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The emerging role of leukemia inhibitory factor in cancer and therapy

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Abstract

Leukemia inhibitory factor (LIF) is a multi-functional cytokine of the interleukin-6 (IL-6) superfamily. Initially identified as a factor that inhibits the proliferation of murine myeloid leukemia cells, LIF displays a wide variety of important functions in a cell-, tissue- and context-dependent manner in many physiological and pathological processes, including regulating cell proliferation, pluripotent stem cell self-renewal, tissue/organ development and regeneration, neurogenesis and neural regeneration, maternal reproduction, inflammation, infection, immune response, and metabolism. Emerging evidence has shown that LIF plays an important but complex role in human cancers; while LIF displays a tumor suppressive function in some types of cancers, including leukemia, LIF is overexpressed and exerts an oncogenic function in many more types of cancers. Further, targeting LIF has been actively investigated as a novel strategy for cancer therapy. This review summarizes the recent advances in the studies on LIF in human cancers and its potential application in cancer therapy. A better understanding of the role of LIF in different types of cancers and its underlying mechanisms will help to develop more effective strategies for cancer therapy.

Keywords

LIF; cytokine; IL-6 superfamily; cancer; cancer therapy

1. Introduction

LIF is a multi-functional cytokine of the IL-6 superfamily. In addition to LIF, this superfamily also includes IL-6, IL-11, Oncostatin M (OSM), cardiotrophin-1 (CT-1), ciliary neurotrophic factor (CNTF), cardiotrophin-like cytokine (CLC), and IL-27 (Murakami et al.,

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2019; Rose-John, 2018; Yue et al., 2015). LIF was initially identified as a factor that inhibits the proliferation of murine myeloid leukemia M1 cells and induces their terminal differentiation (Gearing et al., 1987; Hilton et al., 1988; Lowe et al., 1989). That is why LIF was named leukemia inhibitory factor. Interestingly, at almost the same time, LIF was also identified as the differentiation-inhibitory factor that maintains the pluripotency of mouse embryonic stem cells and suppresses their differentiation (Smith et al., 1988; Williams et al., 1988), the hepatocyte-stimulating factor III that induces liver cells to produce acute-phase proteins in cultured rat hepatoma cells (Baumann et al., 1987), the cholinergic neuronal differentiation factor (CNDF) that causes neurotransmitter switching in neurons (Yamamori et al., 1989), and the melanoma-derived lipoprotein lipase inhibitor (MLPLI) that blocks the transportation of lipid to adipocytes (Mori et al., 1989). These early studies demonstrated that LIF is a multi-functional cytokine that plays different roles in different cells, tissues and organs.

LIF protein is a monomeric glycoprotein which is often modified by glycosylation. While the molecular weight of the unglycosylated LIF protein is ~20–25 kDa, the molecular weight of the glycosylated LIF is in the range of 37–63 kDa (Metcalf, 2011; Simpson et al., 1988; Yue et al., 2015). LIF exists as a compact four-helix bundle topology stabilized by three disulfide bridges, which is important for receptor binding (Boulanger et al., 2003; Robinson et al., 1994). LIF binds to its heterodimer receptor complex on the cell membrane composed of a LIF receptor (LIFR) and a glycoprotein gp130 (Nicola and Babon, 2015). LIF binds to both gp130 and LIFR with high affinity, and the interaction of LIF with LIFR is ~80-fold tighter than with gp130 (Boulanger et al., 2003; Hilton and Nicola, 1992) (Figure 1A–C). The gp130/LIFR complex is also the receptor for several other IL-6 family members, including OSM, CNTF, CT-1 and CLC, all of which signal through the gp130/LIFR heterodimer (Boulanger and Garcia, 2004). The gp130/LIFR complex is constitutively associated with members of the JAK family of tyrosine kinases (Stahl et al., 1994). When LIF binds to its receptor, the JAK family kinases are rapidly activated to initiate the tyrosine phosphorylation cascade of three major signaling pathways, including the JAK/STAT pathway (Stahl et al., 1994), the MAPK pathway (Thoma et al., 1994) and the PI3K pathway (Fahmi et al., 2013; Oh et al., 1998). It has also been reported that LIF can regulate many other signaling pathways, including the mTOR, PTEN, IGF1, TGF β , FGF, VEGF/HIF-1 α , integrin, estrogen receptor, Notch, Toll/NF- κ B, Wnt/ β -catenin, ephrin and YAP pathways (Chen et al., 2012; Rosario and Stewart, 2016; Wang et al., 2019). Through regulation of these different signaling pathways, LIF is involved in many different physiological and pathological processes, including regulating myeloid leukemia cell differentiation, pluripotent stem cell self-renewal, tissue/organ development and regeneration (e.g. the muscle, kidney, bone, and intestine), neurogenesis and neural regeneration, maternal reproduction, inflammation, infection, immune response, and metabolism (Davis et al., 2019; Nicola and Babon, 2015; Pasquin et al., 2016; Rosario and Stewart, 2016; West, 2019) (Figure 1D). Interestingly, a growing body of studies have reported that LIF also plays an important role in initiation and progression of solid tumors in addition to its role in suppression of leukemia. In this review, we summarize recent advances on the functions of LIF in different physiological processes and diseases, especially in cancer, and the potential application of LIF-related therapies in cancer and other diseases.

2. The multiple functions of LIF in biological processes and diseases

LIF is a multi-functional cytokine that plays a wide variety of important roles in different cells, tissues and organs, including the proliferation and differentiation of leukemia and hemopoietic cells, pluripotent stem cell self-renewal, tissue/organ development and regeneration, neurogenesis and neural regeneration, maternal reproduction, immune response, metabolism, as well as cancer (Figure 1D).

2.1 Proliferation and differentiation of leukemia and hemopoietic cells

Although LIF was initially identified as a factor to inhibit proliferation of myeloid leukemia M1 cells, studies have reported that LIF can promote proliferation of hematopoietic cells. For instance, LIF was reported to potentiate mouse megakaryocyte colony formation stimulated by IL-3 (Metcalf et al., 1991) and stimulate the proliferation of human hematopoietic cell line DA1 and the murine leukemic cell line GB2 (Laabi et al., 2000; Moreau et al., 1987). LIF also enhances the proliferation of hematopoietic stem cells *in vitro* (Escary et al., 1993; Leary et al., 1990), and increases the number of platelets and megakaryocytes in mice (Mayer et al., 1993; Metcalf et al., 1990).

2.2 Pluripotent stem cell self-renewal

In contrast to its differentiating role in murine myeloid leukemia M1 cells, LIF displays a differentiation-inhibitory effect on normal embryonic stem cells in mice, which maintains the pluripotency of embryonic stem cells and stimulates their self-renewal (Williams et al., 1988). The JAK/STAT and PI3K pathways were reported to mediate the effect of LIF on maintaining the pluripotency of mouse embryonic stem cells (Paling et al., 2004; Takahashi et al., 2003; Watanabe et al., 2006). In addition, LIF is necessary for the induction of pluripotent stem cells from mature somatic cells and their self-renewal (Yang et al., 2010). Recently, it was reported that LIF promotes the proliferation of marmoset induced pluripotent stem cells (iPSCs) in cultures, and maintains the iPSC self-renewal by activation of pluripotency-associated transcription factor T-box 3 (TBX3) via the PI3K/AKT signaling pathway (Ke et al., 2018).

2.3 Tissue/organ development and regeneration

LIF is involved in development of different tissues/organs and their regeneration in response to tissue damage or injury. (a) The muscle: LIF promotes proliferation of myoblasts (the precursors of skeletal muscle) and inhibits their differentiation towards myotubes *in vitro* (Austin and Burgess, 1991). LIF deficiency reduces muscle regeneration following muscle injury in mice (Kurek et al., 1997), and LIF infusion promotes skeletal muscle regeneration (Barnard et al., 1994). In mouse models, exercise induces LIF expression in the muscle, and LIF-deficient mice fail to show a hypertrophic response to muscle loading (Sakuma et al., 2000; Spangenburg and Booth, 2006). (b) The kidney: LIF is involved in kidney development and regeneration. LIF is secreted by ureteric buds in the kidney and induces conversion of mesenchyme into epithelium (Barasch et al., 1999). ATP depletion in cultured rat renal epithelial cells (an *in vitro* model of acute renal failure) and ischemia-reperfusion injury in mice both induce LIF expression (Yoshino et al., 2003). Furthermore, inhibition of endogenous LIF by a LIF-neutralizing antibody reduces the cell number and DNA synthesis

during the recovery period after ATP depletion *in vitro* (Yoshino et al., 2003). (c) The bone: LIF also regulates the bone remodeling process to restore damaged regions, maintain calcium levels in blood, and respond to diet and hormones. LIF promotes the differentiation of bone marrow stromal cells to osteoblast lineage and inhibits their differentiation towards adipocytes, which enhances bone formation (Walker et al., 2010). LIF enhances the reconstruction of defected bone by binding to the osteoblast cell surface and induces bone formation both *in vitro* and *in vivo* (Dazai et al., 2000). LIF inhibits apoptosis and promotes the expression of extracellular matrix components in degenerated nucleus pulposus cells, and shows a protective role of LIF in intervertebral disc degeneration, a disease characterized by degeneration of one or more of the discs that separate the bones of the spine (Xiao et al., 2019). Treating degenerated nucleus pulposus cells with recombinant LIF promotes the extracellular matrix synthesis through activation of the MAPK-ERK1/2 pathway (Zhou et al., 2018). (d) The intestine: Recently, using LIF knockout mouse models, we found that LIF regulates function of intestinal stem cells in maintaining the intestinal epithelial homeostasis and intestinal regeneration after radiation-induced damage through the AKT/GSK3 β / β -catenin signaling in mice (Wang et al., 2020b).

2.4 Neurogenesis and neural regeneration

LIF plays an important role in differentiation and regeneration of the nervous system, including both neurons and glia. LIF was reported to switch the production of neurotransmitters from catecholamine to acetylcholine in cultured rat sympathetic neurons (Patterson and Nawa, 1993). LIF promotes the neuron development in the spinal cord and induces neurogenesis with CNTF *in vitro* (Galli et al., 2000; Richards et al., 1992). LIF also acts as a neurotrophic factor for motor and sensory neurons, which plays an important role in neuronal maintenance and axonal regeneration after nerve injuries in rats (Curtis et al., 1994). LIF exerts a neuroprotective effect in a rat model of stroke through inducing the expression of transcription factor myeloid zinc finger-1 (MZF-1) and its downstream target superoxide dismutase 3 (Davis et al., 2019). LIF increases neural stem cell (NSC) populations and enhances NSC self-renewal by inhibiting their differentiation (Bauer and Patterson, 2006; Buono et al., 2012), which contributes to neural regeneration after injury (Tian et al., 2019). LIF-transfected NSCs improves glial cell regeneration and ameliorates white matter injury (Tian et al., 2019). Brain injuries, such as intracerebral hemorrhage, were reported to induce LIF, resulting in reactive astrogliosis with increased glial fibrillary acidic protein (GFAP) mRNA expression (a marker in reactive astrocytes) as well as the reduction of intracerebral hemorrhage-induced neurogenesis and angiogenesis (Liu et al., 2019a; Zhou et al., 2017). In addition, cerebral hypoxia-ischemia induces LIF production by astrocytes within the subventricular zone, which in turn triggers the regenerative response to expand the neural stem/progenitors through the Notch signaling pathway (Felling et al., 2016).

2.5 Maternal reproduction

LIF plays an essential role in maternal reproduction. While LIF knockout in male mice does not affect reproduction, LIF knockout in female mice leads to infertility because of blastocyst implantation failure (Stewart et al., 1992). It was later shown that LIF expression is induced in the uterine endometrial cells at the time of blastocyst formation, which is

crucial for blastocyst implantation (Charnock-Jones et al., 1994). Further studies showed that LIF has several additional functions that regulate reproduction. For instance, LIF induces the expression of the EGF family of growth factors (e.g. amphiregulin, epiregulin and heparin-binding EGF-like growth factor) (Song et al., 2000), implantation genes (e.g. Msx-1 and Wnt-4) (Daikoku et al., 2004), and junction proteins (e.g. L-selectins, E-cadherins, claudin and occludin) (Satterfield et al., 2007; Sharma and Kumar, 2012), which contributes to the preparation of the endometrium for the blastocyst implantation. LIF is also important for decidualization and leukocyte recruitment during the blastocyst implantation (Guzeloglu-Kayisli et al., 2009; Shuya et al., 2011). LIF promotes the synthesis of prostaglandins, an important mediator of implantation and decidualization, through increasing the expression of IL-1 and cyclooxygenase-2 (Fouladi-Nashta et al., 2008; Horita et al., 2007; Song et al., 2000). Interestingly, our previous studies showed that LIF is a direct target gene of tumor suppressor p53 and mediates the function of p53 in regulation of maternal reproduction in both mice and humans (Hu, 2009; Hu et al., 2007; Kang et al., 2009). p53 plays a central role in tumor suppression mainly through its function as a transcription factor, and p53 is frequently mutated in human cancers (Levine, 2019; Liu et al., 2019b; Zhang et al., 2020). Our previous study showed that p53 knockout female mice display impaired maternal reproduction due to reduced LIF levels during implantation resulted from loss of p53, which can be restored by administering recombinant LIF protein to p53 knockout female mice at the implantation stage (Hu et al., 2007). We further showed that p53 and estrogen receptor α are activated and coordinately induce LIF expression in endometrial tissues during implantation to ensure the proper blastocyst implantation (Feng et al., 2011). p53 codon 72 single nucleotide polymorphism (SNP; R72 or P72) is the most common SNP in the p53 gene that influences p53 activity and is associated with the cancer risk (Barnoud et al., 2019; Zhao et al., 2018). Analysis of a list of SNPs in the p53 pathway and the LIF gene in the *in vitro* fertilization (IVF) patients, we found that the p53 P72 allele and some SNPs in the LIF gene are enriched in IVF patients as risk factors for recurrent implantation failure, supporting the role of p53 and LIF in human reproduction (Kang et al., 2009). A recent report shows that LIF also regulates male reproductive ability; LIF induces cFOS and represses the gonadotropin-releasing hormone (GnRH) gene in neurons, leading to reduction of GnRH neuron spine density specific for male mice and sex-specific impairment in reproductive function (Lainez and Coss, 2019).

2.6 Infection, inflammation and immune response

(a) Immune response: Many studies have shown that LIF regulates immune response. An early study showed that LIF is essential for normal thymic architecture and LIF knockout mice display reduced responsiveness of their thymocytes to the mitogen concanavalin A (Escary et al., 1993). It was later reported that regulatory T cells (Tregs) produce high levels of LIF, which in turn induces the production of Tregs by increasing the expression of the Treg lineage transcription factor Foxp3 and decreasing the expression of T helper type 17 cell lineage transcription factor ROR γ t (Gao et al., 2009; Metcalfe, 2011). Thus, LIF appears to be tolerogenic by promoting Treg differentiation and inhibiting T helper type 17 cell differentiation (Gao et al., 2009; Metcalfe, 2011). LIF also modulates the maturation of dendritic cells (DCs), leading to the development of semi-mature and tolerogenic DCs, which helps establish the immunosuppressive environment (Yaftiyan et al., 2019). (b)

Inflammation: LIF is also induced in response to inflammatory stimulation in macrophages and switches macrophages from a pro-inflammatory to an anti-inflammatory phenotype (Davis et al., 2018; Jeannin et al., 2011). A recent study further showed that in response to pro-inflammatory stress factors, LIF inhibits IFN γ and granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced activation of STAT1 and STAT5 in macrophages, and inhibits macrophage cell motility via STAT3 and matrix metalloproteinase 9 (MMP-9) (Hamelin-Morrisette et al., 2020). (c) Infection: LIF contributes to immune response to viral and bacterial infections. LIF is upregulated in the placenta from HIV-1-infected women and inhibits HIV-1 replication in placenta and thymus tissues, suggesting a role of LIF in innate immunity against viral infections (Patterson et al., 2001). In response to respiratory syncytial virus infection, LIF is induced to protect the lung from lung injury and enhanced pathology during the viral infection (Foronjy et al., 2014). LIF also plays a critical role in lung tissue protection in bacterial pneumonia; LIF is induced in lung epithelial cells via the NF- κ B pathway to improve tissue resilience during pneumonia (Traber et al., 2017).

2.7 Metabolism

LIF has been reported to regulate metabolism. Earlier studies identified LIF as a lipoprotein lipase inhibitor, suggesting a role of LIF in metabolism, especially in lipid metabolism (Marshall et al., 1994; Mori et al., 1989). Injection of recombinant LIF in mice causes significant weight loss (Metcalf et al., 1990). In cultured adipocytes, LIF treatment promotes lipolysis by inhibiting lipoprotein lipase activity, suggesting that LIF may induce weight loss through its catabolic effects (Marshall et al., 1994). Furthermore, LIF induces fatty acid oxidation and glucose uptake via the PI3K pathway and mTORC2 in the skeletal muscle, which may contribute to the fat loss effect of LIF (Brandt et al., 2015). High-fat diet induces the downregulation of LIF expression in the brain stem (Licursi et al., 2016), and hypothalamic expression of LIF protects mice from the development of diet-induced obesity (Fioravante et al., 2017). LIF also regulates the differentiation of adipocytes. Interestingly, different effects of LIF on the differentiation of adipocytes have been reported in different cell lines. For instance, LIF was reported to promote adipocyte differentiation in the mouse preadipocytes Ob1771 and 3T3-F442A cell lines (Aubert et al., 1999), but show minimal effects on adipocyte differentiation in the mouse 3T3-L1 cell line (Hogan and Stephens, 2005; White et al., 2008), and even prevent adipogenesis in bone marrow stromal cells (Gimble et al., 1994). Interestingly, a recent study reported that LIF can differentially regulate the early and late stages of adipocyte differentiation through its differential regulation of the Wnt signaling pathway; while LIF promotes proliferation and recruitment of preadipocytes from multipotent mesenchymal stem cells at the early stage of adipocyte differentiation, it promotes differentiation of preadipocytes into mature adipocytes at the late stage of adipocyte differentiation (Ikeda et al., 2016).

As summarized above, LIF plays important roles in a variety of physiological and pathology processes, and exerts its functions in a highly cell type-, tissue type-, and development stage-dependent manner through regulation of different signaling pathways (Figure 1D).

3. LIF and cancer

3.1 The role of LIF in cancer

A growing body of studies have shown a complex role of LIF in cancer. Although LIF was initially identified to inhibit the proliferation of leukemia cells, studies have indicated an oncogenic function of LIF in many different types of solid tumors. LIF was found to be frequently overexpressed in many types of solid tumors, including colorectal cancer (Yu et al., 2014), breast cancer (Li et al., 2014; Quaglino et al., 2007), pancreatic cancer (Peng et al., 2014; Shi et al., 2019; Wang et al., 2020a), melanoma (Kuphal et al., 2013; Maruta et al., 2009), osteosarcoma (Liu et al., 2015a), nasopharyngeal carcinoma (Liu et al., 2013a), prostate cancer (Liu et al., 2019c), cholangiocarcinoma (Wang et al., 2016), oral squamous cell carcinoma (OSCC) (Lin et al., 2020), and endometrial carcinoma (Xiao et al., 2015). Furthermore, high LIF expression has been reported to correlate with poor prognosis in patients with different types of cancers, including pancreatic adenocarcinoma, nasopharyngeal carcinoma, prostate adenocarcinomas, cholangiocarcinoma, OSCC, colorectal cancer, and breast cancer (Li et al., 2014; Lin et al., 2020; Liu et al., 2013a; Liu et al., 2019c; Wang et al., 2020a; Wang et al., 2016; Yu et al., 2014). Many studies using *in vitro* cell culture systems and animal models have reported that LIF overexpression promotes cancer cell proliferation, metastasis, immune evasion, stemness, resistance to therapy, and cachexia in different types of solid tumors (Figure 2).

(1) Cell proliferation—Overexpression of LIF in cancers has been reported to promote proliferation of cancer cells through different mechanisms and signaling pathways. (a) The STAT3 pathway: LIF promotes proliferation of choriocarcinoma cells through activation of the STAT3 signaling (Fitzgerald et al., 2005). LIF promotes the growth of lung tumors through activation of STAT3 signaling in the Gprc5a^{-/-} mouse lung tumor model (Chen et al., 2010). LIF was also reported to promote tumor growth in human osteosarcoma via activating the STAT3 signaling (Liu et al., 2015a). (b) The p53/MDM2 pathway: We found that LIF promotes proliferation and chemoresistance of colorectal cancer cells using both *in vitro* cell culture systems and xenograft tumor models through inhibition of tumor suppressor p53 (Yu et al., 2014). Mechanistically, LIF activates STAT3 to transcriptionally induce expression of ID1, a helix-loop-helix protein inhibitor of differentiation and DNA binding, to transcriptionally upregulate MDM2, the most critical negative regulator of p53, to ubiquitinate and degrade p53 (Yu et al., 2014). (c) The mTOR pathway: Our previous study also revealed that LIF promotes growth and metastasis of xenograft breast tumors through activating the AKT/mTOR pathway (Li et al., 2014). LIF was also found to activate the mTORC1/S6K signaling pathway to promote tumor growth, inhibit DNA damage responses and enhance radioresistance in Epstein-Barr virus (EBV)-associated nasopharyngeal carcinoma (Liu et al., 2013a). (d) IL-8: LIF promotes proliferation of pancreatic cancer cells through the induction of IL-8 (also called CXCL-8), a cytokine that has been shown to play an important role in promoting tumor progression in a variety of human cancers (Kamohara et al., 2007b). (e) BMP4/7: In malignant melanoma, LIF promotes cell proliferation and colony formation mainly through inducing the expression of bone morphogenetic proteins 4 and 7 (BMP4 and BMP7), two secreted ligand proteins of the TGF- β superfamily which play important roles in bone formation and promoting the

progression of various types of cancers (Kuphal et al., 2013). (f) YAP: Recently, LIF was reported to promote proliferation of pancreatic cancer cells through activation of the YAP signaling pathway (Wang et al., 2019). (g) MicroRNAs (miRNAs): miRNAs play an important role in tumorigenesis through regulation of gene expression (Hayes et al., 2014; Liu et al., 2017). LIF has been reported to regulate miRNAs to promote proliferation of cancer cells. For instance, LIF represses the expression of miR-141, a miRNA that attenuates embryonic stem cell differentiation and epithelial-mesenchymal transition (EMT) of breast cancer cells, to promote proliferation of choriocarcinoma JEG-3 cells (Morales-Prieto et al., 2011). LIF treatment induces miR-181c, which downregulates the levels of N-Myc downstream-regulated gene 2 (NDRG2), to promote proliferation, chemoresistance, and metastasis of cholangiocarcinoma cells (Wang et al., 2016). Interestingly, NDRG2 can inhibit LIF transcription through disrupting the binding of Smad complex to the LIF promoter (Wang et al., 2016).

(2) Migration, invasion and metastasis—LIF has been shown to play an important role in promoting migration, invasion and metastasis in different types of cancers. (a) STAT3, AKT and mTOR pathways: As we mentioned above, LIF can activate different pathways, including STAT3, AKT and mTOR pathways, which mediate the promoting effect of LIF on migration, invasion and metastasis of cancer cells. For instance, LIF can promote migration, invasion and metastasis of cancer cells through activating STAT3 signaling in choriocarcinoma and osteosarcoma, activating the AKT/mTOR signaling in breast cancer, inducing expression of BMP4 and BMP7 in malignant melanoma, and inducing miR-181c to downregulate NDRG2 expression in cholangiocarcinoma (Fitzgerald et al., 2005; Kuphal et al., 2013; Li et al., 2014; Liu et al., 2015a; Wang et al., 2016). (b) Cancer-associated fibroblasts (CAFs): In addition to being secreted by cancer cells to regulate cancer cells in an autocrine fashion, LIF is also secreted by CAFs, the activated fibroblasts present in the cancer stroma that play a crucial role in cancer progression and metastasis, and regulates cancer cells in a paracrine fashion (Yoshida, 2020). It was reported that LIF produced by CAFs promotes cancer cell migration and invasion in a paracrine fashion in OSCC (Ohata et al., 2018). (c) The TGF- β signaling: A recent study identified that the Inhibin Subunit Beta A (INHBA), a modulator of TGF- β signaling pathway, is a crucial downstream effector of LIF that mediates the function of LIF in promoting metastasis of OSCC (Lin et al., 2020). In addition, LIF can be induced by TGF- β in both fibroblasts and cancer cells to mediate TGF- β -dependent actomyosin contractility and extracellular matrix remodeling in fibroblasts, resulting in pro-invasion microenvironment to promote cancer metastasis *in vitro* and *in vivo* (Albregues et al., 2014). (d) Epithelial-mesenchymal transition (EMT): LIF can regulate the EMT to promote metastasis. Previously, we found that LIF induces the expression of oncomiR miR-21 through activation of the STAT3 signaling to promote EMT in breast cancer cells, and blocking miR-21 function greatly reduces the promoting effect of LIF overexpression on EMT and the migration ability of breast cancer cells (Yue et al., 2016). Recently, it was reported that LIF secreted from pancreatic stellate cells (PSCs) promotes the EMT of pancreatic cancer cells in pancreatic ductal adenocarcinoma (PDAC), contributing to metastasis of PDAC (Shi et al., 2019). (e) Neural remodeling: LIF was also reported to promote tumor metastasis through regulating neural remodeling in tumors (Bressy et al., 2018). Emerging evidence has shown that intratumoral nerves promote tumor progression;

tumor cells promote the growth of nerves in the tumor microenvironment, and in return nerves release neurotransmitters to promote tumor proliferation and metastasis (Venkatesh and Monje, 2017). LIF secreted from stromal cells in PDAC promotes neural remodeling, which is characterized by high nerve densities in PDAC due to peripheral nerve fiber infiltration and axonogenesis. Mechanistically, LIF induces the differentiation and migration of glial nerve sheath Schwann cells via the JAK/STAT3/AKT signaling and promotes neuronal plasticity of ganglia neurons in the dorsal root in PDAC, leading to the increase of nerve density and neural remodeling in PDAC to promote cancer proliferation and metastasis (Bressy et al., 2018). (f) Hippo-YAP signaling pathway: LIF can inhibit the activity of the Hippo pathway by reducing the phosphorylation of YAP and increasing YAP nuclear translocation, resulting in the increased metastasis in gastric cancer (Bian et al., 2020). In addition, LIF was also reported to promote cancer vascular dissemination and local invasion through modulation of YAP1-FAK/PXN signaling in nasopharyngeal carcinoma (Liu et al., 2018).

(3) Immune evasion—Recent studies have revealed an important role of LIF in immune evasion of cancer. The immune system has the potential to recognize and eliminate cancer cells, and evasion of immune surveillance contributes to cancer development (Waldman et al., 2020). (a) Macrophage colony-stimulating factor: It was reported that ovarian cancer ascites contains high concentrations of LIF and IL-6 that can switch monocyte differentiation into tumor-associated macrophage (TAM)-like cells by increasing macrophage colony-stimulating factor consumption (Duluc et al., 2007; Jeannin et al., 2011). (b) Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs): LIF induces the expansion and activation of PMN-MDSCs in Toll-like receptor 9 (TLR9) positive prostate cancers to promote immune evasion (Won et al., 2017). It was reported that blood samples from patients with prostate cancer display increased expression levels of LIF and LIFR in circulating PMN-MDSCs, and furthermore, the LIF expression is positively correlated with TLR9 in prostate cancer specimens (Won et al., 2017). (c) CCL2/CXCL9: In addition, LIF increases CCL2 expression to promote the recruitment of TAMs, and reduces CXCL9 expression to inhibit CD8⁺ T cell tumor infiltration, leading to immune evasion (Pascual-Garcia et al., 2019).

(4) Stemness—LIF can modulate stemness of cancer stem cells to promote tumor progression via different mechanisms. (a) BMP4/7: In malignant melanoma, LIF induces the expression of BMP4 and BMP7, as well as the classical stem cell proteins, such as SOX2, NANOG, OCT3/4 and GBX2, to enhance cancer stem cell-like behavior, which in turn promotes melanoma progression (Kuphal et al., 2013). (b) STAT3: Ovarian carcinoma-associated mesenchymal stem cells produce high levels of LIF, resulting in the elevated the percentage of ovarian cancer stem-like cells and cancer cell stemness through activating the STAT3 signaling, which promotes tumor growth (McLean et al., 2019). Notably, IL-6 plays a redundant role with LIF in regulating ovarian carcinoma-associated mesenchymal stem cells, and therefore, blocking LIF and IL-6 signaling simultaneously shows a stronger inhibitory effect on the pro-tumorigenic activity of ovarian carcinoma-associated mesenchymal stem cells than blocking LIF only (McLean et al., 2019). (c) Notch1: In osteosarcoma, LIF promotes activation of stemness-related genes through the Notch1

signaling pathway, thereby conferring tumor cells with stem cell-like characteristics, such as the increased sphere-forming potential, stimulated self-renewal, and enhanced metastasis ability (Lu et al., 2020).

(5) Therapeutic resistance—(a) mTOR, p53 and miR-181c: As mentioned above, LIF has been reported to promote resistance of cancer cells towards cancer therapies in different types of cancers with different mechanisms, including activation of the mTORC1/S6K signaling pathway in nasopharyngeal carcinoma to enhance radioresistance, inhibition of p53 tumor suppressive function in colorectal cancer to promote chemoresistance, and induction of miR-181c expression in cholangiocarcinoma to promote chemoresistance (Liu et al., 2013a; Wang et al., 2016; Yu et al., 2014). (b) Mcl-1: LIF protects cholangiocarcinoma cells from chemotherapeutic agents-induced apoptosis through the PI3K/AKT-dependent myeloid cell leukemia 1 (Mcl-1) activation (Morton et al., 2015). (c) EMT: The EMT of pancreatic cancer cells induced by LIF from pancreatic stellate cells (PSCs) may also contribute to the impaired efficacy of chemotherapy in PDAC (Shi et al., 2019). (d) Others: In addition, it was reported that LIF increases resistance of endometrial cancer cells to cisplatin and paclitaxel, two widely-used cancer chemotherapeutic agents (Ruan et al., 2020). LIF can also promote resistance of prostate cancer cells to enzalutamide, an androgen receptor inhibitor often used for the androgen deprivation therapy (ADT) in prostate cancer (Liu et al., 2019c). However, their underlying mechanisms are not clear yet.

(6) Cancer cachexia—LIF has been reported to play an important role in cancer cachexia. Cancer cachexia is a multifactorial syndrome with systematic loss of body weight mainly caused by reduction of adipose and muscle mass, as well as chronic inflammation, anorexia, and fatigue (Baracos et al., 2018). Cachexia occurs in ~50% of cancer patients, and cancer patients with cachexia often display poor response to cancer therapies, including chemotherapy and radiotherapy, and have increased treatment toxicity (Baracos et al., 2018). (a) Lipoprotein lipase: In an early study, LIF was identified as a lipoprotein lipase inhibitor from the melanoma cell line SEKI that reduces the intake of fatty acids by adipocytes to promote lipid catabolism in adipose tissues, leading to cancer cachexia in mice (Mori et al., 1989). In line with this finding, later studies reported that intracerebral injection of human epidermoid carcinoma A431 cells, ovarian carcinoma OVCAR3 cells, and glioma GBLF cells (Negri et al., 2001) and subcutaneous injection of thyroid cancer Thena cells in mice (Chang et al., 2003) result in high levels of LIF in serum, which leads to cachexia. (b) JAK2/STAT3: A recent study using C26 mouse colorectal carcinoma cells showed that LIF is elevated in the C26 conditioned medium *in vitro* and the serum of mice bearing C26 xenograft tumors, which induces atrophy in the cultured myotubes and in the muscle of mice (Seto et al., 2015). Furthermore, treatments with the LIF neutralizing antibody or JAK2 inhibitors, or overexpression of a dominant negative STAT3, can block the atrophy in myotubes caused by C26 conditioned medium or the atrophy in the mouse muscle caused by C26 tumors, which indicates that the LIF-JAK2-STAT3 signaling is important for cachexia induced by colon carcinoma (Seto et al., 2015). (c) Adipose triglyceride lipase (ATGL): Recently, it was also reported that LIF induces ATGL-mediated lipolysis through activation of the JAK/STAT signaling in adipocytes and leads to loss of the adipose tissue and body

weight, which contributes to cachexia and can be counterbalanced by downregulating the leptin signaling (Arora et al., 2018).

(6) Tumor suppression function of LIF—While LIF displays an oncogenic effect in most types of solid tumors, LIF was also reported to show a tumor suppressive effect in some special tumor types in addition to its well-known function in inhibiting the proliferation of murine myeloid leukemia M1 cells and inducing their terminal differentiation (Gearing et al., 1987; Hilton et al., 1988; Lowe et al., 1989). (a) Gastric cancer: Although LIF is overexpressed in many types of solid tumors as mentioned above, interestingly, LIF was reported to be downregulated in some gastric cancers, and furthermore, its downregulation is associated with advanced clinical stage, lymph node metastasis, and poor overall survival in gastric cancer patients (Xu et al., 2019). LIF also displays anti-cancer stem cell properties in gastric cancer through activation of LATS1/2 Hippo kinases, thereby decreasing downstream YAP/TAZ nuclear accumulation and TEAD transcriptional activity (Seeneevassen et al., 2020). (b) Medullary thyroid carcinoma: While activation of Ras/Raf/MEK/ERK pathway often promotes cell proliferation, sustained activation of this pathway has also been reported to lead to cell cycle arrest (Park et al., 2003). In medullary thyroid carcinoma, activation of Ras/Raf/MEK/ERK pathway induces LIF expression and secretion, which in turn leads to growth arrest and differentiation through activation of the JAK/STAT3 pathway in both autocrine and paracrine manners (Park et al., 2003). Studies also showed that LIF can suppress progression of medullary thyroid carcinoma through inducing cell cycle arrest in G0/G1 phase and reducing RET and E2F1 expression in both cultured cells and xenograft tumor models (Arthan et al., 2010; Park et al., 2003; Starenki et al., 2013). (c) Cervical cancer: Additionally, in cervical cancer cells, LIF treatment decreases human papillomavirus (HPV) long control region activation and reduces HPV E6 and E7 mRNA levels, which in turn suppresses proliferation of cervical cancer cells (Bay et al., 2011).

Taken together, these results indicate that LIF can impact tumorigenesis in a highly tumor type-specific manner. While LIF displays an oncogenic effect in most types of solid tumors by promoting proliferation, metastasis, immune evasion, stemness, cachexia, and therapeutic resistance, LIF can also show a tumor suppressive effect in some special tumor types (Figure 2).

3.2 LIF regulation in cancer

LIF overexpression has been observed in many types of solid tumors, and different mechanisms have been reported to contribute to LIF overexpression.

(1) Epigenetics—It was reported that LIF expression is epigenetically upregulated via DNA demethylation and changes in histone methylation status within the promoter region of the LIF gene (Shin et al., 2011). While the CpG sites in the LIF promoter region are hypermethylated in normal breast epithelial cells, they are often extensively demethylated during breast tumorigenesis (Shin et al., 2011). The levels of methyl-CpG-binding protein (MeCP2) occupancy and histone H3-Lys9-dimethylation (hallmarks for transcriptional repression) are significantly decreased in the LIF promoter region during breast

tumorigenesis, while the level of H3-Lys4-dimethylation (a hallmark for transcriptional activation) is increased within the LIF promoter region at the same time (Shin et al., 2011). Recently, it was reported that the histone H3-Lys27-trimethylation demethylase UTX, which sustains the proliferation of cancer cells, impairs histone H3-Lys27-trimethylation accumulation and induces histone H3-Lys27-acetylation at the LIF gene locus, leading to increased LIF expression and LIF-mediated expression of the stemness-related genes (Lu et al., 2020).

(2) Stresses and oncogenes—(a) Hypoxia: Our study found that LIF expression can be induced in colorectal cancer by hypoxia, a condition that often exists in solid tumors (Wu et al., 2015). Hypoxia in colorectal cancer stabilizes hypoxia inducible factor 2 α (HIF-2 α), leading to the binding of HIF-2 to the two hypoxia-responsive elements in the LIF promoter region to enhance the transcription of LIF (Wu et al., 2015). (b) TGF- β : TGF- β also induces LIF expression and activates the JAK/STAT pathway in a Smad-dependent manner in glioma-initiating cells, which is responsible for the initiation and recurrence of glioma (Penuelas et al., 2009). Furthermore, TGF- β induces the production and secretion of LIF in many different types of cancer cells and fibroblasts (Albregues et al., 2014). (c) STAT5: LIF was also reported to be directly transcriptionally regulated by STAT5 in myeloid cell lines; STAT5 binds to the LIF promoter to induce LIF expression following the activation of the JAK2/STAT5 pathway (Salas et al., 2011). (d) Oncogenic proteins: LIF expression can also be regulated by some oncogenic proteins. For example, LIF expression is induced by oncogenic KRAS (e.g. KRAS G12D) through the MEK/ERK signaling pathway in PDAC (Wang et al., 2019). ZBTB46, a lineage-specific transcription factor that is crucial for EMT and metastasis of prostate cancer, binds to the promoter region of the LIF gene and induces LIF expression to promote tumor growth and therapeutic resistance in prostate cancer (Liu et al., 2019c). Interestingly, androgen deprivation therapy induces LIF expression through upregulation of ZBTB46 in ADT-resistant prostate cancer (Liu et al., 2019c), suggesting that some cancer therapies can induce LIF expression in cancers and in turn promote cancer progression (e.g. therapeutic resistance). Zinc Finger E-Box Binding Homeobox 1 (ZEB1) was reported to promote EMT and display an oncogenic effect in many cancers, including colorectal cancer, breast cancer, pancreatic cancer, osteosarcoma, lung cancer, etc. (Drapela et al., 2020; Liu et al., 2015b). Interestingly, a recent study reported that ZEB1 deletions were observed in more than 50% of glioblastomas and 15% in low grade gliomas (grade II and grade III) with frequent loss of heterozygosity (Edwards et al., 2017). Furthermore, ZEB1 binds to the promoter region of LIF and represses LIF expression in glioma cancer stem cells, which in turn inhibits glioma cancer stem cell self-renewal and promotes their differentiation (Edwards et al., 2017). It is unclear whether ZEB1 can also repress LIF expression in other types of tumors in addition to glioblastomas and low-grade gliomas.

(3) Inflammation and infection—It was reported that in pancreatic carcinoma cells pro-inflammatory cytokines, such as LIF itself, TNF- α , IL-1 β , IL-6, and IL-8, induce LIF mRNA. The induction of LIF mRNA by LIF treatment can be inhibited by inhibitors of protein kinase C (PKC), protein tyrosine kinase (PTK) and Ca²⁺/Calmodulin. While the precise mechanisms underlying these regulations are still unclear, these observations suggest that inflammatory cytokine network may alter the expression of LIF through these pathways

in the tumor microenvironment (Kamohara et al., 2007a). Additionally, in EBV-associated nasopharyngeal carcinoma, EBV-encoded protein latent membrane protein 1 (LMP1) can induce LIF production through activation of the NF- κ B pathway by its C terminus-activating regions to promote tumorigenesis (Liu et al., 2013a).

(4) Tumor suppressors—Our previous study showed that LIF is a direct transcriptional target of tumor suppressor p53 (Hu et al., 2007). p53 binds to the p53-binding element in the first intron of the LIF gene to upregulate the basal LIF expression levels in various tissues of mice, including the uterine. p53 deficiency reduces the uterine LIF levels at the blastocyst implantation stage, resulting in impaired implantation and infertility in the p53 deficient female mice (Hu et al., 2007). It was also reported that p53 induces LIF expression in medulloblastoma (Baxter and Milner, 2010). Knockdown of WIP1 or SIRT1, which stabilizes and activates p53, was reported to enhance LIF expression and induce apoptosis in medulloblastoma (Baxter and Milner, 2010).

In sum, the regulation of LIF in cells appears to be complicated; LIF is regulated by epigenetic modifications, different stress signals and cytokines in the microenvironment, and some oncogenic transcription factors, as well as the tumor suppressors (e.g. p53). The accurate regulation of LIF by different mechanisms in different cells and tissues in a highly context-dependent manner contributes to the complex functions of LIF in both physiological and pathological processes.

4. The therapeutic role of LIF in cancer and other diseases

4.1 The therapeutic application of LIF in cancer

(1) Neutralizing antibodies—Given the important role of LIF in cancer progression in many solid tumors, LIF has the direct potential to be developed as a therapy target for cancers (Figure 3A). As a cytokine that functions through binding to the gp130/LIFR on cell membrane, LIF signaling has been shown to be blocked by LIF-neutralizing antibodies that efficiently antagonize many of LIF's functions in many different studies (Chen et al., 2013; Fischer et al., 2014; Mao et al., 2016; Nogueira-Silva et al., 2012; Terakawa et al., 2011). The LIF neutralizing antibody has been shown to suppress the proliferation of different cancer cell lines in cultures (Kellokumpu-Lehtinen et al., 1996). The LIF-neutralizing antibody also inhibits the osteoclast recruitment by the mouse tumor cells, which is important for bone metastasis of tumors, to suppress tumor metastasis (Akatsu et al., 1998). Our previous study also showed that the LIF-neutralizing antibody can block the promoting effect of LIF on migration and invasion of breast cancer cells (Li et al., 2014). Moreover, it was reported that the LIF-neutralizing antibody blocks the STAT3 activation and proinvasive extracellular matrix remodeling in stroma fibroblasts, which leads to the inhibition of cancer cell invasion (Albregues et al., 2014). Similarly, the LIF neutralizing antibody was shown to inhibit OSCC migration and invasion induced by LIF produced by normal human dermal fibroblasts (Ohata et al., 2018). The LIF-neutralizing antibody was also reported to reduce the percentage of tumor-infiltrating PMN-MDSCs and inhibit prostate tumor growth in mice (Won et al., 2017). Injection of the LIF-neutralizing antibody into PDAC-bearing mice was reported to reduce the intratumoral nerve density in PDAC and limit the tumor-promoting

effect of the neural remodeling on PDAC progression (Bressy et al., 2018). In addition, the LIF-neutralizing antibody was shown to abolish C26 conditioned media-induced STAT3 activation and myotube atrophy, suggesting the potential role of the LIF-neutralizing antibody in treating cancer cachexia (Seto et al., 2015).

Since LIF promotes the therapeutic resistance in cancer, the combination of LIF-neutralizing antibodies with other treatments for cancer has been reported to display a more effective therapeutic effect in some cancers. For instance, in the PDAC mouse model, the LIF-neutralizing antibody treatment slows the tumor progression, augments chemotherapy efficacy of gemcitabine, and prolongs the survival of mice (Shi et al., 2019). Similarly, the LIF-neutralizing antibody synergizes with gemcitabine to repress the pancreatic tumor progression in a pancreatic xenograft model, a syngeneic KRAS G12D-driven PDAC mouse model, and in patient-derived xenografts as well (Wang et al., 2019). The LIF-neutralizing antibody also increases CXCL9 expression in TAMs and induces CD8+ T cell tumor infiltration in immunocompetent mouse models of glioblastoma and ovarian cancer, which in turn suppresses tumor growth and improves survival of mice (Pascual-Garcia et al., 2019). Further, treating glioblastoma with the LIF-neutralizing antibody and the PD1 immune checkpoint antibody leads to tumor regression, immunological memory and increased overall survival of mice (Pascual-Garcia et al., 2019). A phase I clinical trial was initiated in patients with advanced solid tumors, include NSCLC, ovarian cancer, and pancreatic cancer using a humanized anti-LIF monoclonal antibody MSC-1 (Hyman et al., 2018).

(2) Small molecule inhibitors and other strategies to targeting LIF—In addition to the LIF-neutralizing antibody, LIF inhibitors are being developed to target LIF in cancers. Two first-in-class inhibitors, EC359 and EC330, have been shown to competitively inhibit LIFR complex by occupying LIF-binding site (Viswanadhapalli et al., 2019; Yue et al., 2020). EC359 and EC330 treatment attenuates the activation of the STAT3, mTOR, and AKT pathways by LIF, leading to the inhibited proliferation, increased apoptosis and reduced invasiveness and stemness of breast cancer cells, and inhibition of growth of breast cancer xenografts and patient-derived breast xenografts (Viswanadhapalli et al., 2019; Yue et al., 2020). EC359 was also reported to inhibit the activation of pancreatic cancer stroma in combination with gemcitabine in an organoid model generated by murine pancreatic cancer FC1245 cells and pancreatic stellate ImPaSC cells (Hall et al., 2019). EC330 was also reported to inhibit the development of ADT-resistant prostate cancers and is associated with neuroendocrine differentiation after the ADT, which induces LIF expression (Liu et al., 2019c). It is noted that while EC359 blocks LIF/LIFR signaling, it can also block the signaling of other LIFR ligands (e.g. CTF1, CNTF, and OSM) that interact at LIF/LIFR interface (Viswanadhapalli et al., 2019). Interestingly, a recent study showed that immunizing BALB/c mice with truncated mouse LIF and LIFR proteins as antigens can suppress tumor formation of breast cancer initiating cells derived from mouse MC4-L2 breast cancer cells in mice, with LIFR immunization showing a more superior effect than LIF immunization, suggesting that LIF and LIFR might be effective targets for immunotherapy of the tumors with overexpression of LIF and LIFR (Ghanei et al., 2020).

(3) Recombinant LIF—As mentioned above, LIF shows a growth inhibitory effect on medullary thyroid carcinoma (Arthan et al., 2010; Park et al., 2003; Starenki et al., 2013). Administration of the recombinant LIF locally or systemically was shown to effectively suppress grow of xenografts established by medullary thyroid carcinoma cells in mice, which suggests that LIF can be used as potential anti-cancer agent for medullary thyroid carcinoma (Starenki et al., 2013). It was also shown that the recombinant LIF downregulates p21 and cyclin D1 in gastric cancer cells, and overexpression of LIF delays the progress of gastric cancer xenografts, suggesting that administration of recombinant LIF might be a potential strategy to treat gastric cancers with decreased LIF expression (Xu et al., 2019).

4.2 LIF as a potential cancer biomarker

LIF is overexpressed in many types of solid tumors, and LIF is also secreted into the serum, which make LIF a potential biomarker for some types of tumors. For example, LIF serum levels were found to be elevated in nasopharyngeal carcinoma patients, and the high LIF levels are correlated with a high risk of local tumor recurrence and radioresistance of tumors, suggesting that serum LIF levels can be used as a biomarker to predict local recurrence and radioresistance of nasopharyngeal carcinoma (Liu et al., 2013a). In the serum from human PDAC patients and PDAC mice, LIF levels are positively correlated with intratumoral nerve density, which suggests that LIF is a candidate serum biomarker and diagnostic tool for PDAC (Bressy et al., 2018). In line with this observation, another study reported that LIF levels in the pancreas correlate with PDAC differentiation status as well as overall survival of PDAC patients, and furthermore, the changes in the levels of circulating LIF correlate with tumor response to therapy (Shi et al., 2019). A recent study also reported that higher tumor grade and metastatic prostate cancers exhibit higher LIF levels in patient serum, which suggests that LIF can be used as a serum biomarker for advanced prostate cancer (Liu et al., 2019c). However, the elevation of serum LIF levels can be caused not only by cancer cells and/or cancer surrounding tissues but also by other factors, such as infection and inflammation that are frequently observed in other diseases in addition to cancers, which may limit the application of the levels of serum LIF in early tumor diagnosis and tumor outcome prediction. Therefore, many more studies, especially clinical studies, are needed to further test the potential application of the levels of serum LIF as a biomarker for cancer.

4.3 The therapeutic application of LIF in other diseases

As a multi-functional cytokine involved in many fundamental physiological and biological processes and diseases, therapeutic application of LIF has also been suggested for many diseases in addition to cancer (Figure 3B). For example, satellite cells are stem cells in the skeletal muscle that can be used for transplantation therapy. Recombinant LIF treatment was reported to promote the proliferation of muscle satellite cells *in vitro*, maintain their undifferentiated states, and enhance their transplantation efficiency, which contributes to the optimization of culture conditions for cell transplantation therapy to several muscle diseases, including Duchenne muscular dystrophy (Ito et al., 2016; Spangenburg and Booth, 2002). In mouse models of spinal cord disease (motor neuron disease) and spinal cord injury, systemic administration of LIF was found to increase the number of neural precursor cells (Azari et al., 2005). LIF-transfected NSCs improve glial cell regeneration and ameliorate white matter injury in rats with middle cerebral artery occlusion, which suggests that LIF-transfected

NSCs could be a potential treatment for cerebral infarction (Tian et al., 2019). Our recent study showed that LIF promotes regeneration of the intestinal epithelium in response to radiation and protects against radiation-induced gastrointestinal syndrome in mice (Wang et al., 2020b).

LIF plays an essential role in implantation and reproduction, which has suggested the potential application of LIF in the prediction and treatment for impaired reproduction. We have shown that the SNPs of the LIF gene and genes in p53 pathway that regulate LIF can help the prediction of the success of in vitro fertilization with recurrent implantation failure in patients (Kang et al., 2009). Similar associations were found in patients with recurrent pregnancy loss (Fraga et al., 2014). A recent study also reported the possibility to predict recurrent implantation failure by polymorphisms of the LIF and estrogen receptor-1 genes (Vagnini et al., 2019). LIF is downregulated in recurrent implantation failure patients with the abnormally increased endometrial KLF12, and exogenous LIF reverses the KLF12-mediated repression of BeWo spheroid adhesion, which suggests that LIF administration is a potential therapeutic strategy for recurrent implantation failure (Huang et al., 2018).

Multiple sclerosis, a non-curable demyelinating disease, is characterized by focal areas of inflammation with defacement of myelin and myelin-producing cells (oligodendrocytes and astrocytes) (Metcalf, 2018). TNF- α was reported to stimulate astrocytes to secrete LIF, which in turn induces production and maturation of oligodendrocytes from precursor cells and enhances oligodendrocyte remyelination of axons in the mouse hippocampus after cuprizone-induced demyelination (Deverman and Patterson, 2012; Fischer et al., 2014). In a multiple sclerosis mouse model, treating mice with LIF-overexpressing Wharton's jelly stem cells leads to the reduction of brain lesions and brain cellular infiltration (Hosseini et al., 2017). Parkinson's disease, a neurodegenerative disease, is characterized by the progressive loss of dopaminergic neurons in the substantia nigra. Cell-based neurogenic therapeutic strategies using endogenous NSCs to repair damaged neurons are potential treatments for Parkinson's disease (Katz and Skalka, 1990). In line with the function of LIF in enhancing self-renewal of NSCs, LIF treatment improves the motor functions in the Parkinson's disease mouse model induced by 6-hydroxydopamine, which suggests a potential therapeutic role of LIF in Parkinson's disease (Liu et al., 2013b).

5. Summary and perspectives

As summarized above, LIF displays different functions in different cells, tissues, and organs under different conditions and at different development stages through different mechanisms. While LIF displays an oncogenic effect in many solid tumors, LIF displays a tumor suppressive effect in leukemia and some special types of solid tumors. Further, different signaling pathways are involved in mediating the complex role of LIF in tumorigenesis. The different biological outcomes of LIF might be caused by many different reasons, including different levels and status of the gp130/LIFR complex, different levels of other IL-6 family cytokines especially those sharing the same receptor complex with LIF, different status of downstream signaling pathways that mediate LIF functions, and different levels and status of the proteins and enzymes that are regulated by LIF and carry out the functions of LIF in different types of cells and tissues and under different circumstances. To

make the situation more complicated, LIF is not only produced by cancer cells and functions in an autocrine manner, but also produced by the tumor microenvironment and functions in a paracrine manner.

With more and more studies showing the important role of LIF in tumorigenesis, targeting LIF has become a promising therapeutic strategy for many cancers with LIF overexpression. LIF-neutralizing antibodies as a single agent or in combination with other treatments has been shown as a potential new strategy for cancer treatment. Currently, majority of these studies are still at the pre-clinical stage, and further studies to optimize the condition of LIF-neutralizing antibodies for clinical use are necessary. Small molecule inhibitors present another potential strategy to target LIF in cancers. However, the specificity and potency of these small molecule inhibitors need to be improved for clinical use. The other potential strategies to target LIF-overexpressing cancers include blocking LIF overexpression and/or blocking the critical signaling pathways that mediate the oncogenic effects of LIF in cancers. Given the complex role and mechanism of LIF in cancers, a better understanding of the mechanism underlying LIF overexpression and the downstream signaling pathways of LIF in different cancers is necessary for developing more effective strategies targeting LIF in cancers. As indicated by many studies, LIF itself (recombinant LIF) has the direct potential to be used for treating some special tumor types in which LIF displays a tumor suppressive function as well as some other diseases (e.g. recurrent implantation failure, the brain and nerve injury, multiple sclerosis and Parkinson's disease, etc.). However, majority of these studies are based on cell culture systems and animal models, and there are only a limited number of clinical trials that are mainly focused on fertility. More studies on animal models and clinical trials are required to test the potential application of recombinant LIF in these afore-mentioned diseases. Given that LIF can have different effects on different types of cells and tissues, it is important to develop specific strategies for targeted delivery of recombinant LIF or LIF inhibitors to specific cells and tissues for clinical treatments.

In summary, while accumulating studies have indicated that LIF plays an important but complex role in many physiological and pathological processes, the precise role and mechanism of LIF in these processes are far from clear. A better and more sophisticated understanding of the role and mechanism of LIF in these processes will be crucial for future application of targeting LIF in treating cancers and other diseases.

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Abbreviations List

ADT	androgen deprivation therapy
BMP	bone morphogenetic proteins
CAF	cancer-associated fibroblast

CLC	cardiotrophin-like cytokine
CNTF	ciliary neurotrophic factor
CT-1	cardiotrophin-1
EMT	epithelial-mesenchymal transition
ERK	extracellular signal related kinase
gp130	glycoprotein 130
HIF	hypoxia inducible factor
IFN	interferon
IL	interleukin
iPSC	induced pluripotent stem cell
JAK	Janus kinase
LIF	Leukemia inhibitory factor
LIFR	LIF receptor
MAPK	mitogen-activated protein kinase
MEK	MAPK/ERK kinase
mTOR	mechanistic target of rapamycin
mTORC	mTOR complex
NDRG2	N-myc downstream-regulated gene 2
NSC	neural stem cell
OSCC	oral squamous cell carcinoma
OSM	Oncostatin M
PDAC	pancreatic ductal adenocarcinoma
PMN-MDSC	polymorphonuclear myeloid-derived suppressor cell
α-SMA	alpha-smooth muscle actin
SNP	single nucleotide polymorphism
SOCS3	suppressor of cytokine signaling 3
STAT	signal transducer and activator of transcription
TAM	tumor-associated macrophage
TGF	transforming growth factor

TLR	Toll-like receptor
Treg	regulatory T cell

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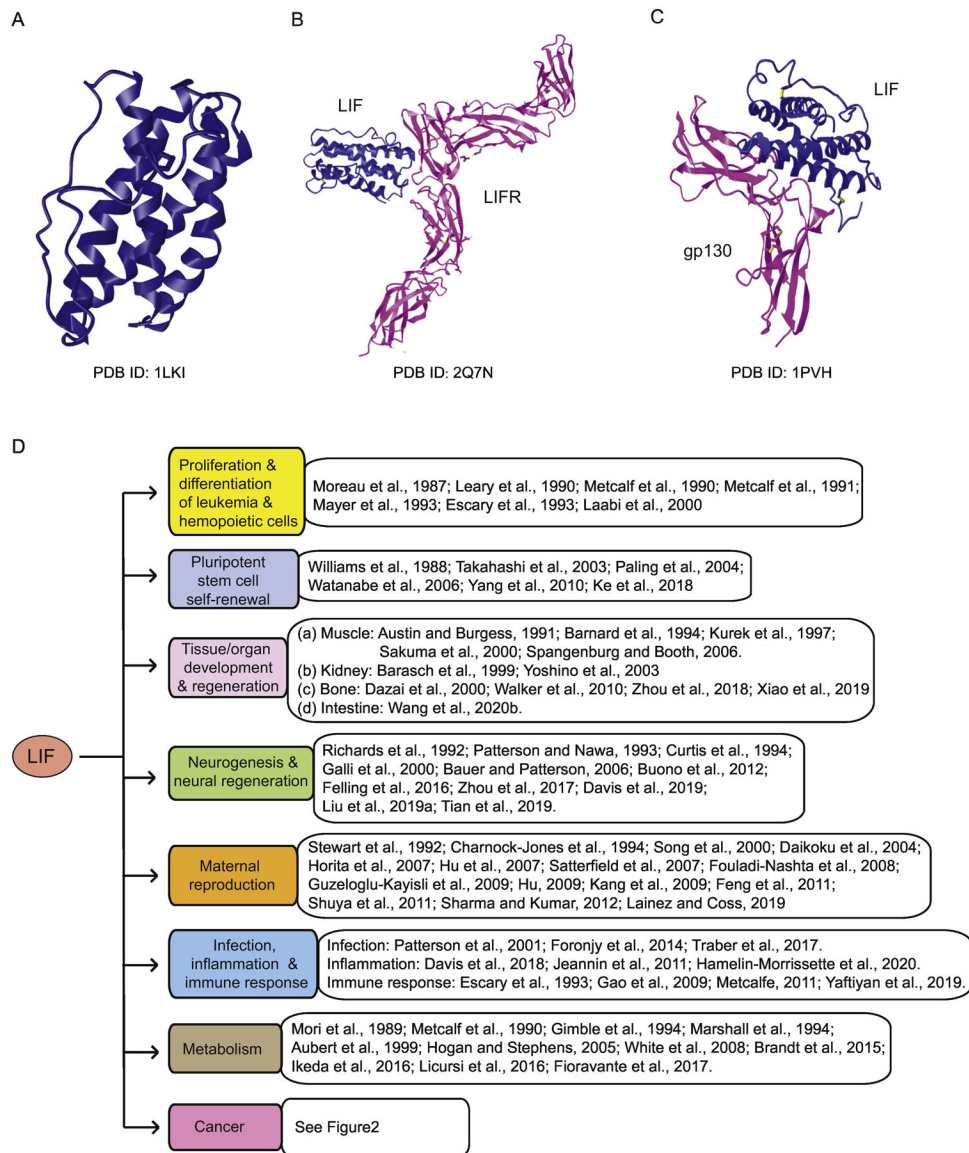


Figure 1. LIF is a multi-functional cytokine.

(A) The crystal structure of LIF protein. (B) The crystal structure of LIF-LIFR complex. (C) The crystal structure of LIF-gp130 complex. A-C: from Protein Data Bank (PDB, <https://www.ncbi.nlm.nih.gov/Structure/pdb/>). (D) As a multi-functional cytokine, LIF regulates many different physiological and pathological biological processes.

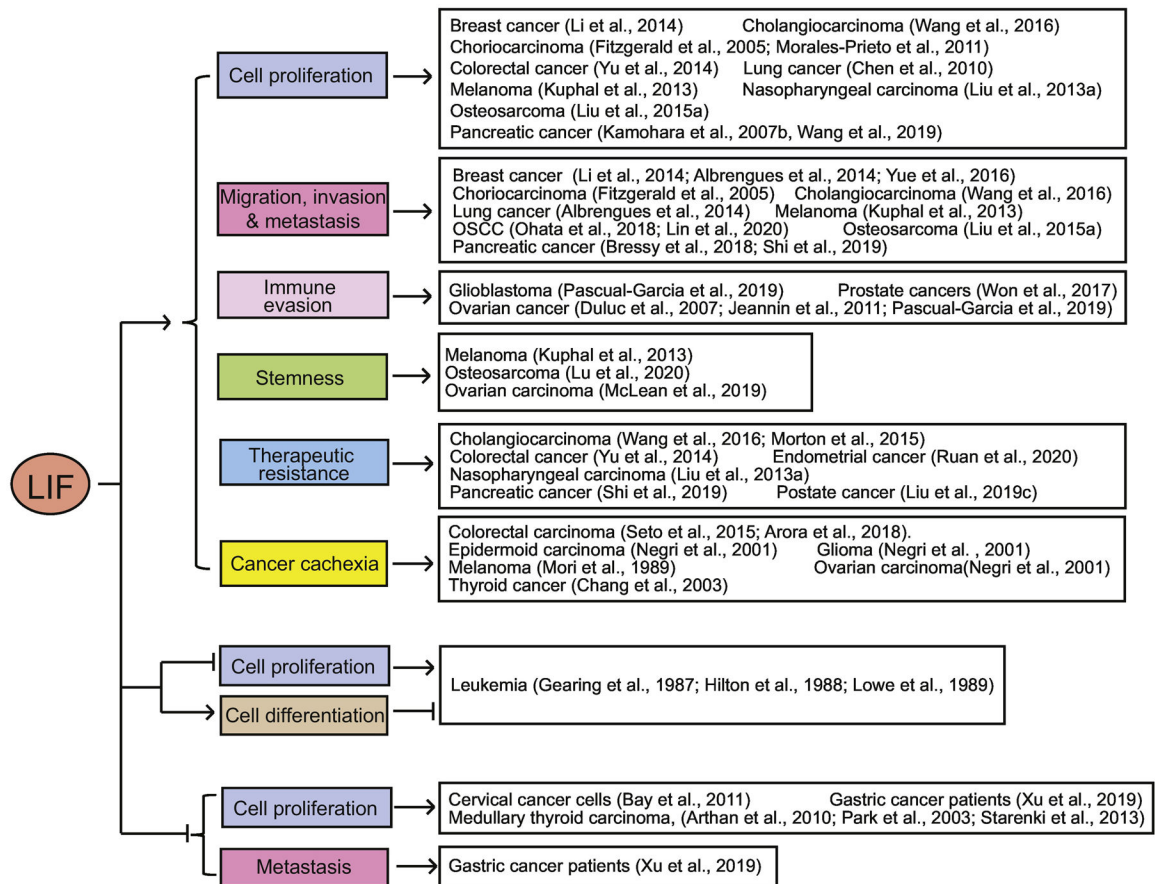


Figure 2. The complex role of LIF in human cancers.

LIF promotes proliferation, metastasis, immune evasion, stemness, and therapeutic resistance of cancer cells, as well as cancer cachexia in many different types of solid tumors. On the contrary, LIF inhibits tumorigenesis in leukemia and some special types of solid tumors, such as gastric cancer, medullary thyroid carcinoma, and cervical cancer.

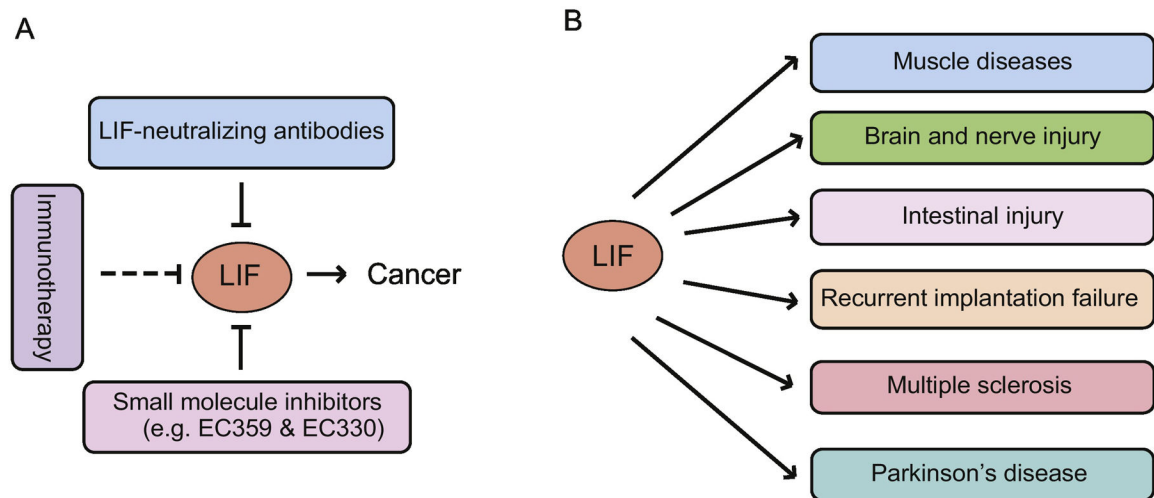


Figure 3. The potential therapeutic application of LIF in human cancers and other diseases.

(A) The therapeutic strategies targeting LIF in cancers include LIF neutralizing antibodies, small molecule inhibitors, and immunotherapy. (B) In addition to cancer, LIF can also be used to treat muscle diseases, brain and nerve injury, intestinal injury, recurrent implantation failure, multiple sclerosis, and Parkinson's disease.