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REVIEW ARTICLE

The LIF cytokine: towards adulthood

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ABSTRACT. The aim of this article is to recapitulate the key features of leukaemia inhibitory factor cytokine (LIF), to review its numerous physiological effects and to comment on the most recent data. We will also present results of transcriptome analyses, which have highlighted different categories of LIF targets, identified in murine embryonic stem (ES) cells and early derivatives. We hope to stimulate new research fields on this puzzling cytokine, which, forty years after its discovery, has still not disclosed all its secrets.

Keywords: LIF, IL-6, ES cells, pleiotropy, chromatin, p53[1]

LIF discovery was performed independently by several research groups in the 1970-80's, and was based on the different biological effects characterized in distinct cellular models, and was hence given different names. The name LIF has remained the most commonly used despite it being the least appropriate [1, 2]. Pleiotropy is the property of a protein to display various and sometimes opposing effects. In this regard, LIF could sustain proliferation or differentiation depending upon cell maturity or type [1-3]. While the physiological, non-redundant function of LIF stands in its effect during blastocyst implantation, an essential role of LIF has also been reported for mammary gland involution after the lactation [4, 5]. Unregulated LIF secretion is also associated with pathological conditions such as cancer [6-9].

LIF turns out to be at the heart of many physiological processes throughout life, starting from embryo implantation. It is involved in uterine maintenance of the foetus by providing an immune-tolerant environment in the decidua. The recent finding that it directly regulates the function of T regulatory (Treg) cells, conferring immune tolerance during transplantation, has added a new twist, and suggests a potential, specific function in immunity [10-12]. The mechanism of action of LIF will be better understood by elucidation of the signal transduction pathways it modulates, and by identification of the gene targets it transcriptionally regulates. In addition, the recent discovery that LIF is a direct cytokine effector of the p53-dependent signaling pathway [13] should allow re-evaluation of results involving LIF and p53, in the light of potential links between these two proteins, which are co-expressed in many cell systems [14].

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A BRIEF HISTORY OF LIF

LIF activity was first reported in 1969 by Ichikawa, who described a biological activity associated with embryo-conditioned medium, which was able to inhibit proliferation and to induce macrophage differentiation of the M1 leukemic myeloid cell line [15]. This biological activity, then called D-factor (for differentiation factor), was partially purified from embryos and Krebs ascites cell-conditioned medium [16], followed by purification to homogeneity of the active protein. At the same time, this protein was characterized from cell line-conditioned media: fibroblasts [17-19], heart cells [20], human alloreactive T-cells stimulated by alloantigens [21] and mitogen-triggered spleen cells [17]. These studies led to the molecular cloning of LIF in many species including human [19, 22-25].

THE LIF LIGAND

Main features

Human LIF is a 180-amino acid glycoprotein and belongs to the IL-6 sub-family of the larger "four-helix superfamily" of cytokines, comprising the following six members: ciliary neurotrophic factor (CNTF), interleukin 11 (IL-11), oncostatin M (OSM), cardiotrophin-1 (CT-1), CLC/CLF (cardiotrophin-like cytokine-cytokine-like factor (CNTF II ligand [26]), and IL-27 [27-30]. Purified human LIF has a MW of 37 to 62 kDa depending on its degree of glycosylation [31, 32]. The glycosylation sites of LIF can hold mannose-6 phosphate residues, creating a ligand site for the mannose-6 phosphate receptor (CIMPR, calcium-independent mannose-6 phosphate receptor), which participates in the cellular recycling of the LIF ligand [33, 34].

LIF exists in at least three isoforms, *i.e.* a soluble form called LIF-D, an intracellular form found in the nucleus, called LIF-i or LIF-T, and a third form localized in the extracellular matrix, termed LIF-M [35-37]. LIF-M and LIF-D are translated from alternative transcripts differing in the first exon, which encodes partially for different signal peptides, which target the mature protein to different locations. The LIF-T isoform is a truncated protein because of the absence of the ATG codon in the first exon, leading to the initiation of translation at the first ATG codon of exon 2. This isoform has pro-apoptotic activity in the COS and 293T cell lines [37], but the function of this internal form of LIF has not been investigated in other cell systems or tissues. Expression of these three isoforms is regulated in an independent way during embryogenesis and adult life, whereas other isoforms have also been identified in liver [38, 39], but their functions await further clarification.

Abbreviations

AP1	activator-protein 1
BMP	bone morphogenetic protein
CD	cluster of differentiation
c-fos	FBJ murine osteosarcoma viral oncogene homolog
CIMPR	calcium-independent mannose-6 phosphate receptor
c-jun	avian sarcoma virus 17 oncogene homolog
CLC/CLF	cardiotrophin-like cytokine/cardiotrophin-like factor
c-myc	avian myelocytomatosis viral oncogene homolog
CNTF	ciliary neurotrophic factor
CNTFR	CNTF receptor
CREB	cAMP response element-binding
CT1	cardiotrophin-1
Dapp	dual adaptator of phosphotyrosine and PI3K
D-factor	differentiation factor
Eed	embryonic ectoderm development
EGF	epidermal growth factor
Egr	early growth response
ERK	extracellular signal-regulated kinase
ES cells	embryonic stem cells
FGF	fibroblast growth factor
Foxp3	forkhead box protein3
Fra	Fos-related antigen
HDAC	histone deacetylase
Hgf	hepatocyte growth factor
HLA	human leukocyte antigen
Ier	immediate-early response
Igfbp3	insulin growth factor binding protein-3
IL	interleukin
IL-6R	IL-6 receptor
IL-11 R	IL-11 receptor
iPS cells	induced pluripotent stem cells
Irg1	immune response gene-1
JAK	Janus kinase
junB	oncogene JUN-B
KLF	Kruppel-like factor
KO	knock-out
LIF	leukaemia inhibitory factor
Lifind	LIF-induced genes
LIFR	LIF receptor
MW	molecular weight
NANOG	from Tir Na Nog
OCT	octamer-binding transcription factor
OSM	oncostatin M
OSMR	OSM receptor
p53	Tp53, tumor protein 53
PI3 kinase	phosphatidylinositol 3-kinase
RSK	ribosomal S6 kinase
RT-PCR	reverse transcriptase polymerase chain reaction
SHP2	Src homology region 2, phosphatase 2
SOCS	suppressor of cytokine signaling
SOX	SRY-related-HMB-box
STAT	signal transducer and activator of transcription
SWS	Stuve-Wiedemann syndrome
TAM cells	tumor associated macrophages cells
Treg	T regulatory cells
VEGF	vascular endothelial growth factor
Wnt	wingless-type mmtv integration site family
Zfp	zinc finger protein

LIF is secreted by many cell types such as fibroblasts, activated T-cells, spleen or macrophage cells, chondrocytes, bone marrow stromal cells, mesenchymal stem cells, endothelial cells, astrocytes and also tumor cells [17, 40, 41]**.** *In vivo*, LIF production is associated with inflammation and autoimmune diseases [42-44]. It also promotes N-cadherin-mediated cell adhesion *via* the STAT3/ Wnt5 pathway in cardiomyocytes [45]. LIF is also naturally produced by the uterine decidua under the control of the estradiol peak, before implantation [14, 46-48] and thereafter is sustained by progesterone, presumably to induce a tolerant environment for the foetus during gestation [49]. Indeed, in endometrium, LIF directly induces the production of the class I non-classical HLA-G protein, whose function is essential for immune tolerance at the maternal-foetal interface during the establishment of gestation [50]. A high level of active LIF is also associated with transplantation tolerance, with direct regulation of Treg cell function in which the expression of the *Foxp3* gene seems to be controlled, at least in part, by LIF [11, 51]. Recent studies, conducted with KO model mice, have also revealed that LIF is a direct transcriptional target of the Fos-related protein Fra2, involved in the regulation of osteoclast functions [52]. A deleterious immunosuppressive function of LIF, which allows tumor cells to escape the immune system, has also been described in a model of ovarian cancer. Indeed, it was shown that LIF was a tumor-secreted factor that induces differentiation of monocytes to highly immunosuppressive TAM cells (tumor associated macrophages), [9].

Excess of LIF

The effect of an excess of LIF has been investigated in mice injected with the FDCP1 hematopoetic stem cells engineered to constitutively produce biologically active, murine LIF. These cells were engrafted normally into bone marrow, spleen and lymph nodes. After two to three months, engrafted animals lost weight, became hyperactive, developed osteopetrosis of long bones, calcifications in liver, heart, pancreas and skeletal muscles as well as abnormalities in the adrenal cortex and ovarian corpora lutea [53]. Studies of excess of LIF in the thymus of transgenic mice have led to the conclusion that LIF is important for maintaining a functional thymic epithelium that will support proper T cell maturation, a property also shared by oncostatin M [54, 55]. In embryos, excess of LIF-M blocks gastrulation by inhibiting the inner-cell mass differentiation into primitive ectoderm, a result also observed *in vitro* with embryoid bodies whose differentiation was blocked in the presence of an excess of LIF [56, 57]. These pioneering experiments, along with those showing that LIF maintains the pluripotency of mouse embryonic stem (ES) cells *in vitro* [23, 58-61], have led to numerous studies aimed at elucidating the mechanisms of action of LIF in stemness.

LIF and pluripotency

Knowledge of LIF signaling in the mouse ES cell system, along with years of expertise in manipulating mouse embryos, have led to the understanding of the species-dependent requirement of LIF for the maintenance of ES cell pluripotency. At first glance, it was puzzling to find that while mouse ES cells (mES) required LIF for maintenance of pluripotency, human ES cells (hES) did not need LIF, but rather have to be grown under the influence of activin and FGF factors in order to maintain their undifferentiated state [62-65]. A pioneering study, conducted using the mouse ES cell system, has already depicted a LIF-independent paracrine activity (named ESRF), secreted by differentiated cells, which allows the maintenance of mES cells pluripotency [66]. However, this activity has not been characterized further and its potential activity on human ES cells has not been evaluated. Since these first observations, transcriptome studies have led to the characterization of similarities and differences in expression profiles of genes in mES and hES cells, suggesting that these cells are probably not derived from equivalent parts of the early embryo [67, 68]. More recently, key results from two independent laboratories have been obtained which demonstrated that hES cells were probably not LIF-dependent because of their derivation from late rather than early epiblast [69-71]. These studies point to the fact that there is a short time frame for LIF dependency, and for maintenance of pluripotency in early embryos, which can be different between species and which deserves careful exploration (see also paragraph "LIF signaling: oldies and novelties"). However, the potential requirement of LIF for hES cell derivation and maintenance, which could depend on the maturity states of the embryos used to derive hES, might explain why some laboratories have used LIF in their culture medium, for growing hES cells [72].

LIF knock-out models

If homozygous LIF$^{-/-}$ mice are viable, they nevertheless present many defects, including a decrease in the survival of hematopoetic stem cells and of their primordial germ cell pools [73], a profound loss of motor neurons [74] and of glial cells, along with an alteration in oligodendrocyte function [75]. In addition, maturation of olfactory neurons is impaired [76]. Recent studies have also shown that LIF represses hypoxia-induced VEGF expression, resulting in regulated capillary network formation [77]. Of major importance, LIF$^{-/-}$ females are fertile, but their blastocysts cannot implant, leading to the definition of LIF as being the "nidation hormone" [73]. This implantation defect is due to the absence of LIF production by the uterus. LIF production is normally induced by estradiol *via* the TP53 loop. Indeed, there are functional TP53 binding sites in the LIF promoter [13, 78-80]. Of note, p53 $^{-/-}$ mice display the same implantation defect phenotype as LIF$^{-/-}$ mice [13]. Interestingly, LIF$^{-/-}$ or p53$^{-/-}$ blastocysts develop normally if implanted in a wild-type female or upon direct injection of LIF into the vagina of TP53$^{-/-}$ or LIF$^{-/-}$ mutated mice. None of the other IL6-related ligands has this specific effect on implantation, as deduced from the knock-out phenotypes reported for these ligands *(table 1)*.

THE LIF RECEPTOR

Members of the IL-6 subfamily activate preformed, heteromeric receptors, which do not have any intrinsic catalytic activity and which all share the gp130 subunit [27, 28, 81-83]. The association of the ubiquitous gp130 (also called "subunit α") with subunits specific for one or a few sub-family members (the so-called "β subunit" (*e.g.* gp190/ LIFRβ; CNTFRβ; gp80/IL-6Rβ; OSMRβ; IL-11Rβ), and whose expression is more or less restrained, is responsible for both the diversity and the redundancy of the cell responses in this sub-family [84]. The functional LIF receptor is an heteromer comprising LIF low affinity binder gp190 together with the high affinity-converter gp130, both being transmembrane subunits with signalling ability. Preformed, inactive receptors are most probably present at the cell surface in the absence of ligand, as shown by co-precipitation of the heterodimeric complex without ligand, with anti-gp130 or anti-gp190 antibodies. However LIF binding increases interaction between subunits, and is essential for cellular responses [85-87]. The stoichiometry of the functional ligand/receptor complex is not known, but recently crystallographic analysis has demonstrated that this complex is a tetramer consisting of two LIF/gp190 molecules, [88, 89]. The intracellular part of both gp130 and gp190 associates with kinases of the JAK family, recruiting transcription factors of the STAT family, especially STAT3, as well as attenuators of LIF signaling such as the SHP2 tyrosine phosphatase and SOCS3 [90-92].

Mice knocked-out for the gp190 subunit, which also has low affinity binding for CT-1, display reduction of bone volume, severe osteopenia, metabolic liver disorder and reduction in astrocyte and motor neuron numbers in cerebral trunk and spinal chord [93-95]. They die perinatally, in part due to feeding difficulties because of their lack of development of sucking muscles. The placenta is also profoundly affected.

Gp130$^{-/-}$ mice have also been generated in several laboratories, but the phenotypes reported are discrepant. Mutant mice produced by Yoshida *et al*. die between days 12 to 16 of embryogenesis with cardiac, hematopoetic and neuronal disorders [96], whereas those generated by Nichols *et al*. showed a critical function of gp130 in the completion of embryogenesis, only after diapause induction. This phenotype suggests a specialized function of gp130 as a response to environmental stress [97]. The reasons for these discrepancies have not been further investigated. Conditional gp130 deficient mouse mutants have also been derived in which gp130 was deleted in specific tissues or organs such as liver, lung or heart. These studies revealed a key role for gp130 signals in counterbalancing stress-dependent apoptotic signals [98].

HUMAN PATHOLOGY ASSOCIATED WITH LIF DEFICIENCY

LIF and fertility

In humans, as demonstrated in mice, LIF is expressed by the decidua following the estradiol peak and seems to be involved in blastocyst implantation. Gp190 is expressed in the luminal epithelium during the proliferative and secretory phases of the uterine cycle [99]. In addition, significant differences in the level of the soluble form of the gp190 protein (sgp190) have been founded in the serum of pregnant *versus* non-pregnant women, suggesting a role for this cytokine system throughout pregnancy, and more specifically in the functioning of the placenta [100]. LIF deficiency may be associated with a subset of female infertility due to an implantation defect. However, the direct effect of LIF is still a matter of debate since sterility has been associated with a decrease in LIF expression [101, 102] or to mutations in the *LIF* gene [103, 104], while other studies have shown that a low LIF level was a good implantation predictor [105]. However, in sterile women with endometriosis, LIF is not detected in the endometrium at the implantation stage [106].

The Stüve-Wiedemann syndrome

The Stüve-Wiedemann syndrome (SWS) or type 2 Schwartz-Jampel syndrome is a severe, autosomal recessive condition characterized by bowing of the long bones, respiratory distress, feeding difficulties, and hyperthermic episodes responsible for early lethality [107]. The molecular defect has been identified as null mutations in the gene encoding for the gp190 subunit of the LIF receptor. Functional studies have indicated that these mutations alter the stability of gp190 transcripts, resulting in the absence of this LIF receptor protein subunit and in the impairment of the JAK/STAT3 signaling pathway in patient cells. Of note, the phenotype of the gp190$^{-/-}$ mice mimicked the complex phenotype of SWS patients, especially regarding the bone and nerve defects and early death [94].

REDUNDANCY AND PLEIOTROPY

LIF induces differentiation of the M1 cell line and apoptosis of normal mammary gland cells, after the lactating period. LIF is a pro-differentiative cytokine for adipocytes, [108], for cardiac muscle cells in a dose-dependent way and in synergy with BMP2 [109], and it induces differentiation of cardiac stem cells into endothelial cells [110]. Conversely, LIF maintains self-renewal of murine ES cells in synergy with serum or BMP4 or Wnt family members (Wnt3A and Wnt5) [111-113]. In addition, LIF regulates the differentiation process of stromal cells from bone marrow. Indeed, LIF secretion by human mesenchymal cells decreases when cells differentiate towards the adipogenic or osteoblast lineages. The LIF level, which is controlled by specific miRNA, is an essential, regulated parameter for proper differentiation of these cells [114]. LIF also favors the proliferation and survival of germ cells, hematopoietic progenitors, megakaryocytes, myoblasts and neural cells [1-3]. Some of these effects have been reported with other IL-6 family members [84]. Indeed, OSM, CNTF, CT1 and IL6 (in the presence of its α receptor subunit soluble gp80, which is not expressed by ES cells) are all endowed with the ability to maintain murine ES cell pluripotency [115, 116]. Additionally, OSM, CT1 and IL-6 induce macrophage differentiation of the M1 cell line [117, 118]. Gene ablation of LIF, CT-1 or CNTF or of their receptors *(tables 1, 2)*, demonstrate their involvement in motor neuron survival [93, 119-121]. Double *Lif*$^{-/-}$/*Cntf*$^{-/-}$ and triple *Lif*$^{-/-}$/*Cntf*$^{-/-}$/*Ct-1*$^{-/-}$ knock-outs prove that these three cytokines have distinct functions for motor neuron survival and that LIF has an important role in post-natal maintenance of distal axons and motor neuron junctions [74].

LIF signaling: oldies and novelties

First identified as an EGF, IL-6 and LIF-dependent phosphorylated protein, STAT3 is present and active in all cells where LIF has an effect, whatever it may be [122-128]. Other factors that are always involved in LIF sig-

Table 1
Physiological effects of IL-6 cytokine family members revealed by KO mice models

Cytokines	Physiological effects	References
LIF	Survival of *lif*$^{-/-}$ adult mouse, but decreased numbers of stem cells in spleen and bone marrow	[73]
	No implantation of blastocysts in mouse lacking LIF gene. Implantation and development to term of the blastocysts when transferred to wild-type pseudopregnant recipients or by injection of LIF	[46, 78]
	Role in survival and differentiation of glial cells and oligodendrocytes of the hippocampus. Alteration of olfactory receptor neuron maturation	[75, 190]
IL-6	Normal development of IL-6-deficient mice. Impairment of the T-cell-dependent antibody response against vesicular stomatitis virus and the inflammatory acute-phase response after tissue damage or infection	[191, 192]
	Hematopoietic stem cell regulation	
OSM	Role in survival of neurons in the adult trigeminal and dorsal root ganglia and in the development of a subtype of nociceptive neurons	[193]
CNTF	Implicated in survival of motor neurons in adult mice	[120, 194]
CT-1	Implicated in survival of motor neurons in spinal cord and brainstem nuclei of mice during a period between embryonic day 14 and the first postnatal week	[121]
LIF/CNTF	Important implication of LIF and CNTF in survival, and in the function of motor neurons in the postnatal period. Co-operation of the two cytokines in the maintenance of motor neurons after lesion in deficient mice of four weeks	[120]
LIF/CNTF/CT-1	Different functions of CNTF, LIF and CT-1 for the survival and the function of motor neurons. A more important role of LIF for postnatal maintenance of distal axons and motor endplates	[74]

Table 2
Physiological effects of IL-6 subunit receptor members revealed by KO mice models

Cytokines	**Physiological effects**	**References**
Gp130	Death of embryos homozygous for the gp130 mutation between 12.5 days *postcoitum* and term. Crucial role in myocardial development and hematopoiesis during embryogenesis	[96]
	Importance of gp130 signalling for the prolonged maintenance of epiblast *in vivo* during diapause period induced by ovariectomy	[97]
LIFRβ/gp190	Disruption of normal placental development in mutant mice leading to poor intrauterine nutrition, but foetuses reach term. Alterations in fetal liver metabolism and formation of bone. Role in the survival of astrocytes and motor neurons in the spinal cord and brain stem	[93, 94]
IL-11Rβ	Infertility in female mice due to a defective decidualization	[195, 196]
OSMRβ	Role in regulation of hematopoiesis. Key role in liver regeneration	[197, 198]
CNTFRβ	Mutant death perinatally. Role of CNTFR in motor neuron survival. Critical effects of CNTFR on the developing nervous system	[119]

naling are the activated JAK tyrosine kinases [129, 130]. JAK1 is essential for LIF signaling in mES cells [131, 132] and in trophoblast differentiation [133], and JAK2 seems to play a critical role in LIF-dependent muscle satellite cell proliferation [134]. The third obligatory component of LIF signaling is the feedback control regulator, which includes members of the *Socs* gene family [135-141]. SOCS3, a STAT3-dependent repressor that attenuates LIF signaling, is critical in many cell types and tissues in which LIF has an effect. Indeed, SOCS3 is essential for maintenance of murine ES cell pluripotency [142-144], for trophoblast differentiation [133, 145, 146] and for the involution of the mammary gland at the end of the lactation period [147, 148]. SOCS3 is also essential for regulation of the immuno-tolerant function of LIF recently described in Treg cells [149].

Other genes are induced by cytokine response, in general. This is the case for the primary response genes *junB*, *c-jun* and *egr1* that are all induced upon LIF treatment in M1 or ES cells, see *tables 3* and *4* [142, 150, 151].

However, so far, the mechanism of LIF pleiotropy has not been elucidated and both transcriptomic and proteomic/phosphoproteomic approaches should help to resolve this complex issue. Several cell-type specific targets of LIF such as hepatocyte growth factor (*Hgf)* induced in SEK1 cells or the insulin growth factor binding protein 3 *(Igfbp3)*, amphiregulin and the immune response gene 1 *(Irg1)*, identified in endometrium cells, also indicate that different end point transcriptional targets might explain pleiotropy [152, 153].

In mouse ES cells, LIF also induces the PI3Kinase pathway, which maintains cell pluripotency [154-156] while activating the ERK/ RSK/ CREB pathways which, along with the FGF pathway induce pro-differentiative programs [157-159]. Thus, several LIF induced pathways are concomitantly required to maintain ES cell plasticity, a peculiar property of stem cells.

Recent transcriptomic analyses performed in mouse ES cells and early derivatives, treated for short period (30 min) with LIF, have allowed identification of common and cell-specific LIF-regulated genes (summary in *table 3*). Primary response genes (*c-fos, JunB*, *Egr1* and *2, Ier2*), the *Socs3* inhibitor and regulators of mRNA stability (such as *Zfp36* and its direct target *Ier3,* [160]), are among the common LIF-induced (*Lifind*) genes found in ES cells and early derivatives [161]. Indeed, these genes are induced by LIF after a 24 or a 48 h period of LIF withdrawal, which respectively correspond to a LIF-dependent reversible (24 h) or irreversible (48 h) state of committed cells [158, 162-164]. These genes are also expressed in differentiated cells which re-express LIF and its receptor, after 10 days of LIF withdrawal [161]. This study has led to the characterization of different time-frames of LIF activity in the ES cell model. It will be a

Table 3
LIF transcriptional targets in different cell contexts

Cell types		**Transcriptional targets**	**References**
ES cells	Pluripotent cells (+LIF)	*JunB*; *c-fos*; *Socs3; Zfp36; Stat3Loc; c-Myc; Cd9; Ypel2; Plscr1*; *Dapp1*	[116, 142, 161, 186, 199]
	ES-derived, reversible committed state (-LIF 24h, induced 30 min. with LIF)	*JunB; c-fos; Socs3; Zfp36; stat3Loc; Egr1; Egr2; Ier2; Ier3; Klf4; Klf5; Rasd1; Nfkbiz; Dapp1; Ypel2; Dystonin; Pabpc1; Etv6; Sbno2; Plscr1*	[161]
	ES-derived, irreversible committed state (-LIF 48 h, induced 30 min. with LIF)	*JunB; c-fos; Socs3; Zfp36; stat3Loc; Egr1; Egr2; Ier2; Ier3; Klf4*	
	ES-derived, differentiated cells (10 days without LIF)	*JunB; c-fos; Socs3;Zfp36; Egr1; Egr2; Ier3; Nfkbiz; Expression of endogenous LIF and of LIFR subunits*	
Tumor cells	M1 myeloid cell line	*JunB*; *c-jun*; *JunD*, *Cis*; *Gp49B1*; *Socs1; Egr1*	[151, 152, 172, 200, 201]
	SEK1 (human melanoma)	*Hgf*	[202]
Normal tissues	Endometrium	*Igfbp-3; Amphiregulin; Irg-1*	[203]
	Cardiomyocytes	*Zfp36*; *Socs1*; *Socs2*; *Socs3*	[153, 204]
	Fibroblasts	*Egr-1*; *c-fos*; *Socs3*	[205]
	Neural progenitors	*Socs2*; *Socs3*	[206, 207]

Table 4
Potential actors of the pleiotropic effects of LIF

	ES $\xrightarrow{\text{LIF}}$ Proliferation Pluripotency		M1 $\xrightarrow{\text{LIF}}$ Differentiation in macrophages		
	−LIF	+LIF	−LIF	+LIF	
c-jun	−	++	−	++	T.
JunB	−	++	−	++	
JunD	++	++	−	++	
Socs1	+	+	−	++	
Socs2	+	+	−	−	
Socs3	−	++	−	−	
Egr1	−	++	−	+	
Egr2	−	++	N.D.	N.D.	
STAT3	+	+	+	+	Post-T.
P-STAT3	−	++	−	++	

The expression profiles of Jun, Socs and Egr family members (detected by northern blots or RT-PCR) and of STAT3 and Phospho-STAT3 (detected by western blots) in mouse ES and M1 cell lines, in which LIF has opposite effects. While STAT3 activation is transient in ES cells, it is sustained in M1 cells.
T: Transcriptional regulation; Post-T: post-translational regulation. - : not expressed or not phosphorylated; + : expressed; ++ : highly expressed or highly phosphorylated.
Compilation of results are from these references: 135, 136, 137, 138, 142, 143, 158, 170, 171, 172, 200.

future goal to unravel the functions of these LIF targets in pluripotent ES cells and at various stages of ES-derived cell maturation. STAT3 was also re-expressed in differentiated cells, and characterization of its interaction networks in stem cells *versus* differentiated cells remains a challenging issue for the further understanding of LIF pleiotropy. Novel *Lifind* genes, whose induction is restricted to ES-derived committed cells (24h of LIF withdrawal), have also been identified. This is the case of *Yippee-like2*, *Strawberry Notch2* (Drosophila orthologs), *Dystonin*, *Phospholipid scramblase1* and *Dapp1* (a regulator of PI3K), whose functions in mouse are still poorly understood and which deserve further attention.

Mechanisms underlying LIF pleiotropy

STAT3/SOCS3 are the common, obligatory, LIF-dependent effectors found in almost all LIF-sensitive cell lines. Surprisingly, it has been shown, in at least two mouse cell systems (ES cells and pituitary tumor cells), that cell type-specific effectors of LIF and STAT3 only partly overlap [161, 163, 165, 166]. Also, depending upon the cell context, STAT3 could be associated with various partners such as NANOG, as recently shown in certain cancer cells [167]. In addition, the proteins encoded by the primary response genes, which are activated in many LIF-sensitive cell types, are themselves part of various transcriptional complexes (*e.g.* AP1 complexes), whose associations with different partners could lead to pleiotropic effects. Interestingly, different members of the Socs and Jun families are induced by LIF in M1 or ES cells *(table 4)*. *Egr1* is induced in both cell systems and is critical for the macrophage differentiation of M1 cells, but its effect in ES cells has not yet been investigated [168, 169].

Another parameter, potentially involved in the pleiotropic effects of LIF, is the duration of the LIF signal. Indeed, while STAT3 activation is transient in ES cells (it starts decreasing after 1h of LIF stimulation), it is sustained in M1 cells where it lasts up to 36h [170-172].

Also and not yet tested in various LIF-sensitive cell types, epigenetic regulations could account for pleiotropic LIF effects. For example, in the ES cell system, a high level of phosphoacetylation of histone H3 has been reported as being a feature of ES-derived differentiated cells [173, 174]. In addition, repression of HDAC (histone deacetylase) activities by chemicals such as TSA (trichostatin A), in mouse ES cells grown with LIF, induces the expression of differentiation markers along with morphological changes similar to those observed upon LIF withdrawal [175, 176]. Furthermore, a specific epigenetic hallmark has been characterized, that is absent in differentiated cells: by mapping the histone methylation pattern in 2.5 % of mouse genome, it has been shown that a bivalent, tri-methylation mark at the histone H3 (H3K4 triMe / H3K27 triMe) was enriched in pluripotent cells only at differentiation gene loci, leading to silencing of these genes in undifferentiated cells. Upon cell differentiation, these bivalent modifications disappear and differentiation genes are expressed according to the remaining level of single H3K4 triMe (correlated with gene activation) or H3K27 triMe (correlated with gene repression). These crucial data led to the hypothesis that bivalent domains silence developmental genes in ES cells while keeping them poised for activation [177, 178]. It has also been demonstrated that Eed, the core component of the repressive polycomb complex, is a LIF-dependent STAT3 target in ES cells that is associated with high levels of H3K27 triMe. Eed could be the critical effector in silencing differentiation genes in pluripotent ES cells [179]. We would therefore propose the hypothesis that the absence of Eed or of a related repressive protein in M1 cells leads to a pro-differentiative effect of LIF, despite the presence of activated STAT3. It will be of great interest to determine the status of phosphorylation, acetylation and methylation at the histone H3 protein in ES and M1 cell lines treated with LIF for various periods of time and to determine whether pleiotropy could also rely on differential epigenetic regulation [176, 180, 181]. We propose a model in which LIF signalling would lead to opposing effects depending on whether it occurs in a context of opened or closed chromatin. Accordingly, some genes would always be activated in the presence of LIF (such as *Stat3*, *JunB* or *Socs3*), because of an unregulated chromatin status at these gene loci, an assumption that remains to be demonstrated. In this regard, the fact that LIF is a direct transcriptional target of the p53 protein, a known chromatin regulator [182, 183], opens also new avenues for understanding the mechanisms underlying LIF pleiotropy.

CONCLUSION

LIF orthologs have been characterized in many species, even in kangaroo in which gestation does not proceed through classical internal implantation [184]. Also intriguing, LIF ortholog has been cloned in chicken [185], but the function of LIF in these species remains to be studied. The evolution of this particular cytokine to become the "nidation hormone" in eutherian mammals is a challenging research area, which deserves particular attention as regards EVO-DEVO concerns, as well as for its potential relevance in the treatment of human infertility.

Let us hope that with accumulating understanding of LIF, and with technical advances in protein function analyses, it will not take another 40 years to unveil LIF's secrets and to understand how some LIF targets (such as c-MYC [186, 187] and KLF4 [143], both shown to be essential for self-renewal of mouse ES cells) can reprogram mouse and human somatic cells to become iPS cells (induced pluripotent stem cells), along with pluripotent factor companions such as OCT4 and SOX2 [61, 188, 189].

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REFERENCES

1. Taupin JL, Pitard V, Dechanet J, Miossec V, Gualde N, Moreau JF. Leukemia inhibitory factor: part of a large ingathering family. *Int Rev Immunol* 1998; 16: 397-426.
2. Metcalf D. The unsolved enigmas of leukemia inhibitory factor. *Stem Cells* 2003; 21: 5-14.
3. Shellard J, Perreau J, Brulet P. Role of leukemia inhibitory factor during mammalian development. *Eur Cytokine Netw* 1996; 7: 699-712.
4. Schere-Levy C, Buggiano V, Quaglino A, *et al.* Leukemia inhibitory factor induces apoptosis of the mammary epithelial cells and participates in mouse mammary gland involution. *Exp Cell Res* 2003; 282: 35-47.
5. Kritikou EA, Sharkey A, Abell K, *et al.* A dual, non-redundant, role for LIF as a regulator of development and STAT3-mediated cell death in mammary gland. *Development* 2003; 130: 3459-68.
6. Dhingra K, Sahin A, Emami K, Hortobagyi GN, Estrov Z. Expression of leukemia inhibitory factor and its receptor in breast cancer: a potential autocrine and paracrine growth regulatory mechanism. *Breast Cancer Res Treat* 1998; 48: 165-74.
7. Hu Y, Sun H, Drake J, Kittrell F, *et al.* From mice to humans: identification of commonly deregulated genes in mammary cancer *via* comparative SAGE studies. *Cancer Res* 2004; 64: 7748-55.
8. Wysoczynski M, Miekus K, Jankowski K, *et al.* Leukemia inhibitory factor: a newly identified metastatic factor in rhabdomyosarcomas. *Cancer Res* 2007; 67: 2131-40.
9. Duluc D, Delneste Y, Tan F, *et al.* Tumor-associated leukemia inhibitory factor and IL-6 skew monocyte differentiation into tumor-associated macrophage-like cells. *Blood* 2007; 110: 4319-30.
10. Metcalfe SM, Muthukumarana PA, Thompson HL, Haendel MA, Lyons GE. Leukaemia inhibitory factor (LIF) is functionally linked to axotrophin and both LIF and axotrophin are linked to regulatory immune tolerance. *FEBS Lett* 2005; 579: 609-14.
11. Muthukumarana PA, Lyons GE, Miura Y, *et al.* Evidence for functional inter-relationships between FOXP3, leukaemia inhibitory factor, and axotrophin/MARCH-7 in transplantation tolerance. *Int Immunopharmacol* 2006; 6: 1993-2001.
12. Mahic M, Kalland ME, Aandahl EM, Torgersen KM, Tasken K. Human naturally occurring and adaptive regulatory T cells secrete high levels of leukaemia inhibitory factor upon activation. *Scand J Immunol* 2008; 68: 391-6.
13. Hu W, Feng Z, Teresky AK, Levine AJ. p53 regulates maternal reproduction through LIF. *Nature* 2007; 450: 721-4.
14. Stewart CL. Reproduction: the unusual suspect. *Nature* 2007; 450: 619.
15. Ichikawa Y. Differentiation of a cell line of myeloid leukemia. *J Cell Physiol* 1969; 74: 223-34.
16. Maeda M, Horiuchi M, Numa S, Ichikawa Y. Characterization of a differentiation-stimulating factor for mouse myeloid leukemia cells. *Gann* 1977; 68: 435-47.
17. Abe E, Tanaka H, Ishimi Y, *et al.* Differentiation-inducing factor purified from conditioned medium of mitogen-treated spleen cell cultures stimulates bone resorption. *Proc Natl Acad Sci USA* 1986; 83: 5958-62.
18. Koopman P, Cotton RG. A factor produced by feeder cells which inhibits embryonal carcinoma cell differentiation. Characterization and partial purification. *Exp Cell Res* 1984; 154: 233-42.
19. Hilton DJ, Nicola NA, Gough NM, Metcalf D. Resolution and purification of three distinct factors produced by Krebs ascites cells which have differentiation-inducing activity on murine myeloid leukemic cell lines. *J Biol Chem* 1988; 263: 9238-43.
20. Smith AG, Hooper ML. Buffalo rat liver cells produce a diffusible activity, which inhibits the differentiation of murine embryonal carcinoma and embryonic stem cells. *Dev Biol* 1987; 121: 1-9.
21. Godard A, Gascan H, Naulet J, *et al.* Biochemical characterization and purification of HILDA, a human lymphokine active on eosinophils and bone marrow cells. *Blood* 1988; 71: 1618-23.
22. Gearing DP, Gough NM, King J, *et al.* Molecular cloning and expression of cDNA encoding a murine myeloid leukaemia inhibitory factor. *EMBO J* 1987; 6: 3995-4002.
23. Moreau JF, Donaldson DD, Bennett F, Witek-Giannotti J, Clark SC, Wong GG. Leukaemia inhibitory factor is identical to the myeloid growth factor human interleukin for DA cells. *Nature* 1988; 336: 690-2.
24. Gough NM, Gearing DP, King JA, *et al.* Molecular cloning and expression of the human homologue of the murine gene encoding myeloid leukemia-inhibitory factor. *Proc Natl Acad Sci USA* 1988; 85: 2623-7.
25. Baumann H, Wong GG. Hepatocyte-stimulating factor III shares structural and functional identity with leukemia-inhibitory factor. *J Immunol* 1989; 143: 1163-7.
26. Elson GC, Lelievre E, Guillet C, *et al.* CLF associates with CLC to form a functional heteromeric ligand for the CNTF receptor complex. *Nat Neurosci* 2000; 3: 867-72.
27. Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J* 2003; 374: 1-20.
28. Murakami M, Kamimura D, Hirano T. New IL-6 (gp130) family cytokine members, CLC/NNT1/BSF3 and IL-27. *Growth Factors* 2004; 22: 75-7.
29. Vlotides G, Zitzmann K, Stalla GK, Auernhammer CJ. Novel neurotrophin-1/B cell-stimulating factor-3 (NNT-1/BSF-3)/cardiotrophin-like cytokine (CLC)-a novel gp130 cytokine with pleiotropic functions. *Cytokine Growth Factor Rev* 2004; 15: 325-36.

30. Rousseau F, Chevalier S, Guillet C, *et al.* Ciliary neurotrophic factor, cardiotrophin-like cytokine and neuropoietin share a conserved binding site on the ciliary neurotrophic factor receptor alpha chain. *J Biol Chem* 2008; 283: 30341-50.
31. Simpson RJ, Hilton DJ, Nice EC, *et al.* Structural characterization of a murine myeloid leukaemia inhibitory factor. *Eur J Biochem* 1988; 175: 541-7.
32. Gascan H, Godard A, Ferenz C, *et al.* Characterization and NH_2-terminal amino acid sequence of natural human interleukin for DA cells: leukemia inhibitory factor. Differentiation inhibitory activity secreted by a T lymphoma cell line. *J Biol Chem* 1989; 264: 21509-15.
33. Blanchard F, Raher S, Duplomb L, *et al.* The mannose 6-phosphate/insulin-like growth factor II receptor is a nanomolar affinity receptor for glycosylated human leukemia inhibitory factor. *J Biol Chem* 1998; 273: 20886-93.
34. Blanchard F, Duplomb L, Raher S, *et al.* Mannose 6-Phosphate/Insulin-like growth factor II receptor mediates internalization and degradation of leukemia inhibitory factor but not signal transduction. *J Biol Chem* 1999; 274: 24685-93.
35. Rathjen PD, Toth S, Willis A, Heath JK, Smith AG. Differentiation inhibiting activity is produced in matrix-associated and diffusible forms that are generated by alternate promoter usage. *Cell* 1990; 62: 1105-14.
36. Haines BP, Voyle RB, Pelton TA, Forrest R, Rathjen PD. Complex conserved organization of the mammalian leukemia inhibitory factor gene: regulated expression of intracellular and extracellular cytokines. *J Immunol* 1999; 162: 4637-46.
37. Haines BP, Voyle RB, Rathjen PD. Intracellular and extracellular leukemia inhibitory factor proteins have different cellular activities that are mediated by distinct protein motifs. *Mol Biol Cell* 2000; 11: 1369-83.
38. Robertson M, Chambers I, Rathjen P, Nichols J, Smith A. Expression of alternative forms of differentiation inhibiting activity (DIA/LIF) during murine embryogenesis and in neonatal and adult tissues. *Dev Genet* 1993; 14: 165-73.
39. Hisaka T, Desmouliere A, Taupin JL, *et al.* Expression of leukemia inhibitory factor (LIF) and its receptor gp190 in human liver and in cultured human liver myofibroblasts. Cloning of new isoforms of LIF mRNA. *Comp Hepatol* 2004; 3: 10.
40. Heymann D, Rousselle AV. gp130 Cytokine family and bone cells. *Cytokine* 2000; 12: 1455-68.
41. Nasef A, Mazurier C, Bouchet S, *et al.* Leukemia inhibitory factor: role in human mesenchymal stem cells mediated immunosuppression. *Cell Immunol* 2008; 253: 16-22.
42. Viallard JF, Taupin JL, Miossec V, Pellegrin JL, Moreau BL. Analysis of interleukin-6, interleukin-10 and leukemia inhibitory factor (LIF) production by peripheral blood cells from patients with systemic lupus erythematosus identifies LIF as a potential marker of disease activity. *Eur Cytokine Netw* 1999; 10: 17-24.
43. Kerr BJ, Patterson PH. Potent pro-inflammatory actions of leukemia inhibitory factor in the spinal cord of the adult mouse. *Exp Neurol* 2004; 188: 391-407.
44. Pan W, Yu C, Hsuchou H, Zhang Y, Kastin AJ. Neuroinflammation facilitates LIF entry into brain: role of TNF. *Am J Physiol Cell Physiol* 2008; 294: C1436-C1442.
45. Fujio Y, Matsuda T, Oshima Y, *et al.* Signals through gp130 upregulate Wnt5a and contribute to cell adhesion in cardiac myocytes. *FEBS Lett* 2004; 573: 202-6.
46. Stewart CL, Kaspar P, Brunet LJ, *et al.* Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. *Nature* 1992; 359: 76-9.
47. Stewart CL. Leukaemia inhibitory factor and the regulation of pre-implantation development of the mammalian embryo. *Mol Reprod Dev* 1995; 39: 233-8.
48. Song H, Lim H, Das SK, Paria BC, Dey SK. Dysregulation of EGF family of growth factors and COX-2 in the uterus during the pre-attachment and attachment reactions of the blastocyst with the luminal epithelium correlates with implantation failure in LIF-deficient mice. *Mol Endocrinol* 2000; 14: 1147-61.
49. Szekeres-Bartho J, Wilczynski JR, Basta P, Kalinka J. Role of progesterone and progestin therapy in threatened abortion and preterm labour. *Front Biosci* 2008; 13: 1981-90.
50. Bamberger AM, Jenatschke S, Schulte HM, Loning T, Bamberger MC. Leukemia inhibitory factor (LIF) stimulates the human HLA-G promoter in JEG3 choriocarcinoma cells. *J Clin Endocrinol Metab* 2000; 85: 3932-6.
51. Metcalfe SM. Axotrophin and leukaemia inhibitory factor (LIF) in transplantation tolerance. *Philos Trans R Soc Lond B Biol Sci* 2005; 360: 1687-94.
52. Bozec A, Bakiri L, Hoebertz A, *et al.* Osteoclast size is controlled by Fra-2 through LIF/LIF-receptor signalling and hypoxia. *Nature* 2008; 454: 221-5.
53. Metcalf D, Gearing DP. Fatal syndrome in mice engrafted with cells producing high levels of the leukemia inhibitory factor. *Proc Natl Acad Sci USA* 1989; 86: 5948-52.
54. Shen MM, Skoda RC, Cardiff RD, Campos-Torres J, Leder P, Ornitz DM. Expression of LIF in transgenic mice results in altered thymic epithelium and apparent interconversion of thymic and lymph node morphologies. *EMBO J* 1994; 13: 1375-85.
55. Blais ME, Louis I, Perreault C. T-cell development: an extrathymic perspective. *Immunol Rev* 2006; 209: 103-14.
56. Conquet F, Peyrieras N, Tiret L, Brulet P. Inhibited gastrulation in mouse embryos overexpressing the leukemia inhibitory factor. *Proc Natl Acad Sci USA* 1992; 89: 8195-9.
57. Shen MM, Leder P. Leukaemia inhibitory factor is expressed by the pre-implantation uterus and selectively blocks primitive ectoderm formation *in vitro*. *Proc Natl Acad Sci USA* 1992; 89: 8240-4.
58. Smith AG, Heath JK, Donaldson DD, *et al.* Inhibition of pluripotential embryonic stem cell differentiation by purified polypeptides. *Nature* 1988; 336: 688-90.
59. Smith AG. Embryo-derived stem cells: of mice and men. *Annu Rev Cell Dev Biol* 2001; 17: 435-62.
60. Niwa H. Molecular mechanism to maintain stem cell renewal of ES cells. *Cell Struct Funct* 2001; 26: 137-48.
61. Niwa H. How is pluripotency determined and maintained? *Development* 2007; 134: 635-46.
62. Xu C, Inokuma MS, Denham J, *et al.* Feeder-free growth of undifferentiated human embryonic stem cells. *Nat Biotechnol* 2001; 19: 971-4.
63. Humphrey RK, Beattie GM, Lopez AD, *et al.* Maintenance of pluripotency in human embryonic stem cells is STAT3 independent. *Stem Cells* 2004; 22: 522-30.
64. Vallier L, Reynolds D, Pedersen RA. Nodal inhibits differentiation of human embryonic stem cells along the neuroectodermal default pathway. *Dev Biol* 2004; 275: 403-21.
65. Greber B, Lehrach H, Adjaye J. Control of early fate decisions in human ES cells by distinct states of TGFbeta pathway activity. *Stem Cells Dev* 2008; 17: 1065-77.
66. Dani C, Chambers I, Johnstone S, *et al.* Paracrine induction of stem cell renewal by LIF-deficient cells: a new ES cell regulatory pathway. *Dev Biol* 1998; 203: 149-62.

67. Richards M, Tan SP, Tan JH, Chan WK, Bongso A. The transcriptome profile of human embryonic stem cells as defined by SAGE. *Stem Cells* 2004; 22: 51-64.

68. Ginis I, Luo Y, Miura T, *et al.* Differences between human and mouse embryonic stem cells. *Dev Biol* 2004; 269: 360-80.

69. Brons IG, Smithers LE, Trotter MW, *et al.* Derivation of pluripotent epiblast stem cells from mammalian embryos. *Nature* 2007; 448: 191-5.

70. Tesar PJ, Chenoweth JG, Brook FA, *et al.* New cell lines from mouse epiblast share defining features with human embryonic stem cells. *Nature* 2007; 448: 196-9.

71. Lengner C, Jaenish R. Pluripotent cell isolation for regenerative medecine. *Nat Rev Mol Cell Biol* 2008; 9 (Poster).

72. Boyer LA, Lee TI, Cole MF, *et al.* Core transcriptional regulatory circuitry in human embryonic stem cells. *Cell* 2005; 122: 947-56.

73. Escary JL, Perreau J, Dumenil D, Ezine S, Brulet P. Leukaemia inhibitory factor is necessary for maintenance of haematopoietic stem cells and thymocyte stimulation. *Nature* 1993; 363: 361-4.

74. Holtmann B, Wiese S, Samsam M, *et al.* Triple knock-out of CNTF, LIF, and CT-1 defines cooperative and distinct roles of these neurotrophic factors for motoneuron maintenance and function. *J Neurosci* 2005; 25: 1778-87.

75. Bugga L, Gadient RA, Kwan K, Stewart CL, Patterson PH. Analysis of neuronal and glial phenotypes in brains of mice deficient in leukemia inhibitory factor. *J Neurobiol* 1998; 36: 509-24.

76. Kim EJ, Simpson PJ, Park DJ, Liu BQ, Ronnett GV, Moon C. Leukemia inhibitory factor is a proliferative factor for olfactory sensory neurons. *Neuroreport* 2005; 16: 25-8.

77. Kubota Y, Hirashima M, Kishi K, Stewart CL, Suda T. Leukemia inhibitory factor regulates microvessel density by modulating oxygen-dependent VEGF expression in mice. *J Clin Invest* 2008; 118: 2393-403.

78. Chen JR, Cheng JG, Shatzer T, Sewell L, Hernandez L, Stewart CL. Leukemia inhibitory factor can substitute for nidatory estrogen and is essential to inducing a receptive uterus for implantation but is not essential for subsequent embryogenesis. *Endocrinology* 2000; 141: 4365-72.

79. Cheng TC, Huang CC, Chen CI, *et al.* Leukemia inhibitory factor antisense oligonucleotide inhibits the development of murine embryos at pre-implantation stages. *Biol Reprod* 2004; 70: 1270-6.

80. Hu W, Feng Z, Atwal GS, Levine AJ. p53: a new player in reproduction. *Cell Cycle* 2008; 7: 848-52.

81. Pflanz S, Hibbert L, Mattson J, *et al.* WSX-1 and glycoprotein 130 constitute a signal-transducing receptor for IL-27. *J Immunol* 2004; 172: 2225-31.

82. Bando T, Morikawa Y, Komori T, Senba E. Complete overlap of interleukin-31 receptor A and oncostatin M receptor beta in the adult dorsal root ganglia with distinct developmental expression patterns. *Neuroscience* 2006; 142: 1263-71.

83. Carl JW, Bai XF. IL27: its roles in the induction and inhibition of inflammation. *Int J Clin Exp Pathol* 2008; 1: 117-23.

84. Taga T, Kishimoto T. Gp130 and the interleukin-6 family of cytokines. *Annu Rev Immunol* 1997; 15: 797-819.

85. Bitard J, Daburon S, Duplomb L, *et al.* Mutations in the immunoglobulin-like domain of gp190, the leukemia inhibitory factor (LIF) receptor, increase or decrease its affinity for LIF. *J Biol Chem* 2003; 278: 16253-61.

86. Giese B, Roderburg C, Sommerauer M, *et al.* Dimerization of the cytokine receptors gp130 and LIFR analyzed in single cells. *J Cell Sci* 2005; 118 (Pt 21): 5129-40.

87. Tenhumberg S, Schuster B, Zhu L, *et al.* gp130 dimerization in the absence of ligand: Preformed cytokine receptor complexes. *Biochem Biophys Res Commun* 2006; 346: 649-57.

88. Huyton T, Zhang JG, Luo CS, *et al.* An unusual cytokine: Ig-domain interaction revealed in the crystal structure of leukemia inhibitory factor (LIF) in complex with the LIF receptor. *Proc Natl Acad Sci USA* 2007; 104: 12737-42.

89. Skiniotis G, Lupardus PJ, Martick M, Walz T, Garcia KC. Structural organization of a full-length gp130/LIF-R cytokine receptor transmembrane complex. *Mol Cell* 2008; 31: 737-48.

90. Auernhammer CJ, Melmed S. Leukemia-inhibitory factor-neuro-immune modulator of endocrine function. *Endocr Rev* 2000; 21: 313-45.

91. Lehmann U, Schmitz J, Weissenbach M, *et al.* SHP2 and SOCS3 contribute to Tyr-759-dependent attenuation of interleukin-6 signaling through gp130. *J Biol Chem* 2003; 278: 661-71.

92. Clahsen T, Lehmann U, Stross C, *et al.* The tyrosine 974 within the LIF-R-chain of the gp130/LIF-R heteromeric receptor complex mediates negative regulation of LIF signalling. *Cell Signal* 2005; 17: 559-69.

93. Li M, Sendtner M, Smith A. Essential function of LIF receptor in motor neurons. *Nature* 1995; 378: 724-7.

94. Ware CB, Horowitz MC, Renshaw BR, *et al.* Targeted disruption of the low-affinity leukemia inhibitory factor receptor gene causes placental, skeletal, neural and metabolic defects and results in perinatal death. *Development* 1995; 121: 1283-99.

95. Koblar SA, Turnley AM, Classon BJ, *et al.* Neural precursor differentiation into astrocytes requires signaling through the leukemia inhibitory factor receptor. *Proc Natl Acad Sci USA* 1998; 95: 3178-81.

96. Yoshida K, Taga T, Saito M, *et al.* Targeted disruption of gp130, a common signal transducer for the interleukin 6 family of cytokines, leads to myocardial and hematological disorders. *Proc Natl Acad Sci USA* 1996; 93: 407-11.

97. Nichols J, Chambers I, Taga T, Smith A. Physiological rationale for responsiveness of mouse embryonic stem cells to gp130 cytokines. *Development* 2001; 128: 2333-9.

98. Fasnacht N, Muller W. Conditional gp130 deficient mouse mutants. *Semin Cell Dev Biol* 2008; 19: 379-84.

99. Cullinan EB, Abbondanzo SJ, Anderson PS, Pollard JW, Lessey BA, Stewart CL. Leukemia inhibitory factor (LIF) and LIF receptor expression in human endometrium suggests a potential autocrine/paracrine function in regulating embryo implantation. *Proc Natl Acad Sci USA* 1996; 93: 3115-20.

100. Pitard V, Lorgeot V, Taupin JL, Aubard Y, Praloran V, Moreau JF. The presence in human serum of a circulating soluble leukemia inhibitory factor receptor (sgp190) and its evolution during pregnancy. *Eur Cytokine Netw* 1998; 9: 599-605.

101. Delage G, Moreau JF, Taupin JL, *et al. In vitro* endometrial secretion of human interleukin for DA cells/leukaemia inhibitory factor by explant cultures from fertile and infertile women. *Hum Reprod* 1995; 10: 2483-8.

102. Chaouat G, Menu E, Delage G, *et al.* Immuno-endocrine interactions in early pregnancy. *Hum Reprod* 1995; 10 (Suppl 2): 55-9.

103. Giess R, Tanasescu I, Steck T, Sendtner M. Leukaemia inhibitory factor gene mutations in infertile women. *Mol Hum Reprod* 1999; 5: 581-6.

104. Kralickova M, Sima R, Vanecek T, *et al.* Leukemia inhibitory factor gene mutations in the population of infertile women are not restricted to nulligravid patients. *Eur J Obstet Gynecol Reprod Biol* 2006; 127: 231-5.

105. Ledee-Bataille N, Lapree-Delage G, Taupin JL, Dubanchet S, Frydman R, Chaouat G. Concentration of leukaemia inhibitory factor (LIF) in uterine flushing fluid is highly predictive of embryo implantation. *Hum Reprod* 2002; 17: 213-8.

106. Dimitriadis E, Stoikos C, Stafford-Bell M, *et al.* Interleukin-11, IL-11 receptor alpha and leukemia inhibitory factor are dysregulated in endometrium of infertile women with endometriosis during the implantation window. *J Reprod Immunol* 2006; 69: 53-64.

107. Dagoneau N, Scheffer D, Huber C, *et al.* Null leukemia inhibitory factor receptor (LIFR) mutations in Stuve-Wiedemann/Schwartz-Jampel type 2 syndrome. *Am J Hum Genet* 2004; 74: 298-305.

108. Aubert J, Dessolin S, Belmonte N, *et al.* Leukemia inhibitory factor and its receptor promote adipocyte differentiation *via* the mitogen-activated protein kinase cascade. *J Biol Chem* 1999; 274: 24965-72.

109. Rajasingh J, Bord E, Hamada H, *et al.* STAT3-dependent mouse embryonic stem cell differentiation into cardiomyocytes: analysis of molecular signaling and therapeutic efficacy of cardiomyocyte pre-committed mES transplantation in a mouse model of myocardial infarction. *Circ Res* 2007; 101: 910-8.

110. Mohri T, Fujio Y, Maeda M, *et al.* Leukemia inhibitory factor induces endothelial differentiation in cardiac stem cells. *J Biol Chem* 2006; 281: 6442-7.

111. Ying QL, Nichols J, Chambers I, Smith A. BMP induction of Id proteins suppresses differentiation and sustains embryonic stem cell self-renewal in collaboration with STAT3. *Cell* 2003; 115: 281-92.

112. Hao J, Li TG, Qi X, Zhao DF, Zhao GQ. WNT/beta-catenin pathway up-regulates Stat3 and converges on LIF to prevent differentiation of mouse embryonic stem cells. *Dev Biol* 2006; 290: 81-91.

113. Ogawa K, Nishinakamura R, Iwamatsu Y, Shimosato D, Niwa H. Synergistic action of Wnt and LIF in maintaining pluripotency of mouse ES cells. *Biochem Biophys Res Commun* 2006; 343: 159-66.

114. Oskowitz AZ, Lu J, Penfornis P, *et al.* Human multipotent stromal cells from bone marrow and microRNA: regulation of differentiation and leukemia inhibitory factor expression. *Proc Natl Acad Sci USA* 2008; 105: 18372-7.

115. Piquet-Pellorce C, Grey L, Mereau A, Heath JK. Are LIF and related cytokines functionally equivalent? *Exp Cell Res* 1994; 213: 340-7.

116. Yoshida K, Chambers I, Nichols J, *et al.* Maintenance of the pluripotential phenotype of embryonic stem cells through direct activation of gp130 signalling pathways. *Mech Dev* 1994; 45: 163-71.

117. Rose TM, Weiford DM, Gunderson NL, Bruce AG. Oncostatin M (OSM) inhibits the differentiation of pluripotent embryonic stem cells *in vitro*. *Cytokine* 1994; 6: 48-54.

118. Pennica D, Shaw KJ, Swanson TA, *et al.* Cardiotrophin-1. Biological activities and binding to the leukemia inhibitory factor receptor/gp130 signaling complex. *J Biol Chem* 1995; 270: 10915-22.

119. DeChiara TM, Vejsada R, Poueymirou WT, *et al.* Mice lacking the CNTF receptor, unlike mice lacking CNTF, exhibit profound motor neuron deficits at birth. *Cell* 1995; 83: 313-22.

120. Sendtner M, Gotz R, Holtmann B, *et al.* Cryptic physiological trophic support of motoneurons by LIF revealed by double gene targeting of CNTF and LIF. *Curr Biol* 1996; 6: 686-94.

121. Oppenheim RW, Wiese S, Prevette D, *et al.* Cardiotrophin-1, a muscle-derived cytokine, is required for the survival of subpopulations of developing motoneurons. *J Neurosci* 2001; 21: 1283-91.

122. Zhong Z, Wen Z, Darnell JE Jr. Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6. *Science* 1994; 264: 95-8.

123. Hocke GM, Cui MZ, Fey GH. The LIF response element of the alpha-2-macroglobulin gene confers LIF-induced transcriptional activation in embryonal stem cells. *Cytokine* 1995; 7: 491-502.

124. Minami M, Inoue M, Wei S, *et al.* STAT3 activation is a critical step in gp130-mediated terminal differentiation and growth arrest of a myeloid cell line. *Proc Natl Acad Sci USA* 1996; 93: 3963-6.

125. Nakajima K, Yamanaka Y, Nakae K, *et al.* A central role for Stat3 in IL-6-induced regulation of growth and differentiation in M1 leukemia cells. *EMBO J* 1996; 15: 3651-8.

126. Boeuf H, Hauss C, Graeve FD, Baran N, Kedinger C. Leukemia inhibitory factor-dependent transcriptional activation in embryonic stem cells. *J Cell Biol* 1997; 138: 1207-17.

127. Niwa H, Burdon T, Chambers I, Smith A. Self-renewal of pluripotent embryonic stem cells is mediated via activation of STAT3. *Genes Dev* 1998; 12: 2048-60.

128. Matsuda T, Nakamura T, Nakao K, *et al.* STAT3 activation is sufficient to maintain an undifferentiated state of mouse embryonic stem cells. *EMBO J* 1999; 18: 4261-9.

129. Stahl N, Boulton TG, Farruggela T, *et al.* Association and activation of Jak-Tyk kinases by CNTF-LIF-OSM-IL6b receptor components. *Science* 1994; 263: 92-5.

130. Stahl N, Farruggella TJ, Boulton TG, Zhong Z, Darnell JE Jr, Yancopoulos GD. Choice of STATs and other substrates specified by modular tyrosine-based motifs in cytokine receptors. *Science* 1995; 267: 1349-53.

131. Ernst M, Oates A, Dunn AR. Gp130-mediated signal transduction in embryonic stem cells involves activation of Jak and Ras/mitogen-activated protein kinase pathways. *J Biol Chem* 1996; 271: 30136-43.

132. Chung BM, Kang HC, Han SY, *et al.* Jak2 and Tyk2 are necessary for lineage-specific differentiation, but not for the maintenance of self-renewal of mouse embryonic stem cells. *Biochem Biophys Res Commun* 2006; 351: 682-8.

133. Takahashi Y, Takahashi M, Carpino N, *et al.* Leukemia inhibitory factor regulates trophoblast giant cell differentiation *via* Janus kinase 1-signal transducer and activator of transcription 3-suppressor of cytokine signaling 3 pathway. *Mol Endocrinol* 2008; 22: 1673-81.

134. Spangenburg EE, Booth FW. Multiple signaling pathways mediate LIF-induced skeletal muscle satellite cell proliferation. *Am J Physiol Cell Physiol* 2002; 283: C204-C211.

135. Naka T, Narazaki M, Hirata M, *et al.* Structure and function of a new STAT-induced STAT inhibitor. *Nature* 1997; 387: 924-9.

136. Starr R, Willson TA, Viney EM, *et al.* A family of cytokine-inducible inhibitors of signalling. *Nature* 1997; 387: 917-21.

137. Hilton DJ. Negative regulators of cytokine signal transduction. *Cell Mol Life Sci* 1999; 55: 1568-77.

138. Kile BT, Alexander WS. The suppressors of cytokine signalling (SOCS). *Cell Mol Life Sci* 2001; 58: 1627-35.

139. Lang R, Pauleau AL, Parganas E, *et al.* Murray, SOCS3 regulates the plasticity of gp130 signaling. *Nat Immunol* 2003; 4: 546-50.

140. Croker BA, Kiu H, Nicholson SE. SOCS regulation of the JAK/STAT signalling pathway. *Semin Cell Dev Biol* 2008; 19: 414-22.

141. Piessevaux J, Lavens D, Peelman F, Tavernier J. The many faces of the SOCS box. *Cytokine Growth Factor Rev* 2008; 19: 371-81.

142. Duval D, Reinhardt B, Kedinger C, Boeuf H. Role of suppressors of cytokine signaling (SOCS) in leukemia inhibitory factor (LIF)-dependent embryonic stem cell survival. *FASEB J* 2000; 14: 1577-84.

143. Li Y, McClintick J, Zhong L, Edenberg HJ, Yoder MC, Chan RJ. Murine embryonic stem cell differentiation is promoted by SOCS-3 and inhibited by the zinc finger transcription factor Klf4. *Blood* 2005; 105: 635-7.

144. Forrai A, Boyle K, Hart AH, *et al.* Absence of suppressor of cytokine signalling 3 reduces self-renewal and promotes differentiation in murine embryonic stem cells. *Stem Cells* 2006; 24: 604-14.

145. Takahashi Y, Carpino N, Cross JC, Torres M, Parganas E, Ihle JN. SOCS3: an essential regulator of LIF receptor signaling in trophoblast giant cell differentiation. *EMBO J* 2003; 22: 372-84.

146. Boyle K, Robb L. The role of SOCS3 in modulating leukaemia inhibitory factor signalling during murine placental development. *J Reprod Immunol* 2008; 77: 1-6.

147. Sutherland KD, Vaillant F, Alexander WS, *et al.* c-myc as a mediator of accelerated apoptosis and involution in mammary glands lacking Socs3. *EMBO J* 2006; 25: 5805-15.

148. Sutherland KD, Lindeman GJ, Visvader JE. The molecular culprits underlying precocious mammary gland involution. *J Mammary Gland Biol Neoplasia* 2007; 12: 15-23.

149. Muthukumarana P, Chae WJ, Maher S, Rosengard BR, Bothwell AL, Metcalfe SM. Regulatory transplantation tolerance and "stemness": evidence that Foxp3 may play a regulatory role in *SOCS-3* gene transcription. *Transplantation* 2007; 84 (1 Suppl): S6-11.

150. Lord KA, Abdollahi A, Hoffman-Liebermann B, Liebermann DA. Proto-oncogenes of the fos/jun family of transcription factors are positive regulators of myeloid differentiation. *Mol Cell Biol* 1993; 13: 841-51.

151. Liebermann DA, Hoffman B. *MyD* genes in negative growth control. *Oncogene* 1998; 17: 3319-29.

152. Nicholson SE, Willson TA, Farley A, *et al.* Mutational analyses of the SOCS proteins suggest a dual domain requirement but distinct mechanisms for inhibition of LIF and IL-6 signal transduction. *EMBO J* 1999; 18: 375-85.

153. Tone E, Kunisada K, Kumanogoh A, *et al.* gp130-dependent signalling pathway is not enhanced in gp130 transgenic heart after LIF stimulation. *Cytokine* 2000; 12: 1512-8.

154. Paling NR, Wheadon H, Bone HK, Welham MJ. Regulation of embryonic stem cell self-renewal by phosphoinositide 3-kinase-dependent signaling. *J Biol Chem* 2004; 279: 48063-70.

155. Watanabe S, Umehara H, Murayama K, Okabe M, Kimura T, Nakano T. Activation of Akt signaling is sufficient to maintain pluripotency in mouse and primate embryonic stem cells. *Oncogene* 2006; 25: 2697-707.

156. Storm MP, Bone HK, Beck CG, *et al.* Regulation of Nanog expression by phosphoinositide 3-kinase-dependent signaling in murine embryonic stem cells. *J Biol Chem* 2007; 282: 6265-73.

157. Burdon T, Smith A, Savatier P. Signalling, cell cycle and pluripotency in embryonic stem cells. *Trends Cell Biol* 2002; 12: 432.

158. Boeuf H, Merienne K, Jacquot S, *et al.* The ribosomal S6 kinases, cAMP-responsive element-binding, and STAT3 proteins are regulated by different leukemia inhibitory factor signaling pathways in mouse embryonic stem cells. *J Biol Chem* 2001; 276: 46204-11.

159. Kunath T, Saba-El-Leil MK, Almousailleakh M, Wray J, Meloche S, Smith A. FGF stimulation of the Erk1/2 signalling cascade triggers transition of pluripotent embryonic stem cells from self-renewal to lineage commitment. *Development* 2007; 134: 2895-902.

160. Lai WS, Parker JS, Grissom SF, Stumpo DJ, Blackshear PJ. Novel mRNA targets for tristetraprolin (TTP) identified by global analysis of stabilized transcripts in TTP-deficient fibroblasts. *Mol Cell Biol* 2006; 26: 9196-208.

161. Trouillas M, Saucourt C, Guillotin B, *et al.* Three LIF-dependent signatures and gene clusters with atypical expression profiles, identified by transcriptome studies in mouse ES cells and early derivatives. *BMC Genomics* 2009; 10: 73.

162. Burdon T, Stracey C, Chambers I, Nichols J, Smith A. Suppression of SHP-2 and ERK signalling promotes self-renewal of mouse embryonic stem cells. *Dev Biol* 1999; 210: 30-43.

163. Sekkai D, Gruel G, Herry M, *et al.* Microarray analysis of LIF/Stat3 transcriptional targets in embryonic stem cells. *Stem Cells* 2005; 23: 1634-42.

164. Duval D, Trouillas M, Thibault C, *et al.* Apoptosis and differentiation commitment: novel insights revealed by gene profiling studies in mouse embryonic stem cells. *Cell Death Differ* 2006; 13: 564-75.

165. Cinelli P, Casanova EA, Uhlig S, *et al.* Expression profiling in transgenic FVB/N embryonic stem cells overexpressing STAT3. *BMC Dev Biol* 2008; 8: 57.

166. Langlais D, Couture C, Balsalobre A, Drouin J. Regulatory network analyses reveal genome-wide potentiation of LIF signaling by glucocorticoids and define an innate cell defense response. *PLoS Genet* 2008; 4: e1000224.

167. Bourguignon LY, Peyrollier K, Xia W, Gilad E. Hyaluronan-CD44 interaction activates stem cell marker Nanog, Stat-3-mediated MDR1 gene expression, and ankyrin-regulated multidrug efflux in breast and ovarian tumor cells. *J Biol Chem* 2008; 283: 17635-51.

168. Shafarenko M, Liebermann DA, Hoffman B. Egr-1 abrogates the block imparted by c-Myc on terminal M1 myeloid differentiation. *Blood* 2005; 106: 871-8.

169. Gibbs JD, Liebermann DA, Hoffman B. Leukemia suppressor function of Egr-1 is dependent on transforming oncogene. *Leukemia* 2008; 22: 1909-16.

170. Piekorz RP, Blasius R, Fey GH, Hocke GM. Kinetics of the activation of the LIF-response factor in M1 myeloid leukemic cells. *Ann NY Acad Sci* 1995; 762: 452-4.

171. Hirano T, Nakajima K, Hibi M. Signaling mechanisms through gp130: a model of the cytokine system. *Cytokine Growth Factor Rev* 1997; 8: 241-52.

172. Piekorz RP, Rinke R, Gouilleux F, Neumann B, Groner B, Hocke GM. Modulation of the activation status of Stat5a during LIF-induced differentiation of M1 myeloid leukemia cells. *Biochim Biophys Acta* 1998; 1402: 313-23.

173. Lee ER, McCool KW, Murdoch FE, Fritsch MK. Dynamic changes in histone H3 phosphoacetylation during early embryonic stem cell differentiation are directly mediated by mitogen- and stress-activated protein kinase 1 *via* activation of MAPK pathways. *J Biol Chem* 2006; 281: 21162-72.

174. Lee ER, Murdoch FE, Fritsch MK. High histone acetylation and decreased polycomb repressive complex 2 member levels regulate gene specific transcriptional changes during early embryonic stem cell differentiation induced by retinoic acid. *Stem Cells* 2007; 25: 2191-9.

175. McCool KW, Xu X, Singer DB, Murdoch FE, Fritsch MK. The role of histone acetylation in regulating early gene expression patterns during early embryonic stem cell differentiation. *J Biol Chem* 2007; 282: 6696-706.

176. Karantzali E, Schulz H, Hummel O, Huebner N, Hatzopoulos A, Kretsovali A. Histone deacetylase inhibition accelerates the early events of stem cell differentiation: transcriptomic and epigenetic analysis. *Genome Biol* 2008; 9: R65.

177. Boyer LA, Plath K, Zeitlinger J, *et al.* Polycomb complexes repress developmental regulators in murine embryonic stem cells. *Nature* 2006; 441: 349-53.

178. Bernstein BE, Mikkelsen TS, Xie X, *et al.* A bivalent chromatin structure marks key developmental genes in embryonic stem cells. *Cell* 2006; 125: 315-26.

179. Ura H, Usuda M, Kinoshita K, *et al.* STAT3 and Oct-3/4 control histone modification through induction of Eed in embryonic stem cells. *J Biol Chem* 2008; 283: 9713-23.

180. Meshorer E, Misteli T. Chromatin in pluripotent embryonic stem cells and differentiation. *Nat Rev Mol Cell Biol* 2006; 7: 540-6.

181. Loh YH, Zhang W, Chen X, George J, Ng HH. Jmjd1a and Jmjd2c histone H3 Lys 9 demethylases regulate self-renewal in embryonic stem cells. *Genes Dev* 2007; 21: 2545-57.

182. Shaked H, Shiff I, Kott-Gutkowski M, Siegfried Z, Haupt Y, Simon I. Chromatin immunoprecipitation-on-chip reveals stress-dependent p53 occupancy in primary normal cells but not in established cell lines. *Cancer Res* 2008; 68: 9671-7.

183. Vrba L, Junk DJ, Novak P, Futscher BW. p53 induces distinct epigenetic states at its direct target promoters. *BMC Genomics* 2008; 9: 486.

184. Cui S, Hope RM, Rathjen J, Voyle RB, Rathjen PD. Structure, sequence and function of a marsupial *LIF* gene: conservation of IL-6 family cytokines. *Cytogenet Cell Genet* 2001; 92: 271-8.

185. Horiuchi H, Furusawa S, Matsuda H. Maintenance of chicken embryonic stem cells in vitro. *Methods Mol Biol* 2006; 329: 17-34.

186. Cartwright P, McLean C, Sheppard A, Rivett D, Jones K, Dalton S. LIF/STAT3 controls ES cell self-renewal and pluripotency by a Myc-dependent mechanism. *Development* 2005; 132: 885-96.

187. Kidder BL, Yang J, Palmer S. Stat3 and c-Myc genome-wide promoter occupancy in embryonic stem cells. *PLoS ONE* 2008; 3: e3932.

188. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; 126: 663-76.

189. Takahashi K, Tanabe K, Ohnuki M, *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; 131: 861-72.

190. Moon C, Yoo JY, Matarazzo V, Sung YK, Kim EJ, Ronnett GV. Leukemia inhibitory factor inhibits neuronal terminal differentiation through STAT3 activation. *Proc Natl Acad Sci USA* 2002; 99: 9015-20.

191. Kopf M, Baumann H, Freer G, *et al.* Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature* 1994; 368: 339-42.

192. Bernad A, Kopf M, Kulbacki R, Weich N, Koehler G, Gutierrez-Ramos JC. Interleukin-6 is required *in vivo* for the regulation of stem cells and committed progenitors of the hematopoietic system. *Immunity* 1994; 1: 725-31.

193. Morikawa Y, Tamura S, Minehata K, Donovan PJ, Miyajima A, Senba E. Essential function of oncostatin m in nociceptive neurons of dorsal root ganglia. *J Neurosci* 2004; 24: 1941-7.

194. Masu Y, Wolf E, Holtmann B, Sendtner M, Brem G, Thoenen H. Disruption of the *CNTF* gene results in motor neuron degeneration. *Nature* 1993; 365: 27-32.

195. Robb L, Li R, Hartley L, Nandurkar HH, Koentgen F, Begley CG. Infertility in female mice lacking the receptor for interleukin 11 is due to a defective uterine response to implantation. *Nat Med* 1998; 4: 303-8.

196. Robb L, Dimitriadis E, Li R, Salamonsen LA. Leukemia inhibitory factor and interleukin-11: cytokines with key roles in implantation. *J Reprod Immunol* 2002; 57: 129-41.

197. Tanaka M, Hirabayashi Y, Sekiguchi T, Inoue T, Katsuki M, Miyajima A. Targeted disruption of oncostatin M receptor results in altered hematopoiesis. *Blood* 2003; 102: 3154-62.

198. Nakamura K, Nonaka H, Saito H, Tanaka M, Miyajima A. Hepatocyte proliferation and tissue remodeling is impaired after liver injury in oncostatin M receptor knockout mice. *Hepatology* 2004; 39: 635-44.

199. Oka M, Tagoku K, Russell TL, *et al.* CD9 is associated with leukemia inhibitory factor-mediated maintenance of embryonic stem cells. *Mol Biol Cell* 2002; 13: 1274-81.

200. Lord KA, Abdollahi A, Thomas SM, *et al.* Leukemia inhibitory factor and interleukin-6 trigger the same immediate early response, including tyrosine phosphorylation, upon induction of myeloid leukemia differentiation. *Mol Cell Biol* 1991; 11: 4371-9.

201. Matsumoto A, Masuhara M, Mitsui K, *et al.* CIS, a cytokine inducible SH2 protein, is a target of the JAK-STAT5 pathway and modulates STAT5 activation. *Blood* 1997; 89: 3148-54.

202. Tomida M, Saito T. The human hepatocyte growth factor (*HGF*) gene is transcriptionally activated by leukemia inhibitory factor through the Stat-binding element. *Oncogene* 2004; 23: 679-86.

203. Sherwin JR, Freeman TC, Stephens RJ, *et al.* Identification of genes regulated by leukemia-inhibitory factor in the mouse uterus at the time of implantation. *Mol Endocrinol* 2004; 18: 2185-95.

204. Manabe T, Fukuda K, Pan J, Nagasaki K, Yamaguchi K, Ogawa S. Hypertrophic stimuli augment expression of cMG1/ERF-1, a putative zinc-finger motif transcription factor, in rat cardiomyocytes. *FEBS Lett* 1999; 463: 39-42.

205. Laszlo GS, Nathanson NM. Src family kinase-independent signal transduction and gene induction by leukemia inhibitory factor. *J Biol Chem* 2003; 278: 27750-7.

206. Turnley AM, Faux CH, Rietze RL, Coonan JR, Bartlett PF. Suppressor of cytokine signaling 2 regulates neuronal differentiation by inhibiting growth hormone signaling. *Nat Neurosci* 2002; 5: 1155-62.

207. Emery B, Cate HS, Marriott M, *et al.* Suppressor of cytokine signaling 3 limits protection of leukemia inhibitory factor receptor signaling against central demyelination. *Proc Natl Acad Sci USA* 2006; 103: 7859-64.