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The Pleiotropic role, functions and targeted therapies of LIF/LIFR axis in cancer: Old spectacles with new insights

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Abstract

The dysregulation of leukemia inhibitory factor (LIF) and its cognate receptor (LIFR) has been associated with multiple cancer initiation, progression, and metastasis. LIF plays a significant tumor-promoting role in cancer, while LIFR functions as a tumor promoter and suppressor. Epithelial and stromal cells secrete LIF *via* autocrine and paracrine signaling mechanism(s) that bind with LIFR and subsequently with co-receptor glycoprotein 130 (gp130) to activate JAK/STAT1/3, PI3K/AKT, mTORC1/p70s6K, Hippo/YAP, and MAPK signaling pathways. Clinically, activating the LIF/LIFR axis is associated with poor survival and anti-cancer therapy resistance. This review article provides an overview of the structure and ligands of LIFR, LIF/LIFR signaling in developmental biology, stem cells, cancer stem cells, genetics and epigenetics of LIFR, LIFR regulation by long non-coding RNAs and miRNAs, and LIF/LIFR signaling in cancers. Finally, neutralizing antibodies and small molecule inhibitors preferentially blocking LIF interaction with LIFR and antagonists against LIFR under pre-clinical and early-phase pre-clinical trials were discussed.

Keywords

LIF; LIFR; gp130; EC359; LIFR-AS1

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1. Introduction

Leukemia inhibitory factor (LIF) receptor (LIFR) is a transmembrane receptor that facilitates the signaling action of its corresponding ligands such as LIF, oncostatin M (OSM), Ciliary Neurotrophic Factor (CNTF), and cardiotrophin 1 (CT1) in various pathological conditions mainly in cancer progression and advancing to metastasis. LIFR is overexpressed and associated with cancer progression, angiogenesis, regulation of stem cells, and developmental systems [1–4]. Among LIFR ligands, LIF is overexpressed and demonstrated to exert a tumor-promoting role and functions in multiple solid cancers, including breast, prostate, endometrial, nasopharyngeal, gastric, colorectal, osteosarcoma, melanoma, pancreatic, and lung cancer [2,6–14]. Recently, the context and cancer type-specific role of LIFR has been explored in multiple cancers, including prostate, gastric, colorectal, breast, endometrial, pancreatic, and lung cancers [1,2,12,13,15–20]. Briefly, Leukemia inhibitory factor (LIF) is a pleiotropic cytokine closely related to the interleukin-6 (IL-6) cytokines family. It is a glycoprotein with a molecular weight ranging from 38 to 67 kDa, depending on the length of the glycosylation pattern, while its unglycosylated protein varies from ~20 to 25 kDa. LIF was first purified from a serum-free conditioned medium from L929 normal fibroblast cell lines isolated from mouse subcutaneous tissues [21]. The name LIF was given based on its mode of growth-inhibitory action and its ability to differentiate myeloid leukemic M1 cells into macrophages and granulocytes [22,23]. Similarly, purified polypeptides from the Buffalo rat liver also displayed a similar inhibitory activity on murine embryonic stem cell differentiation [24]. In addition, LIF also can synergize in cellular differentiation with granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) [25]. Although LIF was initially named based on its inhibitory and suppressive role on Leukemic cells, its growth-promoting activity was later established based on several studies performed on various cancers [2,5–14]. Seminal review articles detailed LIF's role in proliferation, migration, invasion, angiogenesis, inflammation, immune response, metabolism, cancer stemness, metastasis, and cancer-associated cachexia [11,26]. LIF exerts its signaling mechanism by binding with a heterodimeric cell membrane-associated receptor complex comprising of LIF receptor (LIFR) and glycoprotein 130 (gp130). LIFR depends on gp130 to execute the LIF mediated action due to the absence of intrinsic tyrosine kinase activity. Most commonly, LIF binding with LIFR-gp130 complex promotes signaling via Janus kinases (JAK) and Src-homology-2 (SH2) domain-containing signal transducer and activator of transcription 3 (STAT3) pathway. Notably, LIF/LIFR/JAK/STAT signaling is not exclusive to LIF autocrine/paracrine signaling. Specifically, when LIF is exposed to LIFR/gp130 complex, the heterodimer activates JAK kinase, which phosphorylates STAT3 transcription factor on tyrosine residue 705 (Y705). LIFR and its cognate ligands can bind with LIFR in homodimer, heterodimer and oligodimerization (Fig. 1 B).

2. Structure and ligands of LIFR

The LIFR gene is located between 5p12 and p13 in the human chromosome, and similar homology was localized to the proximal region of chromosome 15 of the mouse genome. When the *LIFR* gene was mapped, Gearing *et al.* had identified that both human and mouse *LIFR* locus had a close association with genes encoding three other cytokine receptors

related to growth hormone (GH), prolactin (PRL), and interleukin-7 (IL-7) receptors [27]. The biological function and signaling of cytokines will be initiated upon binding to its cognate receptor present in the cell membrane. These cytokine receptors possess one or more cytokine-receptor domains (CRDs), which hold ligand specificity. The CRDs are composed of two or more fibronectin (FN) type-III-like motifs having cysteine residues and a short-conserved sequence of WSXWS motifs in distal and proximal transmembrane regions, respectively [28]. Similarly, human *LIFR* comprises 20 exons with exon 1 coding for 5' untranslated region followed by exon 2 encoding for a signal peptide with an ATG translation initiator codon. Exon 3–11 (except exon 7) encodes for the cytokine receptor homology domains 1 and 2 (CRH1 and CRH2). The exon 7 encodes for an immunoglobulin-like domain (Ig-like domain). As specified about CRDs in general, Exon 12–17 in *LIFR* possess 3 FN type-like domains specific for LIFR ligands (LIF, OSM, CNTF, and CTF1). Exon 18 codes for the transmembrane domain, followed by exon 19 and 20 coding for the cytoplasmic region, translation termination sequence, and 3' untranslated region (Fig. 1A).

LIFR has multiple ligands, with LIF being the most important IL-6 family member with high affinity. Other IL-6 family ligands, including OSM, CNTF, CT1, and cardiotrophin-like cytokine (CLC), can also regulate signaling by forming a heterodimeric complex consisting of LIFR with gp130 or trimeric complex of LIFR/gp130/CNTFα receptor (CNTFR) [29,30]. These ligands were shown to bind to the Ig-like domain present between CRH1 and CRH2. Specifically, LIFR N-terminus contains the FXXK motif, which is required to bind with all of these ligands on the Ig-like domain of LIFR [31] (Fig. 1A). Recently, another FAM3 cytokine-family member was identified as a ligand for LIFR, namely: interleukin-like EMT inducer (ILEI) [32]. In the same study, the authors identified that ILEI/LIFR signaling activates STAT3 signaling to promote epithelial to mesenchymal transition (EMT) phenotype [32]. Therefore, studies comparing the binding specificity of LIF and various LIF-related ligands (OSM, CNTF, CT1, ILEI) interaction with the specific receptors such as LIFR, oncostatin M receptor (OSMR), CNTFα-receptor (CNTFR) are required by mutating the ligand-receptor interacting region/domain such as extracellular, transmembrane, type III fibronectin, and cytokine receptor homology domains (Fig. 1B).

3. Genetics and epigenetic alterations associated with *LIFR*

Mutation in *LIFRβ* is associated with a rare genetic and developmental disease known as Stűve-Wiedemann syndrome (STWS). This disorder is an autosomal recessive trait with poor survival of the affected infants for up to 1 year [33]. Most infants affected with STWS will show reduced bone density, hypotonia, hyperthermia, and respiratory distress. Children who survive with STWS may develop skeletal deformities, fractures, underdeveloped chin and jaws, facial deformities, protruding and socket eyes, bowing of long bones, etc. [34–36]. The incidence of STWS differs globally, with the disease being more common in the United Arab Emirates (1 out of every 20 000 childbirths). The appropriate frameshift mutation in the LIFR gene was identified in exon 3 duplication at c.l44_145dupGG (p.A49Gfs*6) [34]. In another STWS patient, a duplication of 22 nucleotides in exon 4 was associated with the emergence of premature stop codon resulting in *LIFR* mRNA instability. In addition, deletion of nine nucleotides with exon 12 of the LIFR gene leads to LIFR protein instability [36]. Thus, frameshift or nucleotide deletion mutation in the LIFR gene affects LIFR

protein stability, thereby revocating the JAK/STAT3 pathway, which is required for human development. In a pan-cancer analysis, we inquired about the mutation status of both LIF and LIFR. Across all cancers, none of the mutations had a high frequency (Fig. 2A and B) [153,154]. Apart from a gene mutation, epigenetic alterations play a vital role in cancer progression and advancements. Recently, a study evaluated mutation, promoter methylation, and expression status of LIFR in breast cancer patients. The authors reported that *LIFR* is highly downregulated in breast cancer tissues compared with normal breast tissues. Among the analyzed breast cancer patients, the absence of LIFR mRNA expression was significantly associated with ER status, HER2 positivity, and advanced stages (III and IV) of breast cancer relative to normal breast controls. Subsequently, in immunocytochemistry analysis on serial sections of breast cancer tissues from the same patient also showed corresponding loss/absence of LIFR protein (67.15%, 92/137). The remaining 32.85% of breast cancer cases displayed moderate to high LIFR protein expression, whereas the normal cases displayed mild to moderate expression. In all these cases, LIFR protein expression was predominantly localized to the nucleus of cancer and normal breast cells. They also showed that this loss of LIFR protein has coincided with LIFR promoter methylation and significant association with clinicopathological parameters such as PR status, molecular subtype, histological grade, and tumor stage of breast cancer. Mutation analysis using partial electropherograms showed a mutation in exon 20 with missense mutation of G2968C (Glu>Glu) at the 990th codon [37]. A previous study by Chen *et al.* demonstrated that under-expressed LIFR protein had a strong and significant inverse association with breast cancer lymph node metastasis [16]. A previous study by Okamura and colleagues also demonstrated that *LIFR* is lost in hepatocellular carcinoma tissues relative to normal tissues. This diminishment is not due to gene deletion or loss of heterozygosity (LOH) but due to promoter hypermethylation of the LIFR gene [38]. Interestingly, LIFR reduced expression was correlated with altered DNA methylation in H-35 rat hepatoma cells. In this study, the authors demonstrated that treatment with DNA methyltransferase inhibitor 5-aza-2’-deoxycytidine reactivates *LIFR* transcription and increases the responsiveness of rodent hepatoma cells to IL-6 eliciting LIFR function [39]. A study by Loewen *et al.* also validates the enhancement of LIFR level and LIF responsiveness upon histone deacetylase inhibition using depsipeptide underlying the epigenetic control of LIFR expression by depsipeptide histone acetylase in human bronchial epithelial cells [40]. Consistent with these findings, *LIFR* promoter methylation in CpG islands was identified in colorectal cancer (CRC) cell lines and colorectal cancer tissues excised from patients. In contrast, the normal colon mucosa tissues, HCT116 CRC cells, and human embryonic kidney cells (HEK293) showed strong LIFR gene and protein expression [41]. Indeed, identification of tumor-associated CpG methylation sites using targeted bisulfite PCR sequencing analysis in multiple cancer cells revealed hypermethylation of CpG sites in the *LIFR* promoter in colon cancer cells compared to lung, liver, biliary, and gastric cancer cell lines [42]. All these accumulating evidences show that aberrant epigenetic changes associated with the *LIFR* promoter could be one of the mechanisms regulating the LIF/LIFR axis in cancer progression.

4. LIFR regulation by miRNAs and long non-coding RNAs

The function of the LIFR depends not only on downstream signaling activity but also on the ability of cells to regulate the transcription of LIFR expression. Such regulation in pathological conditions has therapeutic value because it has been progressively upregulated under disease conditions. Hence, a thorough understanding of the regulatory mechanisms of LIFR is imperative. MiRNAs and Non-coding RNAs play a significant role in transcriptional regulation and are gaining prominence because of tissue-specificity. MicroRNAs such as miR-21-5p, miR-93, miR-182, miR-200b, miR-221-3p miR-377-3p, miR-543, miR-589, miR-629-3p, and miR-637 have been recently found to regulate LIFR expression. Global miRNA profiling was performed on matched specimens of the primary tumor, metastasis, and normal adjacent breast tissue from breast cancer patients. Among the differentially expressed miRNAs, the study identified that miR-629-3p was significantly higher in primary and metastatic breast tumor samples [43]. Furthermore, miRNA binding site enrichment analysis identified LIFR as the only possible binding partner predicted to bind with miR-629-3p. Subsequently, 3'-UTR analysis of LIFR revealed that LIFR bound to the miR-629-3p seed region and abrogated the post-transcriptional function of miR-629-3p [43]. Another extensive bioinformatic characterization of adenosine-to-inosine RNA editing strategy identified miRNA 19 hotspots across 20 different cancer types [44]. In the same study, miR-200b editing activity showed a significant difference between normal and tumor samples. Interestingly, 3'-UTR prediction and biological validation revealed that edited miR-200b could bind to LIFR and lead to tumor and metastasis suppressor function of breast cancer cells [44]. Similarly, another miRNA target gene prediction analysis identified miR-377-3p as a predictive partner of LIFR during adipogenic differentiation of bone marrow-derived mesenchymal stem cells [45], where miR-377-3p overexpression is shown to inhibit LIFR levels. In gastric cancer, LIFR was demonstrated to be a downstream target of miR-21-5p [46].

The ubiquitous transcription factor c-Jun involves numerous tumor cell functions and activities. Studies have shown that c-Jun regulates gene expression through post-translational modifications, RTK signaling, and feed-forward regulation [47]. Consequently, a recent study revealed that the oncogenic miR-589 could upregulate LIFR to activate downstream PI3K/AKT/c-Jun signaling. Interestingly, c-JUN, in turn, binds to the miR-589 promoter region and activates miR-589 transcription [48]. Using The Cancer Genome Atlas (TCGA) breast cancer data set, Luo *et al.* [49] showed 37 differentially expressed miRNAs. Further, by using the competing endogenous RNA Network analysis, the authors showed that LIFR-hsa-miR-21-5p-ADAMTS9-AS1 interaction in the early breast tumor development. In addition, long non-coding RNA-CTD210809.1 interacts with LIFR and suppresses metastasis in breast cancer [50].

In hepatocellular carcinoma (HCC), miR-221-3p was identified as an upstream regulator of LIFR [51], where overexpression of miR-221-3p enhanced cellular proliferation, invasion, and migration of HCC cells. Supportively, the altered expression of miR-221-3p prevented LIFR binding and the tumor functional properties on HCC cells [51]. LIF increases the expression of miR-181c, which targets and downregulates the expression of N-myc downstream-regulated gene-2 (NDRG2) and promotes cholangiocarcinoma cell

proliferation, metastasis, and chemoresistance. A negative feedback mechanism operates by which NDRG2 downregulates LIF expression by inhibiting the binding of the SMAD complex to the promoter region of LIF [52].

In addition to the microRNA and IncRNAs, circRNAs play a significant role in tumor progression. Non-coding RNAs, either short (18–23 bp) or long (> 200 bp), regulate gene expression at transcriptional and post-transcriptional levels *via* diverse mechanisms. One of the first studies which described the dysregulated putative IncRNA and miRNA regulation of LIFR has been shown in HCT116 colorectal cancer cells. When HCT116 cells were treated with photodynamic therapy (PDT), IncRNA leukemia inhibitory factor receptor antisense RNA1 (LIFR-AS1) emerged among the top 5 differentially upregulated IncRNAs among 624 upregulated IncRNA from a total of 1096 dysregulated IncRNAs that were screened. The IncRNA-miRNA pairing results revealed that LIFR-AS1 negatively regulates miR-29a in CRC cells. Further, shRNA-mediated depletion of IncRNA LIFR-AS1 attenuated CRC cell apoptosis and enhanced resistance against PDT. Conversely, inhibition of miR-29a reversed LIFR-AS1 suppression in CRC cells [53]. In a seminal study, LIFR-AS1 knockdown in breast cancer (BC) cells promoted proliferation, colony growth, and migration phenotype. Notably, LIFR-AS1 was found to interact with miR-197-3p to upregulate the suppressor of the fused gene (Sufu) in BC cells. The authors also found that the tumor-suppressive effect of LIFR-AS1 could be reversed by treating with a miR-197-3p specific inhibitor in BC cells [54]. Wang *et al*. identified the tumor-suppressive role of LIFR-AS1 by sponging miR-942-59 in non-small cell lung cancer (NSCLC) cells. Specifically, the authors demonstrated that forced overexpression or depletion of *LIFR-AS1* influenced NSCLC cells' motility *(in vitro*) and metastasis *(in vivo)*. To sum up, LIFR-AS1 also plays a tumor-suppressive role in NSCLC, and its downregulation significantly correlates with poor clinical outcomes [55]. Later, a study by Chen and colleagues showed an opposing role of LIFR-AS1 as a tumor promoter in pancreatic cancer. Upregulation or increased expression of LIFR-AS1 correlates with tumor size, advanced TNM stage, and PC metastasis. Mechanistically, LIFR-AS1 elevates VEGFα/PI3K/AKT axis by directly interacting with miR-150-5p [56]. Wang *et al*. reported similar tumor-promoting effects of LIFR-AS1 in gastric cancer (GC). Quantitative PCR-analysis revealed that *LIFR-AS1* is highly expressed in gastric cancer tissues relative to normal adjacent to tumor tissues and is significantly associated with tumor size, TNM stage, lymphatic metastasis, and overall survival of GC patients [57]. Supportively, a recent study also demonstrated an increase in *LIFR-AS1* in GC tissues and cells by regulating its downstream target miR-29a-3p. They identified common binding sites between LIFR-AS1 and miR-29a-3p, and further, with the aid of *in silico* tools, they discovered common binding sites between miR-29a-3p and type I collagen COL1A2. Overall, the study showed that miR-29a-3p/COL1A2 regulates the function of *LIFR-AS1* to promote GC progression [58]. LncRNA-LOWEG increases the translation of LIFR in Gastric cancer [59]. Intriguingly, the biological function of the same *LIFR-AS-1* is opposite and different in GC cells. Bioinformatics analysis of TCGA data specific for GC showed downregulation of *LIFR-AS-1* in GC tissue relative to normal gastric tissues. Overexpression of *LIFR-AS-1* in GC cells reduced GC cell viability, migration, and wound healing capacity [60]. Ding *et al*. found that overexpression of *LIFR-AS-1* could suppress proliferation migration and reduce temozolomide resistance in glioma

cells by controlling miR-4262-mediated NF-κB signaling [61]. In a recent study, *LIFR-AS1* downregulation was correlated with clinicopathological outcomes of papillary thyroid cancer (PTC) patients. Like previous gastric cancer studies, ectopic overexpression of IncRNA *LIFR-AS1* decreased proliferation, growth, and migration by sponging miR-31-5p to upregulate SID1 transmembrane family member 2 (SIDT2). Silencing IncRNA *LIFR-AS1* in PTC cells resulted in the opposite functional effect [62]. Conflicting research in thyroid cancer (TC) cells has shown that silencing of *LIFR-AS1* reduced viability and proliferation by inducing cell cycle arrest at the G2/M phase and affected TC cells' migratory capacity by downregulating MMP 2 and MMP 9 expressions [63]. Thus, it would be meaningful to analyze both *LIFR-AS1* expressions in tissues and their biological behavior in respective cancer cells to find an association between clinical impact and its correlation *in vitro* and *in vivo* functions.

Interestingly, in prostate cancer (PCa), long non-coding RNAs (LncRNA) activated in metastatic prostate cancer (IncAMPC) are shown to be involved in PCa progression [64]. In PCa cells, IncAMPC upregulates LIF levels through miR-637 sponging in the cytoplasm, whereas in the nucleus, IncAMPC enriched LIFR transcript levels, thereby activating LIF/LIFR-mediated PCa metastasis and maintaining PD-L1-mediated immunosuppression. In lung adenocarcinoma, LIFR is regulated by miR-182 and miR-93 mediated by a CRIM1 amplicon (circ_0002346) [65]. In HCC, using *in silico* analysis, luciferase reporter assays, and RNA pulldown approaches, Gu *et al.* [66] showed that circular RNA circARPP21 acts as a sponge to regulate miR-543 which in-turn, controls LIFR expression in the absence of circARPP21. Where circARPP21 overexpression increased LIFR by sponging LIFR expression through endogenous inhibition of miR-543 [66]. Similarly, circ_0001073 was shown to indirectly dictate the regulatory role of miR-626 on LIFR expression [20], where miR-626 overexpression reduced cell proliferation and invasion and increased apoptosis in lung cancer cells through LIFR up-regulation [20]. In GC cells, ectopic expression of circ_0003159 affects viability, migration, and promotes apoptosis. In this study, miR-221-3p and miR-222-3p emerged as common regulators of circ_0003159 and LIFR. Furthermore, LIFR depletion reversed the functional effects of circ_0003159 overexpression [67]. Overall, these studies imply that LIFR can be regulated by miRNA/lncRNA/circRNA and vice versa through various mechanisms in different cancers, as briefly discussed in Table 1.

5. LIF/LIFR in developmental biology

The exact role of LIF and its association with embryonic development was first confirmed by its capacity to induce embryonic stem (ES) cell proliferation while maintaining its totipotent ability [68]. Upon binding with its ligand LIF in ES cells, LIF receptors (LIFR) form a non-covalent association with gp130. This complex recruits at least three JNK kinase family members, especially JNK1, JNK2, and TYK2, which activate one another by trans-phosphorylation. Activated JNK family kinases stimulate at least three signaling pathways, PI-3 kinase pathway, p21/MAP kinase pathway, and STAT pathway, of which STAT pathway activation is most significant in the uterus. ES cells lacking *LIF* in both the copies showed reduced ability to self-renew and differentiate, validating the essential role and function of LIF/LIFR in ES cell proliferation. Dahéron and colleagues showed that human LIF could activate the phosphorylation of STAT3 and subsequent nuclear

translocation by binding with LIFRβ/gp130 subunits in human ES cells (hESC) but fail to maintain their pluripotent/self-renewal status [69]. Supportively, endodermal cells deficient in *LIF* also propagate ES cells through a LIF/LIFR/STAT independent mechanism through the activation of ES cell renewal factor (ESRF) [70]. LIFR was present in the liver, kidney, bone, macrophage, placenta, CNS (central nervous system), uterine epithelial tissue, and ICM (Inner cell mass) of blastocysts. Earlier studies demonstrated the central role and mechanism of LIF/LIFR signaling in mammalian implantation delay, a condition when the supply of nutrients is insufficient for embryonic growth. LIF and LIFR/gp130 are present in the trophoblast and ICM of the blastocyst, respectively. In implantation delay, LIF, produced in the trophoblast, is bound to LIFR/gp130 in the ICM and helps maintain the ICM growth and stability [71–73]. Later, Cheng *et al.*, 2017 showed that LIFR is essential for embryonic implantation by generating LIFR depleted mice that failed to implant embryos. However, upon transplantation to wild-type mice, they did regain their developmental process. Further, they revealed faulty downstream signaling in the luminal epithelium (LE) and STAT3 translocation failure to the nucleus of LE in these mice and downregulation of expression of uterine receptivity gene Msx1 in these mice, thus leading to implantation failure. Commonly, LIF is secreted in endometrial glands and acts on LIFR in uterine LE. A similar consequence of infertility was reported in $LIF^{-/-}$ mice even in the presence of wild type LIFR, and likewise, LIFR mutated mice showed abnormal fetal development in the uterus, thus elucidating a vital role of the LIF/LIFR signaling axis in embryonic implantation [71,72,74,75]. In humans, LIF was able to resurrect the embryonic implantation and receptivity within the uterus of females declared/categorized as infertile. In mice, LIF induced by nidatory E2 ovarian hormone acts on uterine luminal epithelial cells and converts the embryo's non-responsive environment to a responsive state by regulating >40 transcription factors that initiate epithelial-mesenchymal communications, angiogenesis necessary after embryo implantation, and reduction of epithelial polarity [76]. Targeted disruption of *LIFR* in mice model exhibited reduced fetal bone volume (3-fold), increased osteoclasts activity (6-fold), decrease in brain and spinal cord astrocytes, and high storage of glycogen in the liver leading to metabolic disorder, indicative of all these changes that were relative to *LIFR* wild-type control mice [74]. Collectively, all these studies undermine the prerequisite of LIF/LIFR signaling in effective embryo implantation and lack of LIFR, leading to defective bone development.

6. LIF/LIFR in stem cell and cancer stem cell biology

In 1988, the role of LIF (derived from the mouse embryonic feeder cells) as a paracrine signaling molecule required for the maintenance of ES cells and prevention of their differentiation was first identified [24,77]. LIF/LIFR signaling regulates the ES-self-renewal capacity by sustaining embryonic implantation and maintenance of mouse ES pluripotency or induced pluripotent stem cells (iPS) via the putative STAT3/PI3K/ERK signaling cascades. However, the precise downstream regulation of these axes and especially the STAT3 mediated cell reprogramming with additional regulatory target genes remains enigmatic as ever. Knowledge of this complex regulation may have implications in ES and iPS cell-based therapeutics such as tissue engineering and regenerative medicine for addressing several ailments and diseases [78]. In a canine model, Shahsavari *et*

al. demonstrated that transcriptomic signatures of canine induced pluripotent stem cells (ciPSCs) derived canine mesenchymal stem cells (cMSCs) are similar to that of the canine-derived adipose tissue- and bone marrow-derived mesenchymal stem cells (cBM-MSC). They specifically noted that LIF and LIFR are more commonly expressed in cMSCs and iPSCs along with other pluripotent markers such as OCT-4, NANOG, SOX-2, KLF-4, MYC, and LIN-28A [79]. Unlike other IL-6 family members, LIF possesses stem cell self-renewal capacity by activating the YAP signaling pathway [80]. In the context of cancer, variable inhibition of Hippo and activation of YAP or activation of YES to further activate the YAP downstream targets has been reported. The presence of stemness possessing cells with tumor-initiating potential that are differentially regulated in different types of cancer in a cell and context-dependent manner has raised the bar of intrigue and warrants further investigation.

Cancer stem cells (CSCs) are a conspicuous population of stem-like cells within the tumor bulk with the extraordinary ability to initiate and recapitulate the tumor leading to disease relapse and therapy failure, thus exerting tremendous pressure on healthcare and clinical management of cancer patients. Furthermore, CSCs are prone to hijacking or co-opting cell signaling pathways required for their survival maintenance and thus contribute to poor patient prognosis [81,82]. Notably, CSCs possess dysregulated Notch, Wnt, Hedgehog, etc., pathways, and in addition, they function either as an oncogene or a tumor suppressor in a context-based manner. Also, there is a complex mutual cross-talk between these pathways, which complicates the scenario. Hence, single targeting agents or a combination thereof may serve as a relatively superior modality for oncotherapy, especially for CSC populations [81]. Furthermore, CSC plasticity and heterogeneity factors complicate the scenario because they are enriched during oncotherapy, and targeting them is a formidable challenge. As a result, the search for unique and efficacious targets for eradicating these populations across the various stages of the disease and during the patients' treatment phase is the need of the hour (Fig. 3) [155].

Interrogation of various cancer types and tumor models as described below reveals a dynamically pleiotropic role and complex regulation of the LIF/LIFR signaling, which necessitates a more critical and cell type and context-dependent interpretation and demands further systematic exploration of its various feed-forward and backward loops involved in the signaling cascade. Seeneevassen *et al*.[143] explored specific $ALDH^+$ and $CD44^+$ CSC populations in GC cell lines and mouse models of patient-derived xenograft tumors (PDX), where treatment with LIF and Hippo kinase inhibitor XMU-MP-1, JAK1 inhibitor Ruxolitinib, they concluded that LIF exerts an anti-CSC role via activation of Hippo kinases thus serving as a potential therapeutic target. Similarly, upon *in vitro* knockdown of LIFR in $ALDH^+$ endometrial CSCs and *in vivo* LIFR inhibitor EC359 treatment of patient-derived xenografts drastically reduced tumor cell viability, spheroid formation ability, and decrease in expression of OCT4, NANOG, SOX2, AXIN2 markers characteristic of CSC depletion and inhibition of endometrial cancer [6,15]. Another study by Johnson *et al*. [83] involving bone metastases patient specimen and human breast cancer cells (MCF7) cultured in (DMOG inducible) hypoxic conditions demonstrated repression of LIFR and SOCS3 transcription, thus regulating LIFR/STAT3 signaling. Loss of LIFR/STAT3 axis downregulated breast CSC quiescence/dormancy in OCT4, SOX2, NOTCH1, ALDH1A1,

TERT expressing, and $CD44^{high}/CD24^{low}$ CSCs, thus favoring proliferation, enhancing invasion, and bone colonization potential implicated in breast cancer development Ghanei *et al.* [113], on the contrary, showed that CSCs from breast cancer cells MC4-L2 with truncated recombinant LIF and LIFR could be ideal targets for onco-immunotherapy, as immunized mice revealed a delay or reduction in tumor growth, with preferred targeting of LIFR as an efficient approach. Interestingly, $CD133^{+}/CD83^{+}$ CSC populations in bone marrow-derived MSCs driven lung cancer model were probed by protein-protein interaction network by systems biology and microarray analyses. They found that BM-MSC-secreted LIF triggered EMT-MET switch-over and differential phosphorylation of serine residues (LIFR/p-ERK/pS727-STAT3 and IL6R/pY705-STAT3) of LIF signaling cascade members, thus permitting tumor initiation and metastatic niche development by involving the variable combination of signaling axes influencing CSCs [84].

McLean *et al* [140] studied $ALDH^{+}$ CSCs in ovarian cancer (OC) cell lines, and abrogation of JAK2/STAT3 axis by Ruxolitinib and LIF and IL-6 expression revealed that CA-MSC secreted LIF and IL6 enhanced the stemness or tumor-initiating capacity in OC by STAT3 activation. Using approaches such as siRNA, neutralizing antibody for LIF, JAK inhibitor, or recombinant-LIF treatment, and tumor cell invasion and migration ability of $CD133^{+}$ CSCs in glioblastoma and patient-derived neurospheres were investigated by Peñuelas and group [85], who concluded that LIF regulates self-renewal in not only normal and GBM neurospheres, but also glioblastoma initiating cells by increasing neuro-progenitor positive cells in tumor mass thus increasing their oncogenic potential. Another team of researchers led by Inda explored glioblastoma clinical samples and glioma stem cells and observed that conditioned media treatment and LIF repression by siRNA revealed an interesting observation [86]. Paracrine cytokine signaling circuit mediated by a novel gp130-wtEGFR interaction with ΔEGFR minority population in GBM mediates heterogeneity to promote tumor growth by activation of proliferation and survival pathways and implicated Jak/Stat, LIF upregulation of TGFβ. Another study was initiated by Iglesia *et al*; investigated in $Pten^{WT}$ and $Pten^{-/-}$ mice astrocytes of the Glioma model and found that PTEN loss via AKT–FOXO signaling pathway downregulates LIFRβ in astrocytes and inactivation of STAT3 thus linking PTEN–AKT–FOXO axis and the LIFRβ-STAT3 axes [87]. Using a different approach to investigate the ($CD133^{+}$) glioma CSCs in orthotopic xenograft mouse models, Edwards *et al* [136] studied the neurosphere development potential and tumor formation potential by LIF repression. They concluded that IFN-γ activates ZEB1, which represses LIF expression and thus regulates the stemness feature of glioma CSCs. In primary and metastatic melanoma cell line models, Kuphal *et al.* [6] showed that siRNA-based inhibition of LIF affected the SOX2, NANOG, OCT3/4, and GBX2 expressing CSCs. The authors concluded that high LIF expression in malignant melanoma is modulated via hypoxia and HIF1α and induces expression of BMP and stemness features, i.e., CSC renewal, migration, etc., with various tumor functional assays.

7. LIF/LIFR axis in gastrointestinal cancers

Among gastrointestinal cancer, pancreatic and liver cancer reveal an increased death rate and new cases every year. Initial studies in rat pancreatic tissues reported that LIF was expressed in the cytoplasm of normal ducts and metaplastic exocrine cells but not in acinar

cells. Also, upon pancreatic ligation surgery, both protein and mRNA levels of LIF and LIFR were strongly elevated after pancreatic injury, suggesting that LIF and LIFR components are involved in physiology, ductal cell growth, and pancreatic tissue repair and injury [88]. Earlier studies demonstrated the downregulation of LIFR and its association with pancreatic cancer (PC). Ma *et al*. showed that LIFR expression is significantly low in PC and associated with local invasion, metastasis to lymph node, and TNM stages. Further, ectopic overexpression of *LIFR* inhibited colony-forming ability, invasion, and migration ability of PC cells *(in vitro*) by inhibiting mesenchymal markers expression (vimentin and slug) and induction of epithelial marker (E-Cadherin). Supportively, *in vivo* tumorigenicity studies using ectopically, LIFR overexpressed PC cells showed decreased tumor-forming ability in nude mice as compared to vector-transfected PC cells. As predicted, stable silencing of LIFR in PC cells exhibited tumor-promoting function. Further, the authors demonstrated that LIFR suppression leads to lung cancer metastasis through the tail vein injection method in nude mice. Thus, LIFR negatively controls PC tumorigenesis and metastasis by inducing mesenchymal to epithelial transition phenotype [89]. This study was supported by a recent report surveying 8 clinical cohorts having PC and normal adjacent to PC/normal pancreas consisting of 1278 participants. The authors further confirmed that LIF was overexpressed and associated with poor PC survival while opposing results were reported with LIFR expression in the same cases relative to normal counterparts [90]. Similarly, LIF expression increased in PDAC cases and clinically correlated with TNM stages relative to their adjacent normal pancreatic tissues. In the same report, the researchers demonstrated that the transcript level of LIFR is higher in PC cell lines having lower LIF levels validating the clinically contrasted role of LIF and LIFR in PC [91]. However, the major challenging gene in PC is *KRAS*. Kras mutation is more frequent (70–95%) in PC, and among other Kras mutations, KRAS G12D and KRAS G12V are more prevalent (80%) than KRAS somatic alterations in exon 2 codon G12, G13, and exon 3 and 4 [92,93]. A recent report by Liu *et al*. demonstrated the association of LIFR and mutant Kras in PC. LIFR promotes Kras-mediated PC progression by downregulating the expression of key glycolysis pathway gene glucose transporter 1 (GLUT1). Repression of LIFR/STAT3 signaling by mutated KRAS leads to increased GLUT1 resulting in enhanced glycolysis and mitochondrial ATP production, providing energy needs for growing tumor cells. In contrast, the Kras transformed cells also showed an enhanced expression of LIF [12]. In PC, Stat3/Socs3 activation was driven by IL-6 secreted from the myeloid compartment promoting pancreatic intraepithelial neoplasias (PanINs) to progress towards PDAC. Inactivation of IL-6 or Stat3 by genetic means had reduced PDAC progression [94]. On the other hand, LIF/LIFR axis was also associated with a non-STAT3 signaling mechanism in PC. In KRAS mutated PC, LIF/LIFR signaling was associated with the initiation and progression of PC. Furthermore, LIF expression was shown to inhibit the Hippo-signaling pathway, which is responsible for aberrant activation of the YAP pathway in PC. Knockdown of LIF through genetic approach or YAP silencing inhibits LIF function in PC [95]. On the other hand, Yes protein from Hippo/YAP signaling by activation of YAP-TEAD2 is responsible for activating an unknown downstream pathway regulated by LIF signaling to bring about embryonic stem (ES) cell self-renewal in mice and humans [96]. LIF is also shown to be a critical paracrine secretory factor. LIF/LIFR signaling was known to induce the mRNA expression of IL-8, a cytokine that plays an important role in the progression of various types of cancer, including PC [97]. Dense

desmoplasia is the major hurdle in PC therapy. This desmoplastic reaction is supported by activated fibroblasts and pancreatic stellate cells (PSCs). These PSCs will provide soluble factors supporting and promoting the growing pancreatic tumor mass. Integrated mass spectrometry and phospho proteomics-based analysis identified that paracrine factors and the vicious cycle between PC cells and PSCs might exacerbate PC pathogenesis and help develop therapy resistance. In mice models, the LIF secreted by PSCS activated Jak/Stat-3 signaling upon binding to its receptor and mediated pancreatic tumor progression but not acinar to ductal metaplasia (ADM) formation [98]. STAT3 phosphorylation at tyrosine 705 residue in PC has been reported in 30–100% of clinical specimens and several PC cell lines [99]. Also, STAT3 phosphorylation is more prevalent upon LIF/LIFR signaling in PC. Abrogation of LIF/LIFR signaling modulates cancer cell differentiation and epithelial-mesenchymal transition (EMT) state. Blocking LIFR with a small molecule inhibitor or genetic deletion of LIFR in PC mouse models shows slow PC tumor progression and alteration of chemotherapeutic efficacy in PC mouse models [98]. Co-culturing mouse epithelial PC cell line with mouse pancreatic stellate cells exhibited 3D organoids which further treatment with EC359 that targets LIF/LIFR signaling showed a profound effect in reducing LIF derived from mouse dense stromal desmoplasia, that is confirming resistance to gemcitabine [100]. Overall, targeting LIF would be an alternate strategy to prevent stromal activation, a major PC player.

In contrast to PC studies, Xu *et al.*, 2019 reported LIF as a negative regulator of gastric cancer (GC) by its downregulation as detected by immunoblotting and tissue protein expression (IHC) analysis. Furthermore, reduced tissue expression of LIF (70%) was correlated with advanced tumor stage, lymph node metastasis, and worst overall survival of GC patients. They also reported that overexpression of LIF inhibits gastric cancer cell proliferation and delayed xenograft tumor growth by arresting the cell cycle in the G1 phase by upregulating endogenous cyclin-dependent kinase (CDK) inhibitor p21. p21 disrupts the formation of CDK2-cyclin E and CDK4-cyclin D complex [101]. Hence, LIF influences GC cells by activating p21, an effector of the LIF/LIFR/STAT-3 signaling pathway [102]. Another group of researchers believes that LIF/LIFR axis signaling promotes gastric cancer by influencing the Hippo-YAP signaling pathway. They found increased LIF and LIFR in GC compared to adjacent normal tissue. They concluded that LIF/LIFR signaling is involved in GC cell proliferation, metastasis, and invasion mediated by the Hippo-YAP-TEAD pathway [13]. Mechanistically, dose-dependent treatment of LIF in GC cells decreases phosphorylation of Hippo-component kinases such as MAT1 and LATS1, resulting in decreased YAP phosphorylation at serine 127 residue, resulting in YAP nuclear translocation and regulation of multiple-YAP oncogenic targets [13].

Higher levels of LIF expression were detected in the serum of Nasopharyngeal Carcinoma (NPC) patients, whereas undetected levels of LIF were found in most of the normal individual serum. Interestingly, patients with metastatic NPC and tumor remission revealed comparable levels of LIF. Hence, the presence of LIF in the tumor microenvironment (TME) seems to be more critical than that in blood circulation. In NPC, expression of gp130 is not significantly high whereas, LIFR expression is significantly higher compared to adjacent normal tissue [103]. About 20% of the patients suffering from NPC relapse after radiotherapy, and LIF/LIFR signaling is associated with radioresistance. It inhibits DNA

damage and enhances tumor growth after radiotherapy through activating mTOR/p70S6K signaling, thus assuming a crucial role as a prognostic marker in NPCs [14]. LIF promotes colorectal cancer (CRC) by downregulation of p53 protein through STAT-3/ID1/MDM2 pathway. Activation of STAT-3 by LIF induces activation of inhibitor of DNA binding-1 (ID1), a helix-loop-helix (HLH) protein that inhibits differentiation and DNA binding. ID1 increases the expression of MDM2, while MDM2 increases proteasomal degradation of p53. Collectively, LIF induces chemoresistance to CRC cells and xenografted murine tumors through the degradation of p53 protein [8]. In a study by Luo *et al.*, the tumor suppressor role of LIF/LIFR axis signaling in hepatocellular carcinoma (HCC) was reported. Further, it was demonstrated that stable knockdown of LIFR in less aggressive HCC cells promotes invasion and migration without any impact on HCC cellular proliferation. As similar to PC *in vivo* studies [89], orthotopic implantation and tail vein injection of stably depleted LIFR expression in HCC cells revealed lung metastasis, while opposing *in vitro* and *in vivo* functional effects were demonstrated by the researchers upon ectopic overexpression of LIFR in HCC cells. Thus, the authors cued that LIFR expression could be related to HCC progression and metastasis [104]. Based on this evidence, it was specified that LIFR could be an excellent therapeutic marker in HCC [105]. LIF/STAT3 signaling modulates cell proliferation, invasion, and metastasis in choriocarcinoma (CCA) cells [106]. LIF/STAT3 signaling is also found to act as a tumor suppressor in choriocarcinoma JEG-3 cells. In addition, this signaling axis inhibits cell proliferation by downregulating miR-141 [107]. Apart from the discussed status of LIF and LIFR across cancer, we queried LIF and LIFR status between normal and cancer tissues in the Mipanda data portal (Fig. 4).

8. Signal transduction pathways of LIF/LIFR axis in hormone-regulated cancers

Overexpression of LIFR was also observed in several cancers, including PCa, and correlated with cancer metastasis. Recent findings demonstrate that leukemia inhibitory factor (LIF) and its receptor leukemia inhibitory factor receptor (LIFR) signaling was activated by androgen deprivation therapy (ADT). Furthermore, the enhanced expression of LIF/LIFR signaling at castrated or relapse conditions was also observed in PCa. This creates speculation that LIFR might play a major role in enriching and maintaining CSC, which is causative for PCa recurrence after ADT. Specifically, LIFR phosphorylation at serine 1044 was reported to be associated with its activity, oncogenic function, and metastasis [1]. Previously, Schiemenn *et al.* used bacterially expressed protein having a cytoplasmic domain of LIFR to figure out its phosphorylation status/site upon LIF stimulation. They found that LIFR is phosphorylated at Ser-1044, in parallel with phosphorylation of MAPK in the same extracts, thus demonstrating that LIFR is a MAPK substrate [108]. In PCa cells LIFR phosphorylation at serine 1044 was shown to be phosphorylated by extracellular signal-regulated kinase 2 (ERK2) and not through ERK1 activation. Additionally, it was demonstrated that LIFR ser-1044 phosphorylation further phosphorylates AKT at serine 473 to enhance the proliferation and metastasis of PCa cells [1]. Recently, the same group of researchers also demonstrated that post-translational modification of lysine residue (acetylation of K-620) of LIFR by histone acetyl transferase KAT2A resulted in activation of AKT other than intracellular phosphorylation of LIFR [109]. Further

evidence supports the role of ZBTB46 functions as a transcriptional coactivator and binds to prostaglandin-endoperoxide synthase 1(PTGS1) gene promoter to regulate genes involved in neuroendocrine differentiation of PCa [110]. Later, in the same study, LIF was shown to be induced during ADT, and this activated LIF was demonstrated to be influenced by ZBTB46 to support neuroendocrine differentiation of PCa. In clinical PCa specimens, ADT treatment was positively correlated with cytoplasmic expression of LIF and nuclear staining for ZBTB46 [2]. The study by Lin *et al* demonstrated that ADT-induced nuclear EGFR upregulates LIFR, which further contributes to succinate metabolism and neuroendocrine differentiation by regulating succinate-CoA ligase GDP-forming beta subunit (SUCLG2) [111].

The role of LIFR signaling in breast cancer is controversial to other cancers. Iorns and colleagues/Lipmann's group found that LIFR signaling acts as a tumor suppressor in breast cancer by *in-vivo* RNAi screening of the whole human genome [112]. This result is also supported by a study, which has been conducted with immunized LIF/LIFR mice [113]. LIFR axis signaling suppresses breast tumor progression [114] and metastasis [16] by activating the canonical hippo-YAP pathway. Specifically, Chen *et al*. showed that LIFR silencing in less aggressive BC cells promotes migratory and invasive properties of BC cells, which was reversed by the re-introduction of *LIFR*. Further, ectopic overexpression of LIFR cDNA in highly aggressive human and mouse BC cells significantly enhanced invasion and migration of BC cells but no alteration in cellular proliferation and viability, complementing the LIFR gene knock out studies. Interestingly, when the mouse syngeneic BC cells were implanted into the mammary fat pad, the authors showed the invasive property of those mouse BC cells to nearby adipose tissues [16]. LIF/LIFR signaling is involved in HDAC inhibitor resistance by transcribing anti-apoptotic genes by activating the JAK1/STAT-3 signaling pathway [115]. MicroRNA-125a induces breast cancer stem cells through the LIFR-Hippo signaling pathway [116]. LIF/LIFR axis is stimulated by autocrine activation in breast cancer cell lines. The promoter region of breast cancer cells becomes unmethylated and increases LIF transcription, thus implicating its overexpression in breast cancer development [117]. Triple-negative breast cancer cells also possess higher levels of LIF. An increased level of LIF is significantly correlated with poorer relapse-free survival [10]. LIF/LIFR complex (LIFR and GP130) is highly expressed in breast cancer cells with metastatic potential, while the addition of LIF increases the metastatic ability of breast cancer cells. Furthermore, cells having ectopically expressed LIF show increased metastatic ability *in-vivo*. LIF promotes tumorigenesis and metastasis by activating the mTOR pathway through the activation of AKT [10]. LIF expression also reveals its correlation with the poor prognosis of breast cancer patients [10]. Bay *et al* in 2011 showed that LIF is involved in oncogene suppression and inhibition of cellular proliferation by regulating the cell cycle in cervical cancer cells. HPV E6 and HPV E7 are two viral genes encoding oncoproteins that interact with tumor suppressor p53 and retinoblastoma (RB), whose higher expression leads to invasive and metastatic cancer. LIF effectively blocks E6 and E7 in cervical carcinoma cells and reduces proliferation [118].

In contrast to LIF/LIFR signaling in BC, recent studies demonstrate that high OSM and oncostatin M receptor (OSMR) activation is associated with reduced estrogen receptor α (ER α) and progesterone receptor protein and RNA expression resulting in worst recurrence-

free and overall survival of breast cancer patients [119]. OSM can interact with either LIFR or OSMRβ, posing effects on JAK, MAPK, STAT3, and PI3K signaling. A recent study by Araujo *et al*. showed that depletion of OSMR in mice models exhibited a reduction in mammary tumor growth and metastasis. The authors also showed that OSM is secreted by cancer infiltrating myeloid cells, whereas OSMR is expressed majorly by fibroblast but to a smaller extent in epithelial cancer and endothelial cells. Also, the authors showed that recruitment of myeloid-derived OSM reprograms fibroblast cells to support BC progression by increased expression of VEGF, CXCL1, and CXCL16 [120]. Similarly, in another research study related to bone dissemination of BC, the IL-6 family of cytokines such as LIF, OSM, and CNTF and their cognate receptors were found to be underexpressed in ER-negative BC metastatic cells compared with isogeneic BC cells. In contrast, ER-positive cell treatment with OSM increased activation of STAT3, ERK, and AKT signaling, while LIF treatment activated only ERK signaling. On the other hand, in ER-negative BC metastatic cells with non-functional LIFR, OSM treatment still activated STAT3 signaling. Overall this study showed OSM as a potent activator of STAT3 signaling irrespective of ER status in BC cells. Interestingly, stable overexpression of OSM in ER-positive BC cells promoted primary tumor to disseminate towards bone [121]. West *et al*. have demonstrated that OSM can induce EMT features of luminal ER-positive BC cells by reducing epithelial cell marker E-Cadherin and induction of mesenchymal markers (SNAIL and SLUG). At the same time, OSM treatment also displayed CSC-like features of BC cells by enhancing the $CD44^{+/high}/CD24^{-/low}$ population, which further enhanced mammosphere forming ability by increased expression of SOX2 via PI3K signaling [122]. Thus, OSM has pro-tumorigenic, pro-tumor dormancy, and cellular phenotypic changes in BC, which cannot be observed in LIF/LIFR axis in BC.

9. LIF/LIFR axis in other cancers

LIF and its cognate receptor LIFR aberrations are observed in other cancers apart from GI and hormone-regulated cancers. In chordoma, LIFR is associated with chemoresistance by elevating cancer stemness and drug efflux pump, like ABCG2, by activating the LIF-activated pro-inflammatory NF-κB pathway to drive EMT, migration, invasion, and cancer stem-like cell characteristics. In addition, LIF expression is positively correlated with shorter chordoma patient survival [123]. LIFR becomes functional, and LIF expression is present in medulloblastoma cell lines. Dysregulation of LIF was observed in human medulloblastoma. It has been found that LIF indirectly regulates LIFR expression by p53. One of the PI3K isoforms, p110α, also regulates the expression of LIFR by controlling c-myc and miR-125b. In *in vivo* studies, increased LIFR downstream signaling in medulloblastoma is also found. LIFR maintains the survival and growth of medulloblastoma cells by the STAT3 signaling pathway [124]. LIF/STAT3 signaling promotes proliferation, invasion, and metastasis of osteosarcoma. In addition, LIF is overexpressed in osteosarcoma. *In-vivo* and *in-vitro* studies using osteosarcoma xenograft and cell line models reveal that recombinant LIF protein increases the growth and proliferation of osteosarcoma significantly, while HO-3867, an inhibitor of STAT-3, neutralizes the effect of LIF [7]. LIF is expressed in melanoma tumors and cell lines derived from primary and metastatic sites. LIF signaling mediates proliferation, metastasis, and cancer stem cell-like properties of melanoma cells.

LIF signaling in melanoma is mediated by a non-conventional route via BMP4 and BMP7 signaling rather than the canonical STAT-3 signaling to bring about tumorigenesis and its progression [6]. During lung adenocarcinoma developed in G protein-coupled receptor of family C, group 5, member a (Gprc5a) knockout mice reveal an autocrine regulation of LIF and persistent Stat3 activation. Inhibition of tumor-suppressive action of Gprc5a by treating with JAK2 inhibitor or stable overexpression of dominant-negative Stat3 (Y705F) construct in Gprc5a knockout mice-derived cells reduced colony growth and induced apoptosis in those syngeneic mouse lung cells. Mechanistically, the researchers demonstrated that the tumor-suppressive role of Gprc5a is mediated by the stabilization of Socs3, which controls STAT3 activation. The absence of this Gprc5a in mice leads to decreased Socs3 protein and increased phosphorylation of STAT3 [125]. There is little scientific evidence showing that cytokine-mediated proliferative and growth-stimulating effects will be similar for ligands with structural and functional resemblances. For example, OSM acts as a power mitogen in AIDS-associated Kaposi's sarcoma-derived cells (AIDS-KS cells). AIDS-KS cell growth is specifically induced by OSM but does not respond to LIF or IL6 because of the absence of LIFR and the presence of OSM-specific receptors in these cells [126]. All this scientific evidence indicates that the development of inhibitors specifically abrogating LIF/LIFR axis would render a global anti-tumor effect. Various tumor-promoting (Fig. 5A) and tumor-suppressive (Fig. 5B) effects of LIFR signaling regulate multiple biological phenotypes such as metastasis, cellular differentiation, EMT, MET phenotype, feedback LIFR activation, and chemoresistance, and organ-specific metastasis were briefly illustrated as Fig. 5. Signaling regulated by LIF and cross-talk and the direct association of LIF/LIFR signaling was briefly elaborated in Table 2.

10. Targeting LIF/LIFR axis for cancer therapy

As such, LIF and its receptor LIFR and their downstream signaling have been well investigated in various cancer. Unfortunately, little evidence is available regarding targeted agents against LIF and LIFR. A seminal study in breast cancer reported that LIFR-JAK-STAT signaling feedback loop inhibits the HDAC inhibitor activity, and the resultant response is restricted with LIFR. HDAC inhibition accelerates histone acetylation of LIFR gene promoter, thus mediating BRD4 transcriptional activation of LIFR and stimulating the JAK-STAT signaling cascade, thus limiting the HDAC inhibition response [115]. Recently Li *et al.* showed the synergy between the first-in-class LIF/LIFR axis inhibitor EC359 with Histone deacetylase inhibitor (HDACi) vorinostat to decrease TNBC cell viability and growth colony formation and migration by inducing apoptosis. In addition, HDAC1 and EC359 combination therapy inhibits TNBC cell and patient-derived xenograft growth *in vivo* [127]. The same group also demonstrated that EC359 could effectively block the binding of other IL-6-like family cytokines/ligands such as OSM, CNTF, and CTF1 other than LIF in breast cancer cells [128]. Further, EC359 treatment also inhibited endometrial cancer cell growth, viability, and xenografts by reducing cancer stem population and markers OCT4, NANOG, and SOX2 along with LIFR [15]. The LIF/LIFR inhibitor EC359 is also tested in the context of the tumor microenvironment. Hall and colleagues demonstrated that EC359 not only reduces effectiveness *in vitro*, *in vivo*, and in stemness characteristics but also affects stromal markers such as fibronectin 1 (FN1), MMP9, POSTN,

SPARC, COL1A1, COL1A2, COL3A1, and COL5A1 in PC and pancreatic stroma-derived cell line based organoid model. Thus LIF/LIFR inhibitor EC359 can be used as a stromal targeting agent [100]. Recent clinical studies also imply that enhanced LIF level in circulation is also responsible for chemo and radioresistance by eliciting cancer cell growth and induction of differentiation. With 80% homology between mice and human proteins, extrapolation of the manipulation of the LIF/LIFR axis in *in vitro* and *in vivo* animal models might prove promising for clinical implications [113]. Hence, targeting LIF using commercially available neutralizing antibodies or ligand trap methods would help overcome chemo-radioresistance-mediated by LIF/LIFR axis. The currently available agents targeting LIF/LIFR axis were briefly illustrated in Table 3.

11. Conclusion and future prospective

LIF is a pleiotropic glycoprotein belonging to the IL-6 cytokine family and remains highly conserved across species. LIF-LIFR interaction triggers multiple signaling pathways, such as STAT3, AKT, and mTOR [14,26], thus providing an impetus to cancer cell migration invasion, EMT, etc., both in vivo and in vitro. LIF overexpression, as reported in various human cancers such as breast, colorectal, lung, nasopharyngeal carcinoma, melanoma, etc., is responsible for tumor development and its progression. On the other hand, LIF inhibition contributes towards abrogation of proliferation, cell attachment, migration, and colony formation in various cancers such as breast, cervical, clear cell carcinoma, gastric, GBM, hepatocellular carcinoma, melanoma, etc. [6]. Similarly, targeting LIFR may profoundly negatively impact pancreatic, breast, and ovarian cancers, and rhabdomyosarcoma and activate cell death mechanisms while affecting the cancer cell stemness features [129,130]. In the context of cancer, LIF activates the JAK/STAT and PI3K/AKT signaling cascades (by activation of YAP *via* YES/gp130 pathway) to exhibit a pro-tumorigenic effect. In contrast, LIFRβ activation (inhibits YAP via Scribble/Hippo pathway) is linked to the tumor suppressor Hippo pathway to exert an anti-tumorigenic effect, thus mesmerizing researchers about the subtle intricacies and cell-type and context-dependent dichotomy of outcomes [26]. While leaving us poised (at this point) at crossroads towards comprehending and interpreting the possibilities that trigger and initiate the LIF/LIFR signaling, the multitude of factors downstream affecting their variable regulation and the different tumor cell types with hierarchy, heterogeneity, and plasticity features as a therapy acquired, transient phenomenon adds another dimension to the complex regulation which requires further studies.

LIF and LIFR are overexpressed or under-expressed to support cancer progression. In various malignancies, the role and function of LIF/LIFR signaling are still controversial and unclear, with data suggesting both tumor-promoting and tumor-suppressive effects. The biology and LIF/LIFR, OSM/OSMR, and CNTF/CNTFR signaling should be viewed in the context of the subtype of cancer. For instance, ER-Positive MCF-7 BC cells do not respond to EC359 LIF/LIFR inhibitor since they lack LIF ligand and receptor. Whereas MDA-MB231 (ER-negative) TNBC cells were highly sensitive to EC359 since those cells express a high level of both LIF and LIFR [128]. In contrast, other investigators in BC have shown that MCF7 cells do express both LIF and LIFR and when they try to stimulate with LIF, MCF7 cells demonstrated activation of JAK/STAT/ERK/AKT signaling. At the same time, when MDA-MB-231 cells with high LIFR expression did not show such an

effect upon LIF cytokine stimulation, suggesting that some ER-positive breast cancer might respond to LIFR inhibitor but not to cytokines, and vice-versa [83,121]. Cell-based studies confirmed the oncogenic function of the LIF/LIFR axis and further characterized it in xenograft models. Studies lack testing of LIF and LIFR gene depletion function and well-established oncogene or tumor suppressor. For instance, Shi *et al*. demonstrated that the genetic loss of *Lif* function facilitates PDAC progression, but not cancer initiation in Kras and p53 activated and Kras alone activated mice model [98]. The tumor-suppressive function of LIFR was more pronounced in breast cancer as evidenced by various gene knockout and ectopic overexpression studies [16,112,128]. In contrast, LIF was demonstrated to be pro-tumorigenic in breast cancer cells by activating the AKT-mTOR pathway [10]. Currently, studies are required to validate *Lif* knockout effect in the context of Pten, p53, and Rb single or compound knockout mouse models to understand its specific role regarding tumor suppressor/oncogene associated *Lif* function with specific cancer. Several studies suggest that LIFR is downregulated or expressed at a low level. The putative reason behind this LIFR downregulation may be due to LIF or other ligands like OSM acting on LIFR, inducing ligand-receptor mediated endocytosis. Also, it will be of greater interest to thoroughly interrogate this enigmatic LIF-LIFR signaling with its upstream ligands and downstream signaling cascades and target genes at a single cell level within a tumor and in the context of the patient's therapy response/failure. Furthermore, it will be interesting to explore the inflammasome and how cytokine response, instead of leaning towards the conventional 'repair and regeneration,' rambles towards cancer development and at what juncture the oncogenic mutations bring about the chaos in the cell-cell communication, signaling, and reciprocal cross-talk of LIF and LIFR. With recent advancements in a multitude of techniques such as multi-omics, single-cell sequencing, multiplex imaging, 3D organoid platform, and access to genetically engineered and immuno-deficient mouse models, humanized SCID mouse models (patient-derived xenograft) or chimeric models, coupled with Crispr/Cas9 based screening, high-throughput screening platforms for drug screening have enabled researchers with limitless options to explore and systematically solve the puzzle of this complex disease of 'cancer' in a more consolidated manner.

Furthermore, in this era Precision Oncomedicine and therapeutic targeting, investigation of 'tumor evolution' and aspects bestowing tumors with 'therapy-resistant' features and a universal understanding of the contribution of each component of the surrounding tumor microenvironment viz. tumor-associated macrophages, tumor-infiltrating lymphocytes, stromal cells, vasculature, and other TME components that influence aspects of tumor biology such as differentiation, de-differentiation, trans-differentiation, plasticity, epi-genetics, and metabolism, etc. will indeed serve as valuable lessons and legacy to carry forward our battle against this mighty disease. Future studies are required on how LIF/LIFR axis influences the plasticity of cancer cells and EMT switching. Recently, LIF and IL6 were shown to help in the generation of TAM (Tumor-associated macrophages) derived from monocytes, thus sensitizing the tumor cells to T-cell-based anti-tumor immunotherapy and increasing its efficacy [131]. Furthermore, studies are required to combine LIF or LIFR antagonists with traditional chemo-radiotherapy along with check-point inhibitors. Due to the variety of ligands targeting LIFR, it is practical to develop pan-LIF/LIFR small molecule inhibitors targeting a variety of ligands such as LIF, OSM, CTNF1, and CT1.

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Abbreviations:

LIF	Leukemia inhibitory factor
LIFR	Leukemia inhibitory factor receptor
OSM	Oncostatin M
CNTF	Ciliary Neurotrophic Factor
CT1	cardiotrophin 1
IL-6	Interleukin-6
CRH	cytokine receptor homology
CRD	cytokine receptor domain
EMT	Epithelial-mesenchymal transition
ILEI	interleukin-like EMT inducer
TME	Tumor microenvironment
STWS	Stűve-Wiedemann syndrome
LOH	loss of heterozygosity
GM-CSF	granulocyte-macrophage colony-stimulating factor
G-CSF	granulocyte colony-stimulating factor
hESC	human Embryonic stem cell
ECRF	Embryonic stem cell renewal factor
iPSC	Induced pluripotent stem cell
ICM	Inner cell mass
MSC	Mesenchymal stem cell
BM-MSC	Bone marrow-derived mesenchymal stem cells
CSC	Cancer stem cells

ADT	Androgen deprivation therapy
GBM	Glioblastoma
CRC	Colorectal cancer
PDAC	Pancreatic ductal adenocarcinoma
PCa	Prostate cancer
BC	Breast cancer
TNBC	Triple-negative breast cancer
NSCLC	Non-small cell lung cancer
HCC	Hepatocellular carcinoma
TGF-β	Transforming growth factor-β
MMPs	Matrix metalloproteinases
CAFs	Cancer-Associated Fibroblasts
miRNA	Micro RNA
IncRNA	Long non-coding RNA

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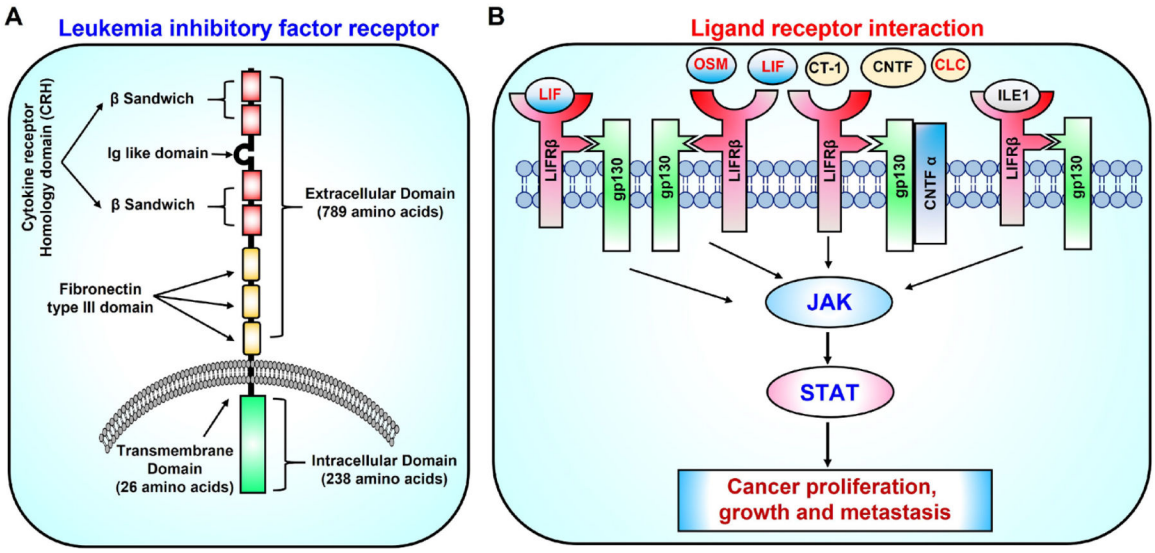

Fig. 1.

Structure of LIFR and its interaction with LIF ligand. (A) LIFR is composed of 8 different domains, and these domains were sub-classified as the extracellular domain (789 amino acids) containing two cytokine binding module/domain (CBM) separated by Ig-like domains which subsequently trailed by 3 fibronectin type III domains, transmembrane domain (26 amino acids, and intracellular domain (238 amino acids). (B) Snapshot of holo complex and heterodimerization of IL6 family ligands and their interaction with LIFR-gp130 in cancer cells. The IL-6 family of ligands (LIF, oncostatin M (OSM), ciliary neurotrophic growth factor (CNTF), cardiotrophin-1 (CT-1, and cardiotrophin-like cytokine (CLC))) bind to LIFR and subsequently dimerize with co-receptor glycoprotein 130 (gp130) to form tertiary complex and signals through JAK/STAT pathway. Interleukin-like EMT inducer (ILEI) a cytokine from the FAM3 family, also functions as a ligand for LIFR-gp130 heterodimer and mediates intracellular signal through STAT activation.

Fig. 2.

Mutations in *LIF* and *LIFR* across pan-cancer cohorts. The figure illustrates the types of mutations, frequency, and their respective change in amino acids in LIF and LIFR genes. The colored circles represent the most frequent mutation type specific to that position. (A) The below annotation bars at the bottom of the figure provide additional information about the LIF gene domain, post-translational modification (PTM), and exons. The color codes of mutations are as follows: dark green dots, putative driver missense mutations; light green dots, missense mutations with unknown significance; black dots, truncating mutations which include nonsense, frameshift deletion, frameshift insertion, and splice variant; brown dots inframe deletion, inframe insertion; orange dots splice mutations; purple dots, fusion mutations. Data were obtained by querying for both Pan-cancer Studies and TCGA Pan-cancer atlas studies (A total of 32 studies; 10967 samples). (B) The figure illustrates the mutation types, frequency, and changes in amino acid positions in the LIFR gene. The colored circles represent the most frequent mutation as denoted in the LIF gene. Data were obtained by querying for both Pan-cancer studies (A total of 10 studies; 76639 samples).

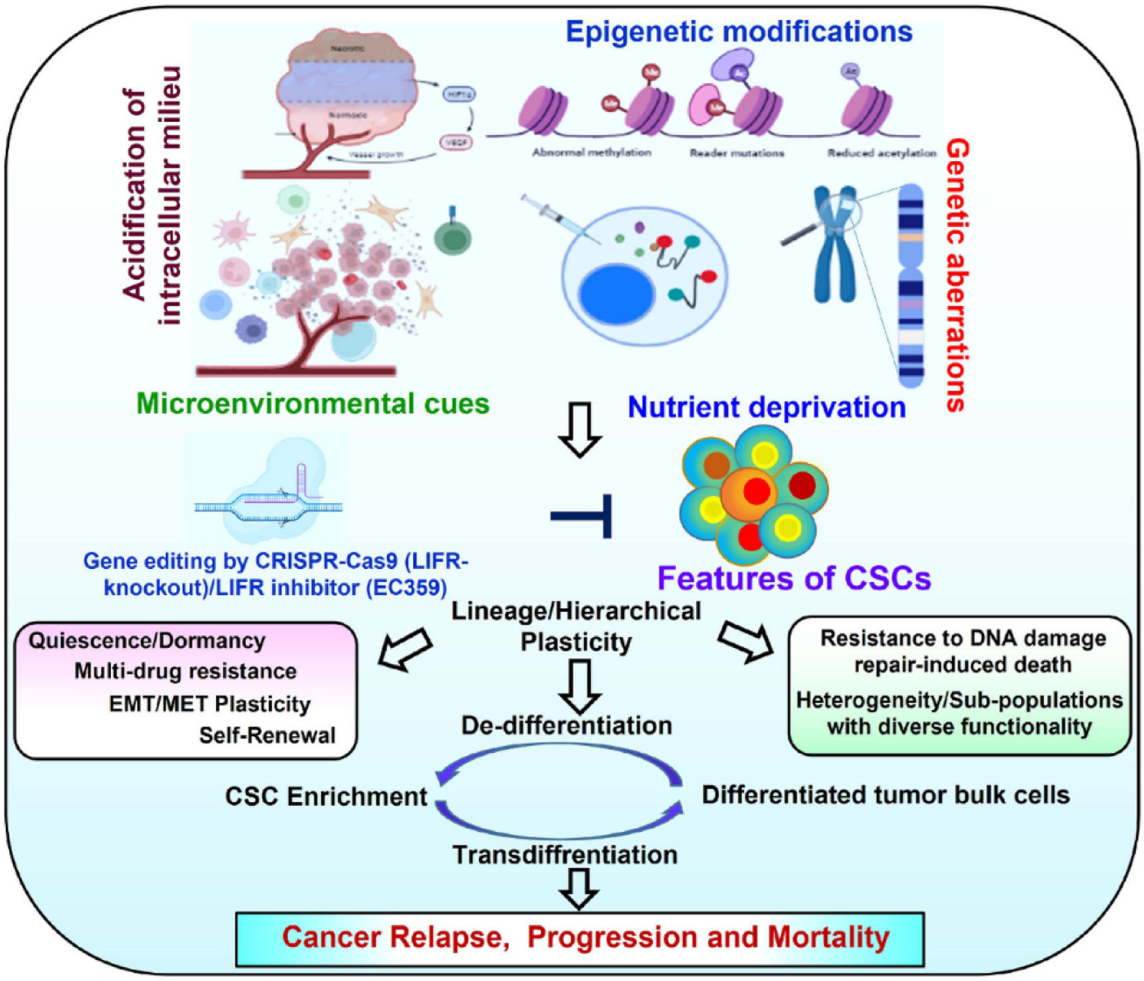

Fig. 3.

Targeting of LIF/LIFR axis and dynamic regulation of CSC and tumor evolution. Tumor evolution is an adaptive and evolving process. The tumor cells develop into different phenotypes in response to the intrinsic and extrinsic cues and ultimately resist death while co-opting the host cell machinery for their survival benefit. While drug-induced stress remains an external trigger, genetic and epigenetic aberrations, hypoxic conditions, acidic milieu of the cancer cells, other cues originating from the tumor microenvironment, and nutrient deprivation are internal cues that contribute to tumor growth evolution. These factors, to an extent, may decide the lineage plasticity of subsets/sub-populations of the tumor cells termed ‘tumor-initiating cells’ or ‘CSCs’ and lead to tumor heterogeneity and establishment of hierarchical supremacy. This LIF Lineage plasticity provides tumor cells with a remarkable and dynamic lineage switching ability, i.e., tumor bulk cells may undergo de-differentiation to a progenitor/stem-like phenotype and assume quiescence. Parallelly, CSCs possess the characteristics to undergo self-renewal and mostly remain quiescent or dormant under stress, and can adopt another differentiated lineage by trans-differentiation while contributing to EMT plasticity, multi-drug resistance, refractoriness to DNA damage-induced cell death, and assume functional diversity/heterogeneity. Thus, tumor cells in totality adapt themselves through various mechanisms and adopt a formidable

form that provides them an edge to survive therapy and culminate into disease relapse, tumor progression, metastasis, and ultimately mortality of the subject. In several cancer cells, LIF/LIFR signaling activation promotes the regulation of CSC features. Therefore, small-molecule inhibitors (EC359) or CRISPR-Cas9 system-based suppression of the LIF/LIFR axis is a viable strategy to reduce stemness, CSC maintenance, CSC self-renewal, de-differentiation, and drug resistance.

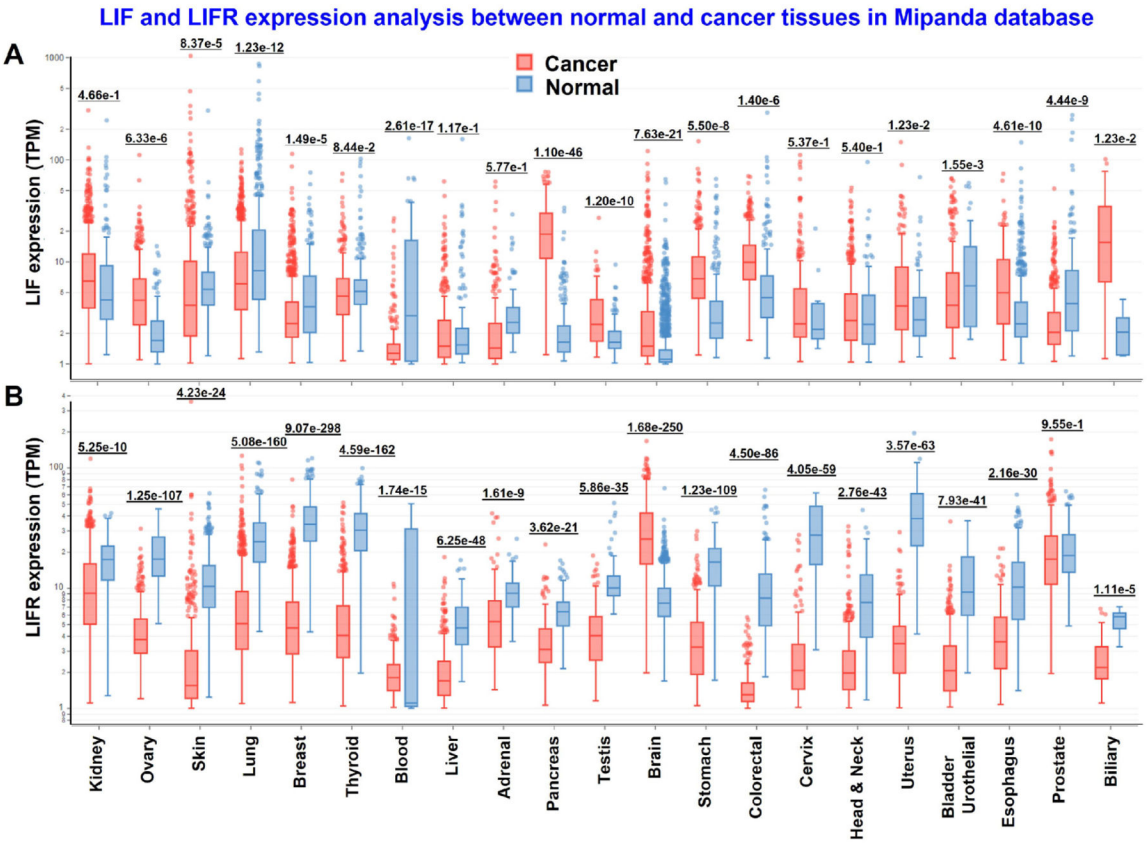

Fig. 4.

LIF and LIFR expression among various cancer cohorts. The boxplots depict LIF (top) and LIFR (bottom) mRNA expression between normal and cancer samples across the 21 TCGA cancer types as analyzed using the Mipanda database.

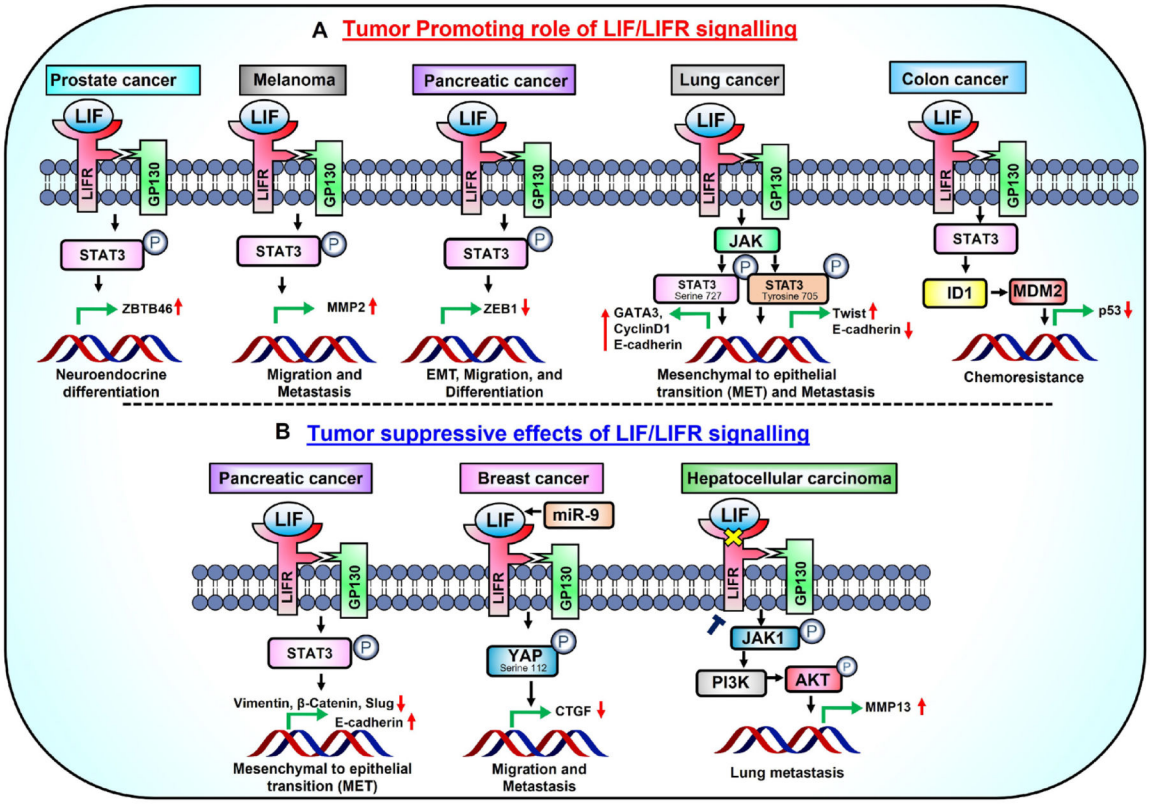

Fig. 5.

Dual and context-dependent role of LIF/LIFR axis as tumor promoter and suppressor supporting cancer progression and metastasis. Several different molecular mechanisms regulate LIF/LIFR signaling in various cancers. LIF and LIFR signals through various mechanism (s) and function as both tumor promoters and tumor suppressors in various malignancies. (A) Cancer promoting role and function of LIF/LIFR signaling. In prostate cancer cells, a lineage-specific transcription factor ZBTB46 is activated upon androgen deprivation therapy. The nuclear association of ZBTB46 induces LIF and subsequently leads to the activation of STAT3. LIF signaling induces ZBTB46 nuclear localization to support ZBTB46 oncogenic function and neuroendocrine differentiation as a positive feedback mechanism. LIFR act as a metastasis promoter in melanoma. LIFR levels progressively increase from normal nevi to primary melanoma, followed by metastatic melanoma. Knockdown of LIFR reduced phosphorylation of STAT3 but not YAP. LIFR was demonstrated to promote metastasis via MMP2 regulation. In pancreatic cancer, a vicious cycle is maintained between stellate cells in the stroma and pancreatic cancer cells in the epithelia. Genetic and pharmacological blockade of LIF/LIFR signaling was demonstrated to inhibit pancreatic cancer growth and metastasis, mainly by modulating epithelial to mesenchymal transition (EMT) phenotype through downregulation of ZEB1. Differential phosphorylation of STAT3 by LIF/LIFR signaling regulates the EMT and mesenchymal to epithelial transition (MET) switch. In lung cancer cells, a specific $CD133^{+}/CD83^{+}$ population acquires early migratory potential by activating LIFR/ERK/STAT3 (Serine 727) phosphorylation, resulting in transcription regulation of Cyclin Dl, GATA3, and E-Cadherin. On the other hand, upon persistent treatment of bone marrow-derived mesenchymal

stem cells, derived media exposure to other specific $CD151^{+}/CD38^{+}$ populations exhibit activation of STAT3 signaling by activating IL-6R/phosphorylated STAT3 (Tyrosine 705), resulting in downregulation of E-Cadherin and upregulation of Twist1 showing the re-differentiation (MET) phenotype. LIF negatively regulates p53 expression. LIF/LIFR signaling mediates STAT3 activation, which in turn induces inhibitor of DNA binding 1 (ID1) gene to upregulate MDM2. Translational increases in the MDM2 by LIF accelerate the degradation of p53 protein expression; thereby, LIF negatively regulates p53 function via STAT3/ID1/MDM2 pathway. (B) Tumor suppressor role and function of LIF/LIFR axis. In pancreatic cancer, LIFR suppresses the growth, invasion, and migration of PC cells *in vitro* and metastasis *in vivo* by inducing epithelial marker E-cadherin and suppressing mesenchymal markers such as vimentin and slug as well as altering β-catenin. LIFR suppresses the metastatic potential of breast cancer cells by inactivation of functional Hippo-Yes-associated protein (YAP) signaling. Similar to breast and pancreatic cancer, LIFR also negatively regulates HCC metastasis by activating JAK1/PI3K/AKT pathway resulting in MMP13 expressional alteration forcing towards lung metastasis.

Table 1

Long non-coding RNA and miRNA on LIF/LIFR axis in cancer.

Sl. No.	LncRNA/ miRNA	Relation to LIF/LIFR axis	Cancer type	Tumor Role-Suppressor/ Promoter	Regulation/Signaling	References
1	miR-629-3p	Bound to the 3'-UTR of LIFR mRNA	Triple-Negative Breast Cancer	Promoter	Tumorigenesis and metastasis through Hippo and PI3/AKT signaling	[43]
2	miR-200b	Repress LIFR by inhibiting ZEB1/ZEB2	20 different cancer types	Suppressor	Suppress metastasis	[44]
3	miR-377-3p	Bound to the 3'-UTR of LIFR mRNA	Human bone marrow mesenchymal stem cells		Differentiation into adipocyte	[45]
4	miR-21-5p	Target LIFR expression	Gastric cancer	Promoter	Enhance proliferation and metastasis	[46]
5	miR-589	Target LIFR expression	Gastric cancer	Promoter	Metastasis and invasion by activating PI3K/AKT/c-Jun signaling	[48]
6	miR-221-3p	Bound to the 3'-UTR of LIFR mRNA	Hepatocellular carcinoma	Promoter	Enhances cell proliferation migratory and invasive abilities.	[51]
7	miR-181c	LIF activates miR-181c	Cholangiocarcinoma	Promoter	Contribute to poorer overall survival and metastasis	[52]
8	LIFR-AS1	–	Colorectal cancer	Promoter	Target miR-29a up-regulates TNFAIP3 and renders resistance to pohotodynamic therapy	[53]
		–	Breast cancer	Suppressor	Binds with miR-197-3p and inhibits cell proliferation and migration	[54]
		–	Non-small cell lung cancer	Suppressor	Sponge miR-942-5p eventually downregulates ZNF471 -and inhibits invasion and metastasis	[55]
		–	Pancreatic cancer	Promoter	Interact with miR-150-5p and stimulate VEGFα/PI3K/AKT axis	[56]
		–	Gastric cancer	Promoter	Associated with poor survival	[57]
		–	Gastric cancer	Promoter	Sponge miR-29a-3p increases COL1A2 expression and is involved in cancer progression	[58]
		–	Glioma	Suppressor	Target miR-4262 and suppress the NF-κB pathway	[61]
		–	Thyroid cancer	Suppressor	sponge miR-31-5p and up-regulate SIDT2	[62]
		–		Promoter	Silencing LIFR-ASI decreases cell viability and proliferation by inducing G2/M phase cell cycle arrest.	[63]
9	IncAMPC	Stimulate LIF/LIFR signaling	Prostate cancer	Promoter	Sponge miR-637 and induce metastasis as well as immunosuppression.	[64]
10	circ_CRIM1	Promote expression of LIFR	Lung adenocarcinoma	Suppressor	Sponge miR-93 and miR-182	[65]
11	circ_ARPP21	Increase LIFR expression	Hepatocellular carcinoma	Suppressor	Sponge of miR-543 and restrain proliferation, invasion, and migration	[66]

Sl. No.	LncRNA/ miRNA	Relation to LIF/LIFR axis	Cancer type	Tumor Role- Suppressor/ Promoter	Regulation/Signaling	References
12	circ_0001073	Increase LIFR expression	Lung cancer	Suppressor	Sponge miR-626 decreases cell viability invasion and stimulates apoptosis.	[20]
13	circ_0003159	Increase LIFR expression	Gastric cancer	Suppressor	Target miR-221-3p and miR-222-3p. Promote apoptosis and block cell viability and migration.	[67]

Table 2

Impact of LIF/LIFR axis signaling in various cancers.

Cancer type	Pathway	Role in tumor (Promoter/ suppressor)	Involvement	Target molecule	References
Breast cancer	JAK1-STAT3 signaling	Promoter	Apoptosis inhibition	BCL-2 and MCL-1	[115]
	AKT-mTOR	Promoter	Tumorigenesis and metastasis	p70S6K and 4EBP1	[10]
	miR-125a	Suppressor	Decrease self-renewal and tumor initiation genes	LIFR/TAZ	[116]
			Metastasis suppressor	YAP	[16]
	STAT3	Suppressor	Rendering dormant phenotype	SOCS3	[83]
		Promoter	Stemness, tumorigenesis, and metastasis	Cancer stem cells	[32]
	Epigenetic modification of LIFR	Suppressor	Induces tumor dormancy	TGFB2 and MSK1	[132]
Melanoma	BMP	Promoter	CSC renewal and upregulation of stemness genes	BMP4 and BMP7	[6]
	STAT3	Promoter	Migration	MMP2 activation	[133]
	TGF-β/STAT3/p21	Suppressor	Growth arrest and metastasis suppressor	Bax and Bim	[134]
Pancreatic cancer	STAT3, HIPPO, and WNT	Promoter	Differentiation and EMT inhibition	Zeb1	[98]
		Suppressor	Perturb glycolysis and abolish transformation	GLUT1	[12]
	JAK/STAT3/AKT	Promoter	Migration and differentiation	p21	[135]
	Hippo	Promoter	Tumor growth and overall survival	$pYAP^{ser127}$	[95]
	Increased E-Cadherin	Suppressor	Metastasis suppressor	β-catenin, Vimentin, and Slug	[89]
Lung cancer	p-ERK/pS727-STAT3	Promoter	Mesenchymal to epithelial transition (MET)	GATA3, cyclin D1, and E-cadherin	[84]
Chondroma	–	Promoter	CSC Renewal	TNFAIP2, MET, and KLF4	[123]
Colorectal cancer	JAK/STAT Downregulation of p53	Promoter	Anti-apoptosis	Inhibitor of DNA-binding 1 (ID1) and MDM2	[8]
Glioblastoma	ZEB1	Promoter	CSC Renewal	Represses LIF	[136]
Nasopharyngeal carcinoma	YAP	Promoter	Metastasis	FAK/PXN	[137]
	LMP1/LIF		Increase tumor growth and decrease	mTORC1/p70S6K	[14]
			DNA damage response		
Oral squamous carcinoma	Tumor cells stimulate fibroblasts to secrete LIF and TGF-β2	Promoter	Migration and invasion	LIF	[138]
Osteosarcoma	JAK/STAT3	Promoter	Growth, metastasis, and CSC maintenance	LIF	[7]
	JAK/STAT and EMT	Promoter	Stemness maintenance	NOTCH1	[139]
Ovarian cancer	JAK/STAT3	Promoter	Survival, proliferation, metastasis, and stemness	IL6 and LIF	[140]

Cancer type	Pathway	Role in tumor (Promoter/ suppressor)	Involvement	Target molecule	References
Prostate cancer	JAK/STAT3	Promoter	Immunosuppression	TLR9/LIF	[141]
			Proliferation and castration resistance	ZBTB46	[2]
	EGFR and STAT-3	Promoter	Castration resistance and neuroendocrine differentiation	SUCLG2	[111]
	$pLIFR^{ser1044}$	Promoter	Proliferation, invasion, metastasis, and	ERK2	[1]
	AKT		adhesion		
Clear Renal Cell Carcinoma	Hippo	Suppressor	Metastasis suppressor	YAP	[142]
Gastric cancer	PI3/AKT	Suppressor	Cell migration, Invasion/metastasis suppressor	c-Jun	[48]
		Suppressor	Growth inhibition and cell cycle arrest	p21 and cyclin D1	[101]
	Hippo	Suppressor	Recurrence and tumor maintenance.	Cancer stemness genes	[143]
	Hippo-YAP	Promoter	cell proliferation, migration, and invasion	MST1, LATS1, YAP, Cyr61, MMP7, and E-cadherin	[13]
Hepatocellular carcinoma	PI3K attenuation	Suppressor	Metastasis suppressor	MMP13	[104]
Endometrial cancer	STAT3 and AKT/mTOR	Promoter	Required for cancer progression	Sox2, OCT4, NANOG and Axin 2	[15]
Cholangicarcinoma	PI3K/AKT	Promoter	Decreases apoptosis	Mcl-1	[144]
Medulloblastoma	PI3K-p110α	Promoter	Decreases cell proliferation and xenograft tumor growth reduction	c-Myc/miR-125b/LIFR	[124]

Table 3

LIF/LIFR axis targeting agents

Inhibitor/Agent	Mode of action	Biological effect	References
EC359	Binds with LIFR extracellular Fc region and confers steric hindrance to ligands, like LIF, CNTF, CTN-1, and OSM.	Decrease cancer cell viability and invasion. Induces apoptosis. Decreases PDX tumor growth. Tested in TNBC, endometrial, and pancreatic cancer	[15,100,128]
PEGLA (LIFR antagonist)	Upon binding with LIFR, it reduces STAT3 phosphorylation.	Prevents LIF action on embryo implantation into the uterus. Preclinical tested in mice and cynomolgus monkey	[145,146]
MH-35-BD (LIFR antagonist)	Action on Glycosaminoglycan (GAG) release. Inhibits the activity of other IL-6 subfamily-related ligands.	Treatment options for Rheumatoid Arthritis and other diseases related to LIF and IL-6 family ligands.	[147]
Q29A/G124R MH35-BD.	Inhibition of proliferation of Ba/F3 murine pro B lymphocytes. LIF mutants as a super antagonist	Abrogate cell signaling and LIF-induced bioactivity	[148]
hLIF-05	Blocks LIFR/gp130 receptor tyrosine phosphorylation. Diminution of moderate oxidative stress-induced STAT3 activation	LIFR antagonism prevents receptor oligomerization. Blocks protective effects of LIF/LIFR in neuroprotection in retinal cells	[149,150]
MSC-1 Humanized anti-LIF antibody	Neutralizing antibodies against LIF increases interferon-γ and IL-2 cytokines as a measure of cellular immunity against recombinant truncated LIF and recombinant truncated LIFR.	Neutralizing antibodies blocked embryo implantation, and breast xenograft tumor growth was restricted.	[113]
LIFR-Fc “ligand trap.”	Sequester human LIF in circulation.	Inhibits LIF-mediated *in vitro* and *in vivo* cancer cell growth.	[151]
hLA	Affects STAT3 and p65 phosphorylation in endometrial ECC-1 cells	The antagonist for human LIFR	[152]