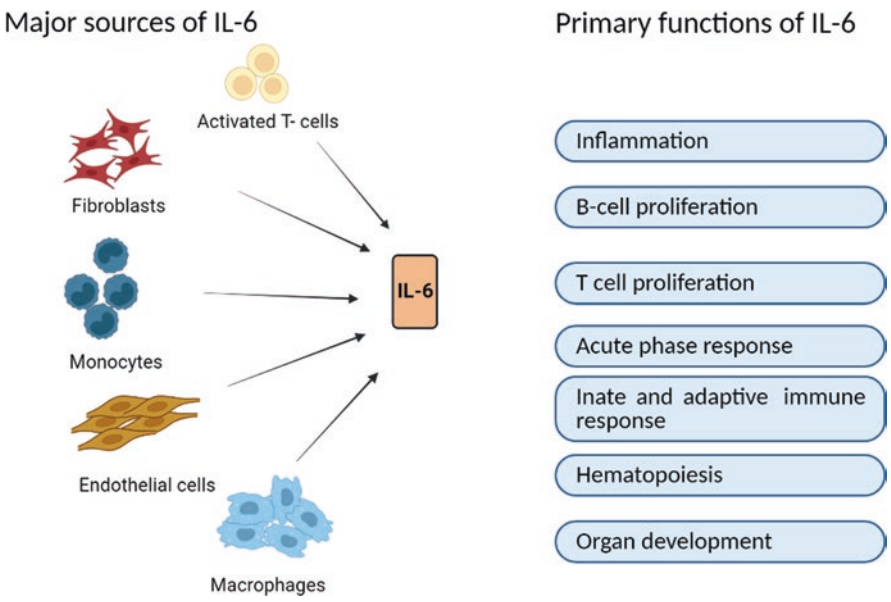


**Fig. 5.1** The major cell types linked to the secretion of IL-6

be identical to MGI-2A, also known as myeloid blood cell differentiation-inducing protein, macrophage and granulocyte inducer, type 2A, reflecting the cytokine's myeloid-differentiating capabilities (Shabo et al. 1988). Lastly, in 1988, this multifunctional cytokine was finally named "IL-6" (Hirano 2014).

IL-6 influences various metabolic and immune system functions, such as inflammation, generation of the acute-phase protein (CRP) in hepatocytes, antigen-specific immune responses, apoptosis, hematopoiesis, mitochondrial activity, insulin resistance (for instance, mice develop glucose intolerance and insulin resistance in the absence of IL-6, and, at the same time, liver inflammation is also seen) (Wunderlich et al. 2010), cell differentiation, vascular disease, and lipid metabolism (Ji et al. 2011), and it has also been reported to be associated with the neuroendocrine and neuropsychological systems (Rohleder et al. 2012; Rose-John et al. 2015). Moreover, as mentioned, it contributes to the progression of various disease types such as cancers and autoimmune diseases (Hirano et al. 1987, 1988; Hodge et al. 2005; Schafer and Brugge 2007).

In this chapter, we will discuss the function of interleukin-6 (IL-6) and its signaling, how it helps in regulating tumor progression, and learn exactly how agents targeting the IL-6/IL-6R/JAK/STAT3 or JAK/STAT signaling inhibitors can be therapeutic for various cancers.

## 5.2 IL-6 and Its Receptor Structure

IL-6 belongs to the hematopoietic cytokine family and is a glycosylated protein with a molecular weight of about 21–26 kDa (Fig. 5.2). In 1986, the IL-6 gene was cloned that encoded IL-6 precursor protein containing 212 amino acids that comprised of a mature segment of 184 amino acids and a signal sequence of 28 amino acids (Hirano et al. 1986). In 1986, the IL-6 gene was cloned that encoded IL-6

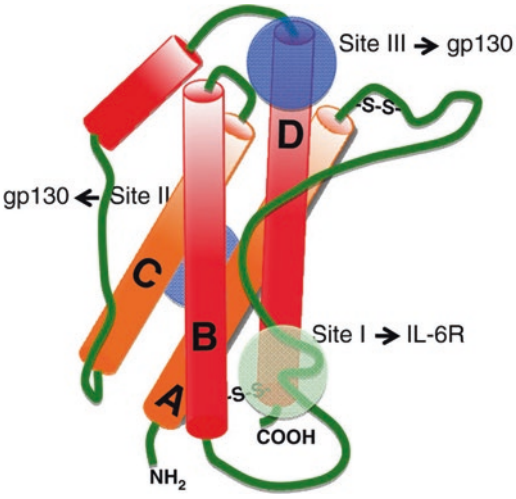


**Fig. 5.2** The structure of interleukin-6 (https://www.researchgate.net/figure/Schematic-representation-of-the-domain-structure-of-human-IL-6-notes-The-human-IL-6_fig1_281674578)

precursor protein containing 212 amino acids that comprised of a mature segment of 184 amino acids and a signal sequence of 28 amino acids (Simpson et al. 1997). The mature segment of IL-6 consists of long antiparallel α-helices A, B, C, and D connected through various loops. These helices are structured in such a way that they have an up-up-down-down geometry (Scheller et al. 2011), resulting in the formation of three binding sites for epitopes, namely, sites I, II, and III, at which binding of the receptor occurs (Brakenhoff et al. 1990, 1994; Ehlers et al. 1994).

Helix D and AB loop's C-terminal residues form site I, which serves as a requisite site for a nonsignaling component of the interluekin-6 receptor (Savino et al. 1994a, b; Paonessa et al. 1995). Site II is produced by the dual association of IL-6 and IL-6R with the signal transducer glycoprotein (gp130), which is located on helices A and C and in the middle of domains 2 and 3 (Yawata et al. 1993; Savino et al. 1994a, b; Boulanger et al. 2003). Site III is composed of residues found at the C-terminal of helix D and at the N-terminal of the AB loop. This location is known as domain 1 (D1) because it interacts with immunoglobulin G (IgG) to produce a reliable signaling complex, much like the gp130 (glycoprotein 130) domain does (Yawata et al. 1993).

The IL-6 receptor is a member of the family of cytokine receptors that comprise of IL-6 binding chain domain and a signal transducing chain (gp180) both of these proteins have a Trp-Ser-X-Trp-Ser motif and are cytokine receptors. Two isoforms of the IL-6-binding chain have been found: one is a transmembrane receptor (mbIL-6R) with a molecular weight of 80 kDa and the other is soluble IL-6R (sIL-6R) of molecular weight 50–55 kDa. The interleukin-6 receptor consists of an 80-kDa IL-6-binding protein (α-chain) (CD126), with a cytoplasmic domain containing only 82 amino acids, and gp80, which is present only in limited cell types. IL-6 binds to low-affinity receptors by means of the residues present in the interior of domains 2 and 3, which subsequently recruit the gp130 signal transducer, a β-subunit of the interluekin-6 receptor, to create a high-affinity IL-6R complex that transmits signals and carries out signal transduction. It is worth mentioning that the cytoplasmic and the transmembrane domains of the interluekin-6 receptor are not competent for signaling, and, as such, if both these domains are removed, it will not affect IL-6 signaling (Yamasaki et al. 1988; Taga et al. 1989). Interleukin-6 is not able to transduce signals alone. The IL-6/IL-6R complex is associated with the signal transducer glycoprotein 130 (gp130), also known as CD130, and IL-6Rβ, a glycoprotein of molecular weight of about 130 kDa, has about 277 amino acids in its cytoplasmic domain containing several motifs and sites for phosphorylation. It is universally expressed as the IL-6-type cytokine family's signal transducer, which comprises leukemia inhibitory factor (LIF), OSM (oncostatin M), IL-11 (interleukin-11), ciliary neurotrophic factor (CNTF) , and cardiotrophin-1 (CT-1) (Sprang and Bazan 1993). Since the gp130 subunit exclusively interacts with the complex of IL-6/IL-6R through the generated dual site II engages with gp130's multiple CBDs ( cytokine-binding domains) D2 & D3 as well as via site III is present at D1 of gp130, neither IL-6 nor IL-6R can be activated by themselves (Hibi et al. 1990). Meanwhile, functional investigations indicate that two distinctive copies of IL-6, IL-6R, and gp130 combine to form the hexameric structure of the high-affinity IL-6/IL-6R

complex. One molecule of IL-6, one molecule of IL-6R, and two molecules of gp130 are already part of a tetrameric model (Grötzinger et al. 1999; Takeuchi and Akira 2010).

## 5.3 IL-6 Signaling in Cancer

Malignant cells as well as lymphoid and nonlymphoid cells exhibit the type I cytokine receptor on their cell surfaces, and this is how IL-6 communicates. There are two categories of IL-6 receptors: the first is the cell membrane-bound IL-6 receptor (IL-6R), which has a low affinity and binds to gp130 to activate a classical signaling pathway, and the second is the soluble IL-6 receptor isoform that activates trans-signaling.

By attaching to a soluble variant of the IL-6 receptor (sIL-6R), IL-6 may be able to "trans-signal" in a way that is more convenient (sIL-6R). It first attaches to IL-6 and then to the membrane receptor b-chain (gp130), resulting in an intracellular signal. An IL-6/IL-6R or an IL-6/sIL-6R complex, formed with the membrane-associated signal transducer, triggers signal transduction. The stimulation of particular signaling, including JAK/STAT3 (signal transducer and activator of transcription 3)/IL-6, as well as other signaling pathways involved, leads to the amplification of pro-inflammatory cytokine IL-6. This condition is a hallmark of chronic inflammatory conditions, autoimmune diseases, vascular diseases, and, in a large percentage of patients, several neoplastic disorders, such as hematological malignancies, ovarian cancer, colon cancer, breast cancer, and prostate cancer (Fig. 5.3) (Mir and Mehraj 2019).

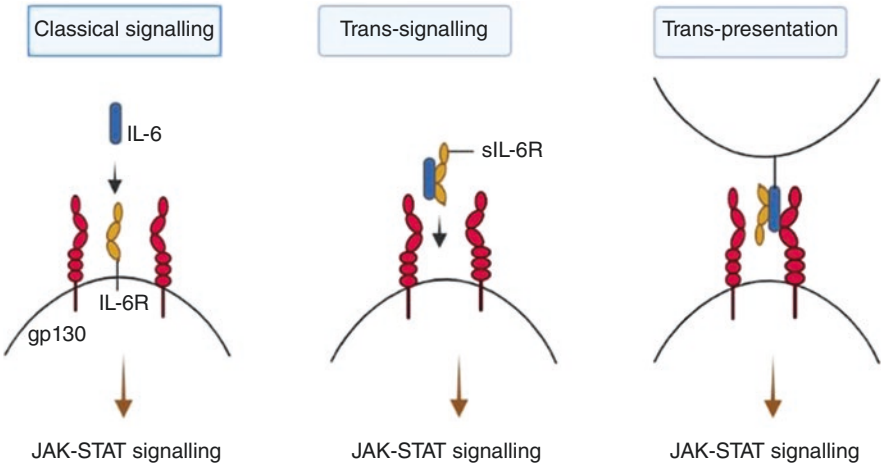


**Fig. 5.3** Modes of IL-6 signaling

## 5.4 Classical Signaling and Trans-Signaling

The two known isoforms of the interleukin-6 receptor, namely, mbIL-6R (a membrane-bound receptor) and sIL-6R (a soluble isoform), are the factors that will determine whether classical signaling or trans-signaling will occur. The proteolysis of the ectodomain of mbIL-6R by a disintegrin and metalloproteases 17 and 10 (ADAM17 and ADAM10, respectively) results in the shedding of the soluble receptors of IL-6, ADAM17, and ADAM10. These are zinc (Zn dependent metalloproteinases. sIL-6R is produced via alternative splicing of the messenger RNA (mRNA) of IL-6 and also that of IL-6R, but the latter occurs less commonly, i.e., about 1–20% (Mülberg et al. 1993; Lust et al. 1992; Riethmueller et al. 2017). Both these isoforms of IL-6R have a similar affinity toward IL-6 binding (Fig. 5.4) (Narazaki et al. 1993).

It is notable that an IL-6/sIL-6R complex can induce IL-6 signaling through autocrine and paracrine mechanisms in any cell type with a gp130 signal transducer, which results in activation of the trans-signaling of sIL-6R. On the other hand, only few epithelial cells, hepatocytes, and few leukocytes express cell membrane-bound

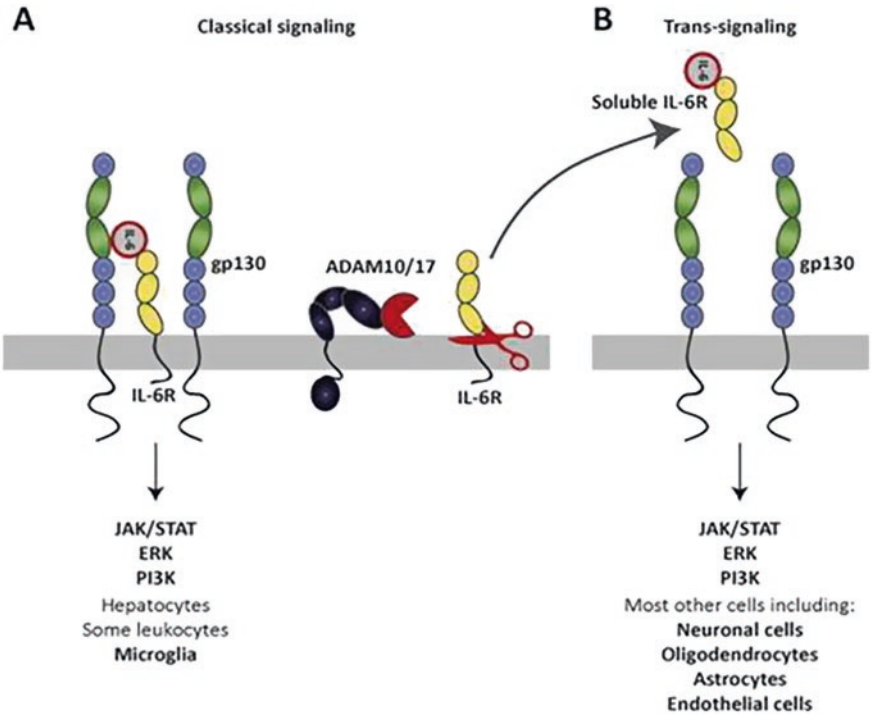


**Fig. 5.4** Classical signaling and trans-signaling via ADAM17-mediated cleavage of IL-6R or other events; soluble isoforms of IL-6R are produced

IL-6R (mbIL-6R), and, as such, classical signaling of IL-6 gets activated. Classical signaling is anti-inflammatory, whereas trans-signaling stimulates pro-inflammatory processes. Both times, signaling is brought on by gp130 homodimerization.

The term "IL-6 trans-presentation," which has recently been established, was used to describe the third way of IL-6 signaling. Once dendritic cells (DCs) specifically interact with an antigen, IL-6 binds intracellularly to its receptor and moves to the cell membrane, where the membrane-anchored receptor of IL-6 interacts with the gp130 subunit of T cells when combined with transforming growth factor-beta 2 (TGF-β2) to form prime T-helper (Th)17 cells that lead to chronic inflammation and regulatory T (Treg) cell suppression by IL-27 (Qayoom et al. 2023; Narazaki et al. 1993; Heink et al. 2017). It is still not known whether this novel IL-6 signaling mechanism works in humans because this study was conducted experimentally using a murine model of multiple sclerosis of humans. gp130 dimerization is necessary for IL-6 signaling through the traditional or trans-signaling pathways because it activates the JAK protein that is linked to gp130 (Heink et al. 2017).

Trans-signaling plays an important role in the tumor microenvironment by regulating leukocyte recruitment and inducing the inflammatory activation of stromal cells that are linked to the tumor (Mehraj et al. 2021a, b, c). It is notable that alternative splicing of gp130 mRNA generates four different soluble isoforms of gp130 (sgp130). This adds to the complexity, given that when secreted sgp130 proteins interact with the IL-6/sIL-6R complex, they specifically prevent the trans-signaling facilitated by IL-6 (Baran et al. 2018). As a result of its binding, an inactive ternary complex is formed. The inhibitory activity of trans-signaling occurs at low doses and also depends on the IL-6/sIL-6R ratio because the classical signaling mediated by IL-6/mIL-6R is not affected by it (Nakajima et al. 1993; Jostock et al. 2001). Numerous downstream signaling processes occur after the formation of the IL-6/IL-6R/gp130 complex, enabling IL-6 to exhibit cell differentiation, proliferation, survival, and death, among a wide range of other biological processes. The signaling of IL-6 involves the Ras/Raf/mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), JAK/STAT, and Src/yes-associated protein (Src/YAP) pathways (Fig. 5.5) (Nakajima et al. 1993; Taniguchi et al. 2015, 2017).

## 5.5 Signaling Pathway for IL-6/JAK/STAT3

The JAK/STAT3 signaling pathway is essential for mediating IL-6's diverse effects on tumor promotion, i.e., cancer cell survival, proliferation, invasion, metastasis, and immunity-suppressing properties (Kumari et al. 2016; Qayoom et al. 2021). The JAK/STAT (Janus kinase/signal transducer and activator of transcription) signaling pathway is highly conserved. IL-6 signaling can happen via traditional or trans-signaling routes, and the heterohexameric complex formed between IL-6R, IL-6, and gp130 is what initiates intracellular signaling. This complex activates JAKs that are linked to gp130. There are four mammalian JAKs: tyrosine kinase 2 (TYK2), JAK1, JAK2, and JAK3. There are seven members of the STAT family: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 (Seif et al. 2017).

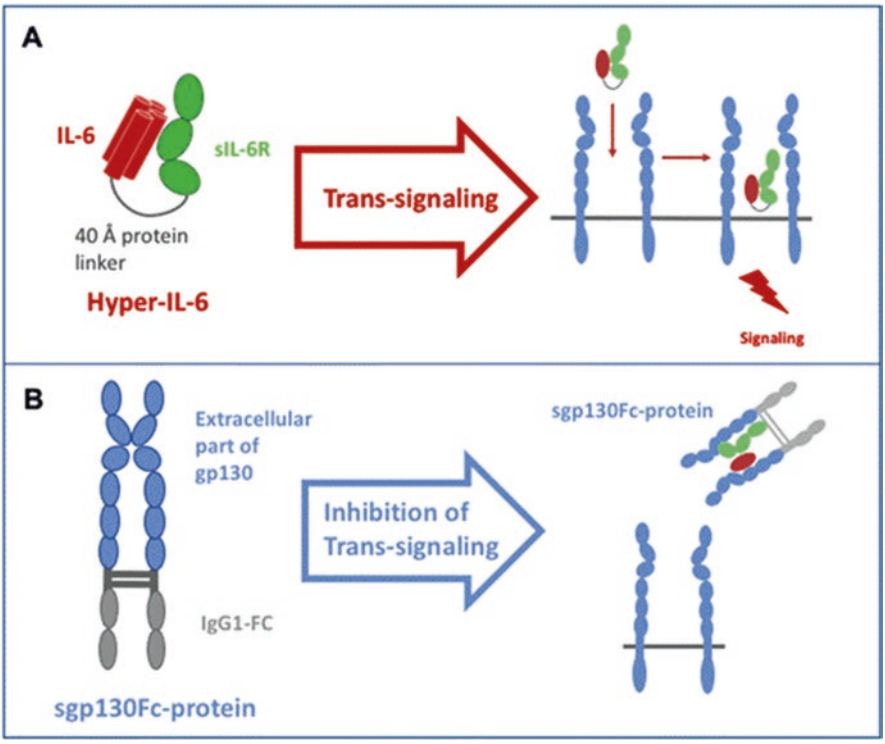


**Fig. 5.5** Inhibition of trans-signaling

**The JAK Family**: This consists of protein tyrosine kinases that are not receptors. JAK tyrosine kinases TYK2, JAK1, JAK2, and JAK3 are stimulated when cytokines connect to their receptors. The other members of JAK3 are uniformly present in all tissues, whereas JAK3 is restricted only to the lymphatic system, bone marrow, vascular smooth muscle cells, and endothelial cells (Rane and Reddy 1994; Takahashi and Shirasaw 1994; Lai et al. 1995; Verbsky et al. 1996). Members of the JAK family consist of seven different JAK homology domains (JH). There is the first JH, JH1, which originates from the carboxyl terminus and has roughly 250 amino acid residues. JH1 is also known as the kinase domain because it creates the kinase structural domain and phosphorylates a substrate by encoding a kinase protein. Although JH2 shares structural similarities with the kinase domain, it lacks kinase activity. It is known as the Pk domain or pseudo kinase domain and takes part in the interaction between JAK and STAT. Its major aim is to regulate the kinase domain's activity, and, by binding to the kinase domain, it can also inhibit Tyr kinase activity. JH3 and one-half of JH4 make up the Src homology 2 (SH2) domain, whereas JH4 and one of each of JH5, JH6, and JH7 make up the FERM (F for four point one protein, E for ezrin, R for radixin and M for moesin) domain. When the IL-6/IL-6R complex homodimerizes gp130, JAK1, JAK2, and/or TYK2 are selectively activated through the SH2 and FERM domains, mostly through interactions

of these enzymes with gp130's Box domains 1 and 2, which are membrane-proximal areas. Due to the disruption of JH2-mediated inhibition of JH1 kinase activity caused by these contacts, reciprocal transphosphorylation that results in complete activation of JAKs takes place. After the JAK enzyme is activated in the cytoplasm of gp130, numerous tyrosine residues undergo phosphorylation. These residues later act as docking sites for proteins that start the IL-6/JAK/STAT3 signaling pathway and additional distinct signaling pathways (Frank et al. 1995; Velazquez et al. 1995; Ferrao and Lupardus 2017).

The STAT family members include 750–900 amino acid residues. The STAT structure consists of a coiled-coil domain (CCD), a linker domain (LD), an amino terminal domain, an Src homology 2 domain, a DNA-binding domain (DBD), and a transactivation domain. STAT3 is closely linked to the stimulation of tumor progression and immune suppression among the STAT protein family members (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6). STAT3 normally resides in the cytoplasm of cells in the dormant state as a monomer. When JAK enzymes get activated, they subsequently phosphorylate multiple tyrosine residues of growth factor receptors like gp130. This places STAT3 in close proximity to active JAK enzymes, which then phosphorylate STAT3 at Tyr705. The phosphorylation of Tyr705 residues results in dimerization of the STAT3 protein in a head-to-tail manner, which is mediated by the Src homology 2 domain. The STAT3 dimer translocates from the cytoplasm to the nucleus through an importin-α–importin-β1-dependent mechanism (Chang et al. 2013a, b).

The STAT3 dimer attaches to the target genes' promoter consensus response elements inside the nucleus. As a result, transcription of genes in charge of controlling cell proliferation (like cyclin D1 and Myc) and cell survival (like survivin and Bcl-xL) as well as transcription of angiogenesis-promoting genes (like vascular endothelial growth factor (VEGF)), immunosuppressive growth factors, and cytokines are stimulated to be expressed (such as IL-6). The capability to phosphorylate or activate STAT3 is not restricted to only JAKs, as the tyrosine kinases Src and BCR–ABL1 can also directly activate STAT3. In addition, it has been reported that posttranslational changes, including phosphorylation of the Ser727 residues, and methylation, acetylation, SUMOylation, and ubiquitylation of other residues, may influence the stability or function of STAT3. Compared to Tyr705 phosphorylation, Ser727 phosphorylation has received less attention in research. It can be regulated by a number of kinases such as various MAPKs, JNKs, and protein kinase C, which typically increases STAT3 action. When nonmalignant cells are stimulated with IL-6 or other cytokines, STAT3 is momentarily phosphorylated and/or activated (Chang et al. 2013a, b).

To regulate the termination of cytokine signaling transduction few protein families are involved that have been documented quite recently and are known to downregulate the signal transduction that include: Several cellular phosphatases, including dual-specificity phosphatase 22 (DUSP22), Src homology 2 protein phosphatase 1 (SHP1), protein tyrosine phosphatase receptor type D (PTPRD), Src homology 2 protein phosphatase 2 (SHP2), protein tyrosine phosphatase nonreceptor types 1 and 2 (PTPN1 and PTPN2, respectively), and protein tyrosine

phosphatase receptor type T (PTPRT), as well as a minimum of three distinct types of negative regulators comprising suppressors of cytokine signaling (SOCS1, SOCS2, and SOCS3) proteins, protein inhibitors of activated STAT (PIAS) proteins, and cytokine-inducible SH2 (Src homology 2) domain-containing proteins (CISH), can control STAT. All of them function as feedforward regulators, which eventually reduce signaling of IL-6 (Tartaglia et al. 2003; Nozawa et al. 2006; Zhang et al. 2007; Buchert et al. 2016; Peyser et al. 2016). According to reports, mice with mutant gp130 omit their ability to bind to SOCS3, which results in continuous stimulation of STAT3 and STAT1, leading to the onset of cancer and chronic inflammatory illness (Nozawa et al. 2006).

## 5.6 How IL-6 Regulates Tumor Progression

Sources of IL-6 that are most prevalent in the tumor microenvironment include tumor stromal cells, tumor-infiltrating immune cells, and tumor cells along with $CD4^+$ T cells, TAMs (tumor-associated macrophages), fibroblasts, and MDSCs (myeloid-derived suppressor cells) (Nolen et al. 2008; Oh et al. 2013; Nagasaki et al. 2014; Mehraj et al. 2021a, b, c). In the tumor microenvironment, IL-6 directly affects cancer cells by modulating both their intrinsic and extrinsic actions, thereby directly supporting tumorigenesis and influencing stromal cells, and by indirectly supporting tumorigenesis (Fisher et al. 2014). We can say that IL-6 creates a complex of cytokines, proteases, and growth factors consisting of granulocyte macrophage colony-stimulating factor (GM-CSF), VEGF, and matrix metalloproteinase-1 (MMP-1) in prostate and skin cancer, which promotes the advancement of the malignancy.

As IL-6 is made by tumor cells to aid in their survival and growth, stromal cells' paracrine release of IL-6 is not necessary for the autocrine action of interluekin-6 on tumor cells. However, it is found that interluekin-6 trans-signaling affects tumor growth and metastasis through both paracrine and autocrine processes of IL-6 (Lederle et al. 2011; Fisher et al. 2014). It is generally acknowledged that cancer is driven by inflammation. One of the main factors driving this association is nuclear factor-kappa B (NF-κB) signaling, which plays a major role in the overexpression, and many pro-inflammatory cytokines are stimulated by a range of cell types in the tumor microenvironment. Both adaptive and inborn immunity are regulated by interleukin-6. Certainly, IL-6 knockout mice have altered inborn and acquired immune responses to bacteria, parasites, and viruses. IL-6 regulates the natural immune response in many ways. Upregulation of receptors that recognize patterns, including toll-like receptors (TLRs), causes macrophages, monocytes, or neutrophils to produce IL-6. Furthermore, when pattern recognition receptors are activated, stromal cells such as endothelial cells, fibroblasts, epithelial cells, mesothelial cells, smooth muscle cells, and myofibroblasts produce interleukin-6. IL-6 controls the action of cells of innate immunity as it recruits neutrophils, cells of myeloid lineage, and tissue-resident monocytes and also promotes their differentiation, adhesion, activation, and survival. IL-6's ability to regulate acquired immunity

depends on its capacity to regulate T-helper cell differentiation. There are a few potent cytokines that promote inflammation caused by immune cells of adaptive or innate immunity, which control the progression of cancer cells and tumors (Krishnamoorthy et al. 2007; Zhao et al. 2008; Mitchem et al. 2013; Mehraj et al. 2021a, b, c). IL-6, one of these cytokines, is vital for the development of human cancer and is found to be dysregulated in cancer. It activates oncogenic pathways. In many types of cancers, elevated levels of IL-6 are found, for example, in colorectal cancer(CRC), ovarian carcinoma, prostate cancer, breast cancer, pancreatic cancer, pulmonary cancer, cervical cancer, renal cell carcinoma, multiple myeloma (MM), and lymphomas (Altundag et al. 2004; Culig and Puhr 2012; Waldner et al. 2012; Chang et al. 2013a, b; Dethlefsen et al. 2013; Miura et al. 2015). This shows a strong relationship between the IL-6 cytokine and cancer. It is found that males with higher levels of IL-6 show high susceptibility to the occurrence of a liver malignancy. As opposed to this, IL-6 production is inhibited by estrogen and steroid hormones to guard female mice from developing cancer (Naugler et al. 2007; Wei et al. 2015). The hyperactivation of the JAK/STAT3/IL-6 signaling axis regulates various signaling pathways, which is responsible for survival of cancer cells, and thus promotes tumorigenesis (Landskron et al. 2014).

IL-6 controls almost all hallmarks of cancer, such as cell survival, cell proliferation, angiogenesis, inhibition of apoptosis, and metastasis. It is also known for regulating tumor cell metabolism. The bulk of the characteristics of a tumor are regulated by interluekin-6, including a range of biological abilities developed during tumor growth. IL-6's involvement in controlling cancer cell growth stems from the fact that some regulatory mechanisms that downregulate or negatively influence cell growth are avoided by cancer cells. These mechanisms primarily rely on the activity of tumor suppressor genes like the retinoblastoma gene (Rb) and the p53 gene, which go through either gain of function or loss of function to control cell proliferation and cell growth, respectively (Mir et al. 2020). The Rb protein, which is controlled by phosphorylation, interferes with the cell cycle passage from the G1 phase to the S phase (Fig. 5.6). Normally, the retinoblastoma protein is in its active form in the dephosphorylated state, which is bound by E2F, and leads to cell arrest at the G1 phase. On the other hand, Rb is in its inactive form after phosphorylation. In this state, Rb is unable to bind to E2F that triggers cyclin-dependent kinase (CDK) activation in such a manner that it facilitates cell transition into the S phase (Qayoom et al. 2022; Sofi et al. 2022). IL-6 facilitates the phosphorylation of Rb in multiple myeloma (MM) cells, thereby promoting cell growth. Moreover, in MM cells, phosphorylation of Rb also enhances the generation of interluekin-6 (Urashima et al. 1996; Nevins 2001; Giacinti and Giordano 2006).

In cervical cancer, esophageal carcinoma, gastric cancer, myeloma cells, basal cell carcinoma cells, and myeloma cells, IL-6 controls the process of apoptosis by stimulating NF-κB and STAT3 signaling, which trans-activates many antiapoptotic proteins like B-cell lymphoma-2 (Bcl-2), Bcl-xL, and Mcl-1, among others. Additionally, these pro-survival or antiapoptotic proteins, particularly Bcl-2, encourage cell division. It has been suggested that increased amounts of IL-6, both in IL-6-treated cells and in transgenic mice that express IL-6, may alter the

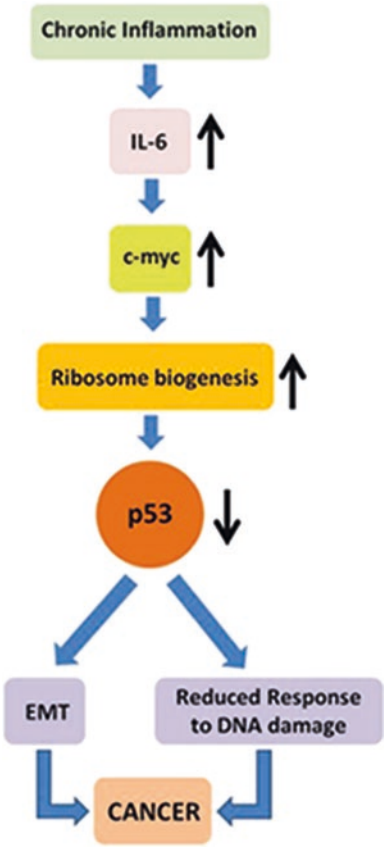


**Fig. 5.6** Downregulation of p53 by overexpression of IL-6

proportion of pro- and antiapoptotic proteins, which is crucial for the decision to undergo apoptosis. Moreover, Bcl-2 produced by IL-6 controls interactions between mitofusins and Bak by inhibiting the dissociation of Bak from Mfn2, which, in turn, prevents the interaction of Bak with Mfn1. These are the two major mitochondrial events that determine cell death. Along with Bcl-2 and Bcl-xL, IL-6 promotes the production of survivin by direct binding of STAT3 to the promoter survivin gene. This helps tumor cells survive. Additionally, the expression of the survivin gene is downregulated, which suppresses STAT3, causing tumor cells to undergo apoptosis. NF-κB, MAPK/extracellular signal-regulated kinase (ERK), and PI3K/Akt signaling pathways are all increased by IL-6 in kidney cancer, hepatocellular carcinoma (HCC), prostate cancer, and multiple myeloma cells, which results in an increase in cyclin A1 expression in these cells. Overall, it seems that interleukin-6 primarily promotes tumor growth by reducing cell death and promoting cell proliferation (Gritsko et al. 2006; Brooks et al. 2007; Waxman and Kolliputi 2009; Mir et al. 2023). In addition to promoting the growth of tumor cells, IL-6 is used to create resistance to anticancer treatments that trigger the body's natural death processes. Direct targets of STAT3 upregulation include the bulk of the genes that control cell

differentiation, proliferation, and survival, including p21, Mcl-1, Bcl-xL, Bcl-2, Fas, cyclin E1, and cyclin D1. Moreover, these, including c-Jun, cMyc, and c-Fos, are other transcription factors that promote proliferation and are also targets of STAT3. When STAT3 is activated in tumor cells, p53 expression is transcriptionally repressed, whereas STAT3 inhibition upregulates p53 expression and triggers p53-mediated apoptosis (Hirano et al. 2000; Niu et al. 2005).

## 5.7 Inflammation Promotes Cancer

Inflammation encourages all phases of carcinogenesis and predisposes to the growth of cancer and promotion of malignant transformation. Many inflammatory mediators like IL-6, TGF-β, IL-10, and tumor necrosis factor-α (TNF-α) have all been implicated in the beginning and progression of cancer. Cancer and inflammation have shown a strong association with cancer prevention, and the use of anti-inflammatory drugs is encouraged. Inflammation related to cancer consists TAMs, white blood cells, and inflammatory mediators such as cytokines (IL-1, IL-6, and TNF-α) and chemokines (CXCL8 and CCL2), which promote tissue remodeling and vasculogenesis (Colotta et al. 2009; Mir et al. 2022a, b, c).

In the tumor microenvironment, interluekin-6 is one of the highly expressed inflammatory mediators, and, in colorectal cancer, IL-6 secretion is associated with STAT3-dependent tumorigenesis and its associated trans-signaling within the tumor milieu induces inflammation. In ulcerative colitis, M2-type macrophages release IL-6 and contribute to the growth of colorectal tumors. These investigations have discovered a connection between IL-6 and inflammation in tumors. Inflammatory cytokines (IL-6, IL-1b, and TNF) as well as transcription factors like NF-κB and STAT3 are the main players in inflammation. Inflammation is heavily regulated by NF-κB, which is dysregulated in many malignancies. IL-6 is a crucial part of the NF-κB/IL-6/STAT3 signaling pathway, which is involved in carcinogenesis, as it is a primary effector molecule of NF-κB that is activated through the JAK/STAT3 signaling pathway. NF-κB activation in tumors must be maintained by STAT3, and IL-6 encourages carcinogenesis by causing inflammation and cell growth. Meanwhile, the stimulation of IL-6-mediated STAT3 signaling promotes inflammation and boosts the progression and development of gastrointestinal cancers, so it is now evident that IL-6, inflammation, and tumor promotion are all strongly associated (Qayoom et al. 2023a).

### 5.7.1 IL-6 Promotes Invasion, Metastasis, and Angiogenesis

It is common knowledge that inflammation encourages epithelial-to-mesenchymal transition (EMT), which allows cancer cells to spread from the primary tumor site to the nearby tissues and organs. Cancer cells do this by acquiring a mesenchymal phenotype from an epithelial one, which allows them to do so. Tumor cells transform back into epithelial cells after settling into the new organ and multiply to

produce metastatic tumors. It is widely known that inflammation encourages EMT. The terms "epithelial-to-mesenchymal transition" (EMT) and "mesenchymal-to-epithelial transition" (MET) refer to the mechanisms by which cells go from having an epithelial phenotype to bearing mesenchymal characteristics (Kalluri and Weinberg 2009; Ricciardi et al. 2015).

Increased levels of IL-6 in the blood are related to the enlarged size of the tumor as well as invasion (EMT), metastasis, and worse survival rate in people with colorectal cancer. According to reported evidence, IL-6 promotes CXCR4 expression through c-Jun and STAT3, which promotes the metastasis of numerous bone tumors, including breast, pulmonary, prostate, neuroblastomas, adenocarcinomas, multiple myeloma, and melanomas (Ricciardi et al. 2015). By boosting the production of growth factors, such as DNA methyltransferase 1 (DNMT1), VEGF, and MMP-9, IL-6 induces hyperactivation of JAK/STAT3, which is involved in EMT, metastasis, and angiogenesis in bladder cancer. It has also been demonstrated that the autocrine production of IL-6 enhances the ability of tumor cells to infiltrate the extracellular matrix in breast cancer. By increasing the expression of several growth factors, including MMP-9, VEGF, tumor-associated macrophages, and basic fibroblast growth factor (bFGF) in tumor-associated endothelial cells and MDSCs, IL-6/JAK/STAT3 signaling promotes angiogenesis in numerous malignancies (Helbig et al. 2003; Kujawski et al. 2008; Tawara et al. 2011; Chen et al. 2013; Sofi et al. 2023).

### 5.7.2 At Elevated Levels, IL-6 Acts as a Prognostic Marker for Various Cancers

Nearly 1 pg/ml of IL-6 in present in normal blood circulation, under several conditions. An increase in its level is found during acute hyperglycemia, during/after surgery, after a high-fat meal, during a normal menstrual cycle, and during physical activities. IL-6 levels fluctuate throughout the course of pregnancy, peaking at around 128 pg/ml when the baby is delivered and, immediately afterward, dropping by more than twofold (~58 pg/ml). As mentioned earlier, chronic inflammation promotes carcinogenesis (Sakamoto et al. 1994; Angstwurm et al. 1997; D'Auria et al. 1997; Devaraj et al. 2005; Blackburn et al. 2006; Narbutt et al. 2008; Reihmane and Dela 2014). IL-6 is a potent pro-inflammatory marker, and it exhibits multiple biological activities. Elevated levels of IL-6 in the serum have been reported during cancer; IL-6 acts as a biomarker for various malignant diseases such as gastric cancer, pancreatic cancer, colon cancer, hepatobiliary cancer, prostate cancer, pulmonary cancer, renal cell carcinoma, breast cancer, and ovarian cancer. According to reports, increased IL-6 levels are related to the overall poor prognosis in hepatocellular carcinoma (HCC) patients (Altundag et al. 2004; Groblewska et al. 2008; Culig and Puhr 2012; Waldner et al. 2012; Chang et al. 2013a, b; Dethlefsen et al. 2013; Miura et al. 2015).

#### 5.7.2.1 Colon Cancer

In 32 patients with colorectal cancer, significantly increased levels of IL-6 were seen in comparison to those of normal colorectal tissues, indicating that interluekin-6 plays an important role in tumor development (Komoda et al. 1998). In addition, it has been shown that increased IL-6 levels in the blood are associated with a poorer prognosis in CRC. This is because IL-6 expression is greater in colon rectal cancer tissues than in nonmalignant tissues (Chung and Chang 2003; Zeng et al. 2017). In addition, as compared to cells from a healthy colon epithelium, CRC cells shows high expression of IL-6 and higher levels of STAT3 phosphorylation (Corvinus et al. 2005). Studies have shown that whereas sIL-6R is strongly elevated during carcinogenesis, mbIL-6R is scarcely detectable. This suggests that IL-6 affects CRC through trans-signaling. An increased ADAM17 expression observed in malignant cells in comparison to normal cells serves to authenticate this fact. A sign of this disease's worse prognosis is elevated IL-6 levels (Becker et al. 2005).

#### 5.7.2.2 Breast Cancer

IL-6's effect on breast cancer cell lines has been studied in vitro; the results are inconsistent, displaying tumor-suppressing actions in some models and tumor-promoting activities in others. The results also showed that there was a large concentration of interleukin-6 in Michigan Cancer Foundation-7 (MCF-7)/adriamycin multidrug-resistant breast cancer cell supernatants. However, in parental sensitive cell supernatants, IL-6 was not detectable (Conze et al. 2001). Furthermore, exogenous IL-6 is added to MCF-7 cells, which leads to an increase in their doxorubicin resistance by 8–10-fold, while engineered MCF-7 cells express IL-6, thus showing a 70-fold rise in their sensitivity to various medications. A protein linked to treatment resistance is G96, which was produced by MDA-MB-231 triple-negative breast cancer cells when exogenous interleukin-6 was added to the cells. In line with this, the scientists discovered that IL-6 and G96 protein levels were substantially increased in breast tumors than in normal, noncancerous breast tissues (Haverty et al. 1997; Qayoom et al. 2023).

However, additional research indicates that interluekin-6 may exhibit antitumor activity against a few types of breast cancers. For instance, it has been noted that IL-6 causes MCF-7 breast cancer cells to undergo apoptosis. According to these discoveries, insulin-like growth factor-I (IGF-I), tumor necrosis factor (TNF), and IL-1, along with interluekin-6, are associated with decreased proliferation of MCF-7 cells by suppressing IGF-I, a molecule known to promote DNA synthesis in MCF-7 (Danforth Jr and Sgagias 1993; Chiu et al. 1996). IL-6 can accelerate the migration of breast malignant cells, indicating its function in metastasis, and, despite its contentious role in survival and proliferation, an epithelial-to-mesenchymal transition is induced by IL-6, which then promotes the spread of breast cancer cells. Other findings have shown that IL-6 inhibits the adhesion of breast malignant cells and that this outcome was related to tumor cells' reduced production of E-cadherin (Arihiro et al. 2000).

The IL-6 levels of breast cancer survivors were considerably higher in their blood in comparison to those of healthy women. In patients, elevated blood levels of

IL-6 have been linked to a bad prognosis of this disease, despite the fact that different investigations have produced conflicting consequences concerning the usefulness of the predictive value of IL-6 levels in breast tumor tissues (Bachelot et al. 2003; Salgado et al. 2003; Bozcuk et al. 2004). It was also discovered that as compared to individuals with only one metastatic site, patients with extensive metastatic breast cancer had considerably higher amounts of IL-6 in their blood. Additionally, they discovered that patients with higher IL-6 levels had poorer chemo-endocrine treatment response and lower survival rates (Nishimura et al. 2000; Yokoe and Morishita 2000; Bachelot et al. 2003; Salgado et al. 2003; Bozcuk et al. 2004).

#### 5.7.2.3 Ovarian Cancer

Increased blood levels of the pro-inflammatory cytokine IL-6 is associated with ovarian cancer as well, and a compromised immune function is frequently seen in individuals suffering from advanced epithelial ovarian cancer (EOC), which is linked to overexpression of IL-6. Several research studies have revealed the association of interluekin-6 with the progression of EOC, chemotherapy resistance, and poorer prognosis (Macciò et al. 1998; Hagemann et al. 2007). Advanced epithelial ovarian tumors have elevated expression levels of interleukin-6 in their ascites and cystic fluid in comparison to benign ovarian tumors, and these levels are correlated with the growth/size of the tumor and the ascites volume (Paladugu et al. 1985; Nowak et al. 2010). There is evidence that shows that IL-6 may directly contribute to the progression of ovarian tumors. As discussed earlier, IL-6/JAK/STAT3 signaling hyperactivation upregulates the production of antiapoptotic molecules, for instance, Bcl-xL and Bcl-2 (B-cell lymphoma 2), which promotes EOC cell survival In addition, research has revealed that IL-6 in ovarian cancer cells changes the distribution of the cell cycle. IL-6 also stimulates the release of MMP-9 (matrix metalloproteinase-9), and it adds to increase the invasiveness of ovarian cancer cells. MMP-9 levels were lower in anti-IL-6-treated antibody SKOV-3 ovarian cancer cells in comparison to SKOV-3 ovarian cancer cells in control cultures (Rabinovich et al. 2007; Macciò and Madeddu 2013).

In many ovarian cancer models, IL-6 has also been demonstrated to function as a powerful angiogenic agent. Additionally, it has been noted that ovarian cancer cells, particularly SKOV-3 cells, produce more secreted sIL-6R. This finding suggests the potential role of IL-6 trans-signaling in the development of ovarian tumors and tumor angiogenesis (Nilsson et al. 2005; Macciò and Madeddu 2013).

#### 5.7.2.4 Other Types of Cancers

It is not possible to fully summarize the function of interleukin-6 and its signaling in all forms of cancer in a single chapter. Here, an overview has been provided, including how overexpression of IL-6/JAK/STAT signaling is linked to prolonged inflammation, cancer progression, invasion, tumor cell proliferation, metastasis, and inhibition of expression of proapoptotic genes (Fig. 5.7).

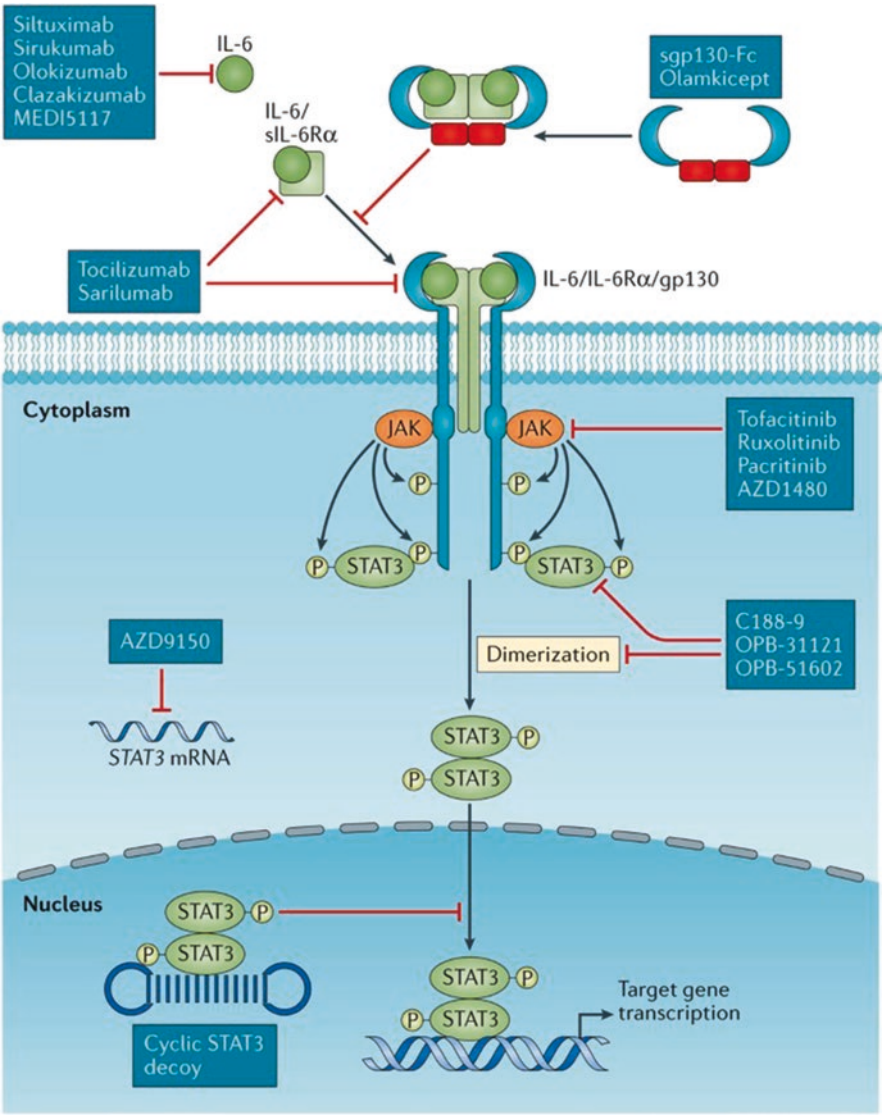


**Fig. 5.7** IL-6/JAK/STAT3 inhibitors in cancer targeting (ref: https://www.nature.com/articles/nrclinonc.2018.8)

## 5.8 IL-6/IL-6R Axis Targeting in Cancer

Accumulated findings have shown that increased levels of interleukin-6 are reported in the pathophysiology of several persistent inflammatory conditions and in various malignancies. By inhibiting IL-6 signaling, it can provide beneficial treatment opportunities for diseases like autoimmune diseases and cancer (Nilsson et al. 2005;

Mir et al. 2022a, b, c). This can be performed by targeting IL-6, its receptor, or its signaling. There are three main approaches that are currently in use for blocking the signaling mediated by IL-6 at either the ligand level or the receptor level. The first strategy is to directly target the ligand interluekin-6 with antibodies like siltuximab; the second strategy is to directly use antibodies like tocilizumab to target IL-6R; and the third strategy is to directly target the complex of IL-6-soluble interluekin-6 receptor utilizing fusion proteins, including sgp130 that directly prevents trans-signaling. Targeting IL-6 and its receptors prevent traditional signaling and trans-signaling; however, when IL-6/sIL-6R complexes are targeted with sgp130 fusion proteins, only trans-signaling is prevented (Klein et al. 1989, 1991; Puthier et al. 1999; Hideshima et al. 2001; Gislén et al. 2003).

In 2014, after siltuximab underwent effective clinical testing, The US Food and Drug Administration (FDA) authorized it as a means of treating multicentric Castleman illness. Siltuximab is presently the most extensively researched therapeutic drug targeting interleukin-6; it is actually a chimeric antibody of mice and humans (Van Rhee et al. 2010, 2014). However, there are no abundant data showing siltuximab's effectiveness in clinical studies against solid tumors. These data show that inhibiting IL-6 by itself may not have much of an impact on patients with solid tumor prognoses (Angevin et al. 2014; Liu et al. 2016). The development of efficient combination medicines is necessary to address this issue, as is the development of a dependable, strong biomarker that can predict a response (Finkel et al. 2016; Liu et al. 2016; Yanaihara et al. 2016).

A humanized monoclonal antibody called tocilizumab targets the 6R and impairs both trans-signaling and classical signaling. The FDA has approved tocilizumab for use in treating pediatric patients, cytokine release syndrome patients, and patients with systemic juvenile idiopathic arthritis and rheumatoid arthritis. Preclinical research results point to tocilizumab's potential as a treatment for ovarian cancer. A monoclonal antibody sarilumab, which blocks the receptor of IL-6, is presently going through clinical research trails.

Patients with tumors that do not express any or little IL-6R may benefit from selective trans-signaling suppression. Proteins that include the sgp130 sequence bind to interleukin-6 and its receptor there by blocking the construction of the IL-6/IL-6R complex, which is capable of precisely inhibiting trans-signaling (Finkel et al. 2016).

## 5.9 JAK Inhibitors

The most widely examined JAK inhibitors are tofacitinib, ruxolitinib, and pacritinib with numerous other agents under preclinical development. JAK inhibitors have mostly been utilized to treat myeloproliferative neoplasms and chronic inflammatory diseases; patients with solid tumors are currently receiving less attention when taking these medications.

JAK1 and JAK3 are only selectively inhibited by the oral JAK inhibitor tofacitinib, which has a lesser affinity to JAK2. Rheumatoid arthritis can be treated with

tofacitinib, according to the FDA. Other inflammatory disorders being studied clinically for tofacitinib treatment include psoriasis, Crohn's disease, chronic plaque ulcerative colitis, and chronic plaque. Tofacitinib has been FDA-approved for treating individuals at a high or intermediate risk of myelofibrosis and for those with polycythaemia vera that is hydroxyurea-resistant or intolerable. Ruxolitinib is a JAK inhibitor that is oral and selective for JAK1 and JAK2 (Johnson et al. 2018).

## 5.10 STAT3 Inhibitors

In most cases of human malignancies, STAT3 is hyperactivated and has been shown to have tumor-promoting qualities. It is also frequently linked to a bad prognosis for disease. As a result, the current emphasis is on finding and creating STAT3 inhibitors that can be utilized to treat human malignancies. As an intracellular transcription factor, STAT3 lacks enzymatic activity; it is frequently regarded as an intractable target, and the discovery or development of potential STAT3 inhibitors has proven challenging. Several drugs that block STAT3 expression are now under clinical trials.

The first direct inhibitors of STAT3 were made from peptidomimetics (ISS-610, PM-73G) and tyrosine-phosphorylated peptides (PY*LKTK), which attach to STAT3's SH2 domain and reduce DNA-binding activity (205–208) and STAT3 dimerization. These medications have antitumor and proapoptotic effects on cancer cells that have STAT3 hyperactivation. STA-21, LLL-3, WP1066, STATTIC, and other nonprotein inhibitors of the SH2 domain have also been found, and it has been demonstrated that they can stop the growth of tumors that contain high levels of activated STAT3 (Johnson et al. 2018).

The interactions between the promoter regions of the target genes and STAT3 are competitively inhibited as an alternate strategy for suppressing STAT3 function. It has been demonstrated that a 15-bp, double-stranded oligonucleotide matches the response region of STAT3 and that the FOS promoter competitively reduces DNA binding of STAT3 and inhibits the development of tumors in clinical models of ovary, lung, brain, breast, acute myeloid leukemia (AML), and skin cancer. Antisense oligonucleotide inhibition of STAT3 expression further offers quite a different strategy for reducing STAT3 activity in cells. AZD9150 is a next-generation antisense oligonucleotide inhibitor of STAT3, which outperforms its earlier variants by including ethyl-modified residues with a 2′–4′ constraint (Johnson et al. 2018).

## 5.11 Conclusions

Interleukin-6 exhibits both anti- and pro-inflammatory activities, upon its interaction with its receptor isoforms via various modes of IL-6 signaling. In addition to aiding in the development of therapeutic resistance, interleukin-6, which is secreted by tumors and a large number of other cells in the tumor milieu, influences and controls almost every characteristic of cancer. This aids in the advancement and

maintenance of tumors. Our knowledge of the possible involvement of IL-6 in the interaction between the tumor and its milieu has improved as a result of recent investigations. The majority of IL-6's actions that promote tumor growth appear to be primarily regulated by the JAK/STAT3/IL-6 signaling pathway. Therefore, neutralizing IL-6 or the IL-6 receptor to stop the beginning of signaling or preventing the completion in the end by reducing the action of two additional members, JAK and STAT3, has demonstrated treatment effectiveness in systemic and cellular carcinoma models. The stimulation of interleukin-6/STAT3 signaling occurs via classical signaling or trans-signaling. Typically, prolonged inflammation encourages various malignant diseases. The hyperactivation of JAK/STAT3/IL-6 signaling is classically linked to patients' overall reduced survival, as it promotes cancer cell survival, angiogenesis, invasiveness, and metastasis, thus severely suppressing the antitumor activity. Employing agents that block interluekin-6 signaling may be potentially therapeutic for cancer.

**Further Reading**

For further reading, some textbooks mentioned below also provide further understanding of the cytokine and chemokine network.

- *Cytokines and Their Therapeutic Potential* by Manzoor Ahmad Mir
- *The Cytokine Handbook* by Angus W. Thomson and Michael T. Lotze

The below links for video lectures may also be helpful:
https://youtu.be/TAqO0Mq19JQ
https://youtu.be/6wEnYfvoBqk
https://youtu.be/A9fRRCUlMms
https://youtu.be/zIWvmCsKr34

For more insights into the topic, we would suggest detailed findings from the books of Mir et al. (2022a, b, c) https://doi.org/10.1016/C2021-0-02565-7 and https://doi.org/10.1016/C2022-0-00074-X, and Mir (2021) https://doi.org/10.52305/WXJL6770, Mir (2015a, b, c) https://doi.org/10.1016/C2014-0-02898-5, and from the cancer.net website on the following mentioned links:
https://www.cancer.net/cancer-types/breast-cancer/types-treatment
https://discovery.ucl.ac.uk/id/eprint/1472740/
https://www.jmedsciences.com/doi/JMEDS/pdf/10.5005/jp-journals-10045-00138

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