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Ubiquitin-mediated regulation of JAK-STAT signaling in embryonic stem cells

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Abbreviations: LIF, leukemia inhibitory factor; ESC, embryonic stem cell; LIFR, LIF receptor; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; SH2, src-homology-2; FGF2, fibroblast growth factor 2; bFGF, basic FGF; D-factor, differentiation factor; IL-6, interleukin-6; OSM, oncostatin M; CT-1, cardiotrophin; CNTF, ciliary neurotrophic factor; SHP, src-homology-2-containing tyrosine phosphatase; PTP1B, protein tyrosine phosphatase 1b; PTP-BL, protein tyrosine phosphatase basophil-like; PIAS, protein inhibitor of activated STAT; PI3K, phosphoinositide 3-kinase; GSK3β, glycogen synthase kinase 3β; E1, ubiquitin-activating enzyme; E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; HECT, homologous to E6-AP COOH terminus; TRIM, tripartite motif; Siglec, sialic-binding immunoglobulin-like lectin; IFN-γ, interferon-γ; SLIM, STAT-interacting LIM protein; GERP, glioblastoma-expressed RING finger protein; iPSC, induced pluripotent stem cell

LIF activates several intracellular signaling pathways including JAK-STAT, PI3K/AKT and MAPK pathways. LIF is an important cytokine for maintenance of pluripotency and self-renewal of mouse ES cells. The JAK-STAT signal plays a key role in maintenance of the pluripotency of ESCs. Recent evidence shows that several post-translational modifications regulate activation or inhibition of intracellular signal transductions. The JAK-STAT signal is also modulated by several modifications including phosphorylation, acetylation and ubiquitination. In this review, we discuss regulation of the LIF-mediated-JAK-STAT signaling pathway that contributes to self-renewal of pluripotent ESCs.

Introduction

Embryonic stem cells (ESCs) are pluripotent cells established from preimplantation embryos.[1,2] ESCs are nontransformed mammalian stem cells that can continuously proliferate in vitro. Self-renewal of ESCs is maintained by culture with the cytokine leukemia inhibitory factor (LIF).[3-5] LIF inhibits differentiation and promotes proliferation of undifferentiated cells. Actually, LIF is always provided to the culture medium of mouse ESCs and the removal of LIF causes rapid differentiation of mouse ESCs.

Upon binding to the LIF receptor (LIFR), LIF causes heterodimerization of the low-affinity LIFR and gp130, which acts as the main receptor for intracellular signal transduction (**Fig. 1**).[6] Briefly, ligand binding leads to phosphorylation and activation of Janus kinase (JAK), which is tethered to the intracellular region of gp130.[7-9] Activated JAK phosphorylates gp130 at four sites of tyrosine, and the phosphorylated tyrosine interacts with SH2-bearing proteins such as signal transducer and activator of transcription 3 (STAT3). Then STAT3 is also tyrosine-phosphorylated by JAK and is homodimerized via its src-homology-2 (SH2) domains. The dimerized STAT3 translocates to the nucleus and activates target gene transcription.[10] Consequently, activation of several genes by translocated STAT3 plays a role in suppression of the differentiation of mouse ESCs.[11] JAK-STAT3 activates Klf4, which maintains Oct3/4 expression via Sox2 and Nanog.[12] The molecules including Oct3/4, Sox2 and Nanog are known to be crucial for maintenance of pluripotency in ESCs. Therefore, STAT3 is one of the main players in the signaling pathway dependent on LIF in ESCs to maintain a pluripotent state. Importantly, it has been reported that activation of STAT3 is regulated by the ubiquitin system and translocation from the cytosol to the nucleus via molecular chaperones such as HSP90.[13-16]

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Maintenance of Pluripotency and Self-Renewal of Mouse ESCs via LIF

LIF-mediated signaling regulates proliferation or differentiation depending on the cell type or differentiated stage of the cell.[17] Past evidence showed that stage of the cell and uncontrolled secretion of LIF are associated with pathological conditions.[18] LIF is also a key cytokine for maintaining self-renewal and pluripotency of mouse ESCs. Therefore, it is important to clarify molecular mechanism of LIF signaling in mouse ESCs. In contrast to mouse ESCs, fibroblast growth factor 2 (FGF2), also called basic FGF (bFGF), and activin A are used to maintain self-renewal in human ESCs.[19,20] Recent studies have shown that human ESCs are slightly differentiated cells in the "primed state" and that mouse ESCs are fully undifferentiated cells in the "naïve state," suggesting that LIF maintains the "naïve state" of pluripotency (**Fig. 2**).[21] Actually, transcriptome analyses showed differences in the expression profiles of genes in mouse and human ESCs,

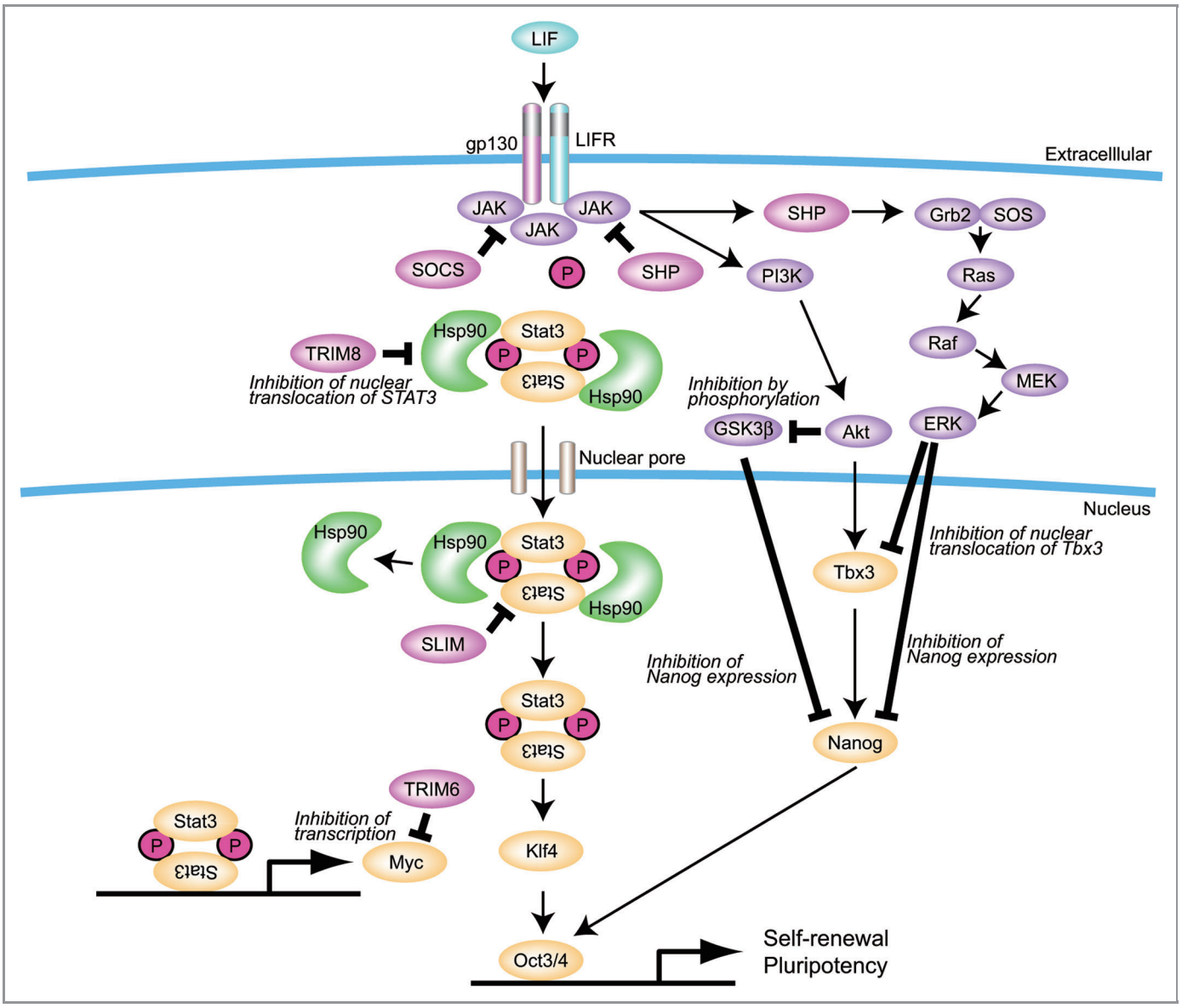

Figure 1. Regulation of the LIF-mediated signaling pathway in mouse ESCs. LIF causes heterodimerization of LIFR and gp130. LIF causes phosphorylation and activation of JAK, which is tethered to the intracellular region of gp130. Activated JAK phosphorylates gp130 and its tyrosine phosphorylations causes interaction with STAT3. Then STAT3 is also tyrosine-phosphorylated by JAK and is homodimerized via its SH2 domains. The dimerized STAT3 translocates to the nucleus and activates target gene transcription. JAK-STAT3 activates Klf4, which maintains Oct3/4 expression via Nanog. JAK activates PI3K, which acts as an activator for AKT. AKT then upregulates Tbx3 as another pluripotency gene. The JAK-STAT pathway is negatively regulated by several inhibitory systems: dephosphorylation by tyrosine phosphatases including SHP and physical inhibition or ubiquitin-mediated degradation of JAK by SOCS. JAK phosphorylates SHP and then SHP interacts with the Grb2/SOS complex to activate the MAPK pathway, leading to inhibition of Tbx3 and Nanog. TRIM8 likely negatively regulates Hsp90β-mediated translocation of STAT3 into the nucleus of ESCs. SLIM is an E3 ubiquitin ligase that negatively regulates the JAK-STAT signal pathway, but SLIM is expressed at a low level in mouse ESCs. P, phosphorylation.

indicating that these cells may not be derived from the same lineages of early embryos and that human ESCs are likely to be LIF-independent because of the establishment from cell lineages later than early epiblast.[22-25]

LIF-Mediated Signaling Pathway in ESCs

The activity of LIF was first identified in 1969 by Ichikawa, and it was shown that its activity could inhibit proliferation and induce macrophage differentiation of the M1 leukemic myeloid cell line.[26] This biological activity, called "differentiation factor (D-factor)," was partially purified from a cell-conditioned medium prepared from mouse embryos.[27] Gearing et al. purified mouse D-factor/LIF from a Krebs II ascites cell-derived conditioned medium and isolated a mouse *D-factor/LIF* cDNA clone.[28] Human LIF and mouse LIF are 180-amino-acid glycoproteins and belong to the interleukin-6 (IL-6) subfamily.[29,30] LIF proteins have at least three isoforms: a soluble form called LIF-D (soluble form), LIF-i/

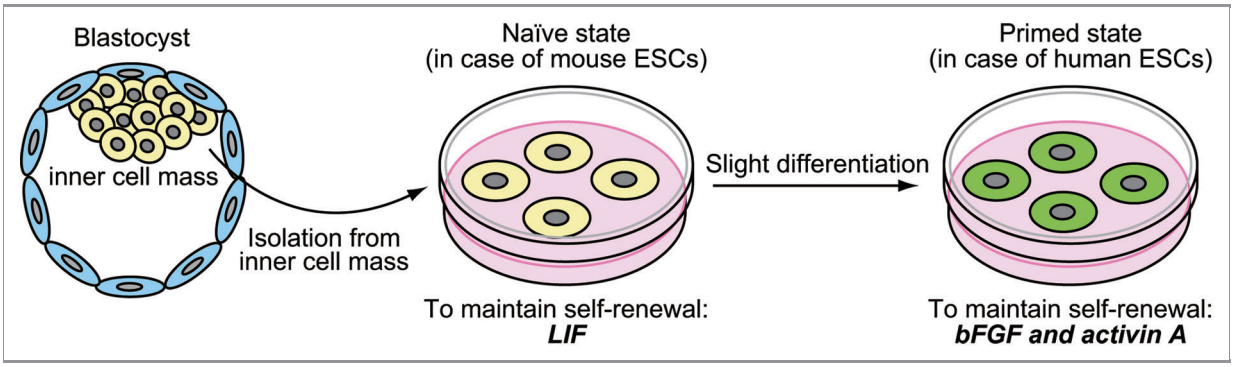

Figure 2. Factors required for maintaining self-renewal and pluripotency of mouse and human ESCs. LIF is a key cytokine for maintaining self-renewal and pluripotency of mouse ESCs. In contrast to mouse ESCs, fibroblast growth factor 2 (FGF2), also called basic FGF (bFGF), and activin A are used to maintain self-renewal in human ESCs. Human ESCs are likely to be slightly differentiated cells in the "primed state" and mouse ESCs are fully undifferentiated cells in the "naïve state."

LIF-T (intracellular form) and LIF-M (a form localized in the extracellular matrix).[31-33] LIF-M and LIF-D are synthesized as alternative transcripts differing in the first exon. LIF-T is a truncated isoform because of the initiation of translation at the first ATG codon of exon 2. LIF knockout mice have been established and analyzed in detail. Although homozygous $LIF^{-/-}$ mice are viable, they have many defects including decrease in cell lineages such as hematopoietic stem cells, primordial germ cells and motor neurons.[34,35] Notably, female $LIF^{-/-}$ mice are fertile, but their blastocysts cannot implant in the uterine epithelium because of the absence of LIF secretion as a nidation hormone from the uterus.[34]

LIF-related cytokines, including LIF, oncostatin M (OSM), cardiotrophin (CT-1) and ciliary neurotrophic factor (CNTF), function within a gp130 receptor complex and can sustain ESC self-renewal.[36-39] Furthermore, ESCs can be maintained by using a combination of interleukin-6 and soluble interleukin-6 receptor (IL-6/sIL-6R) and their intracellular signaling is engaged via formation of gp130 homodimers even without LIFR.[40,41] Therefore, intracellular signals from gp130 are sufficient for self-renewal of mouse ESCs. In addition to ESC self-renewal, activation of gp130 receptor complexes causes differentiation and growth inhibition in M1 myeloid leukemic cells, survival and differentiation of neurons, astrocytes and hypertrophy in cardiomyocytes.[37,42-45] An $LIFR^{-/-}$ mouse has already been established and analyzed. $LIFR^{-/-}$ mice showed decrease in bone volume (osteopenia), reduction in the numbers of motor neurons and astrocytes, abnormality of placenta and metabolic liver diseases.[46,47] $LIFR^{-/-}$ mice perinatally die probably due to developmental disorder of muscles including sucking muscles. Mice lacking gp130 have also been established. $gp130^{-/-}$ mice die between 12 to 16 d of embryogenesis, due to hematopoietic, neuronal and heart disorders.[48] These findings suggest that LIFR and gp130 are critical receptors for early embryogenesis and organogenesis.

LIF causes heterodimerization of LIFR and gp130 (**Fig. 1**).[6] Ligand-induced dimerization of the receptors leads to phosphorylation at tyrosine 1022 (Y1022) of JAK1 and activation of associated JAK1.[7,8,49,50] Four tyrosine residues (Y765/812/904/914) of the cytoplasmic domain of gp130 and three tyrosine residues (Y976/996/1023) of LIFR are phosphorylated by the activated JAKs. These phosphotyrosine residues then interact with the SH2 domain of STAT3. JAK then phosphorylates STAT3 at tyrosine 705 (Y705), leading to homodimerization of STAT3 via its SH2 domain and its translocation to the nucleus to transcribe target genes. Homodimerized STAT3 is imported into the nucleus through interaction with importin-α3 and importin-α6 and binds to the consensus sequence TTCCSGGGAA (S = C or G) at the promoter or enhancer regions of target genes.[51,52] A previous study showed that dominant interfering mutants of STAT3 inhibit macrophage differentiation of myeloid M1 cells after stimulation with LIF.[53] Furthermore, studies using knockout mice have shown that homologous disruption of the *STAT3* gene causes early embryonic lethality, while ESCs in which both *STAT1* genes have been deleted are phenotypically normal.[54,55] STAT5 has two genes, STAT5A and STAT5B, that are 96% identical. STAT5A and STAT5B knockout mice fail to response to prolactin and growth hormone, respectively. However, STAT5A/B double knockout mice develop a full complement of hematopoietic lineages and display subtler defects in embryonic hematopoietic development. However, homologous disruption of both *STAT5* genes does not cause embryonic lethality.[56] These findings suggest that STAT3 is important for maintenance of ESC proliferation and pluripotency, whereas STAT1 and STAT5 are dispensable for maintenance of pluripotency.

Other Regulations in the LIF-Mediated Signaling Pathway

The JAK-STAT pathway is negatively regulated by several inhibitory systems: dephosphorylation by tyrosine phosphatases including SH2-containing tyrosine phosphatase (SHP), protein tyrosine phosphatase 1b (PTP1B) and protein tyrosine phosphatase basophil-like (PTP-BL), inhibition by sumo-1 conjugation via protein inhibitor of activated STAT (PIAS), and physical inhibition or ubiquitin-mediated degradation by SOCS3 (**Fig. 1**).[57]

As a second signal via LIF, JAK activates phosphoinositide 3-kinase (PI3K) through tyrosine-phosphorylation of the regulatory subunit p85, which acts as an activator for AKT (**Fig. 1**).[58] AKT inhibits glycogen synthase kinase 3β (GSK3β) by direct phosphorylation of GSK3β at serine 9 (S9) and nuclear export of GSK3β independent of phosphorylation.[59,60] Consequently, AKT suppresses the action of GSK3β, which inhibits Nanog expression. Hence, a GSK3β inhibitor supports self-renewal of mouse ESCs in the absence of LIF. Moreover, AKT upregulates Tbx3 as another pluripotency gene and causes acetylaton of STAT3 at lysine 686 (K686), which induces more stable homodimer formation of STAT3, probably followed by the activation of Klf4 and Oct3/4.[61] Actually, a constitutively active form of AKT is sufficient for self-renewal of mouse ESCs even without feeder cells and LIF.[62]

As a third signal via LIF, JAK phosphorylates SHP2 recruited by binding to tyrosine 757 (Y757) of gp130 and tyrosine 969 (Y969) of LIFR (**Fig. 1**).[63] SHP2 then interacts with the Grb2/SOS complex and activates the MAPK pathway, leading to downregulation of Tbx3 and Nanog probably via nuclear export.[64] Therefore, the MEK inhibitor PD98059 inhibits differentiation of mouse ESCs and promotes ESC self-renewal.[65]

Ubiquitin-Proteasome System

Ubiquitination is one of the post-translational modifications used by eukaryotic cells, and the ubiquitin-mediated proteolytic pathway plays an important role in the degradation of short-lived regulatory proteins including those that contribute to cellular signaling, transcriptional regulation, cell cycle, DNA repair and protein quality control. Ubiquitin modification is mediated by a ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin ligase (E3). E3 is a scaffold protein that mediates between E2 and the substrate. The resulting polyubiquitinated conjugates are quickly recognized and degraded by 26S proteasome. E3 is thought to be the component of the ubiquitin conjugation system that is most directly responsible for substrate recognition. On the basis of structural similarity, E3 enzymes have been classified into two major families: the HECT (homologous to E6-AP COOH terminus) family and the RING-finger protein family.[66-70]

Members of the superfamily of tripartite motif (TRIM)-containing proteins are defined as E3 ubiquitin ligases by the presence of a RING-finger domain.[71] There are now more than 70 known TRIM proteins in humans and mice. TRIM proteins are characterized by the presence of a RING-finger domain, one or two zinc-binding motifs named B-boxes, and an associated coiled-coil region and are classified in subfamilies I to XI on the basis of differences in C-terminal domains.[72,73] TRIM proteins exist in invertebrate species as well as vertebrates.[74] Comparative analysis has shown that vertebrates have many TRIM family proteins with an SPRY domain in the C-terminal region, whereas invertebrate species have only a small number of TRIM family proteins with the SPRY domain. So far, TRIM proteins have not been identified in *Arabidopsis thaliana*, whereas proteins belonging to the U-box type E3 ligase family, another type of E3 ubiquitin family, have evolutionally been vastly amplified in *A. thaliana* genomes.[75] However, there are 32 proteins with N-terminal B-boxes such as COL, STO and STH1/2 in *A. thaliana*.[76]

TRIM family proteins are involved in several biological processes including cell proliferation/differentiation and diverse pathological conditions such as cancer, developmental disorders, neurodegenerative diseases, inflammation and autoimmune diseases.[77] Most of the TRIM proteins have roles as E3 ubiquitin ligases in the ubiquitination process, and several TRIM family members are involved in various biological processes, such as transcriptional regulation, cell proliferation and differentiation.

Ubiquitin System in JAK-STAT Signal

The JAK-STAT signal is negatively regulated by several mechanisms (**Fig. 1**).[78] The SOCS family has eight proteins (SOCS1~7 and CIS), which are induced by activation via cytokines, growth factors and hormones, and they were originally identified as negative molecules that form negative feedback loops.[79,80] All SOCS proteins have SH2 domain that is involved in binding to phosphorylated tyrosine, and a SOCS-box that functions as a binding motif for Cullin-2 as a component of E3 ubiquitin ligase. There are three molecular mechanisms to negatively modulate JAK-STAT activation signals. First, the N-terminal domain of SOCS likely becomes a pseudosubstrate for JAK to inhibit activated signals.[81] Second, SOCS competes with downstream signal molecules by binding to tyrosine-phosphorylated receptor proteins.[82] Third, SOCS proteins form E3 ubiquitin ligase complexes with Cullin-2, Elongin B, Elongin C and Rbx1 and ubiquitinate JAK and receptor molecules, followed by their degradation and internalization, respectively. SOCS1 mediates ubiquitination of JAK2 and TEL-JAK2 oncogene dependent on a SOCS-box.[83,84] SOCS3 induces proteasome-dependent degradation of target receptors including CD33 and sialic-binding immunoglobulin-like lectin (Siglec) 7.[85,86]

It has been reported that STAT-interacting LIM protein (SLIM), which is a nuclear protein with both PDZ and LIM domains, functions as an E3 ubiquitin ligase for STAT proteins (**Fig. 1**).[87] SLIM overexpression suppressed STAT1/4-mediated transcription by degradation of STAT proteins, whereas SLIM knockout caused increased STAT expression, followed by enhancement of interferon-γ (IFN-γ) production from Th1 cells. These findings suggest that SLIM is a bona fide E3 ubiquitin ligase that negatively regulates the JAK-STAT signal pathway. However, based on results of transcriptome analysis, SLIM is weakly expressed in mouse ESCs, indicating that SLIM may not be a main negative regulator for mouse ESCs (personal communications). Further detailed analysis of SLIM expression in mouse ESCs is needed to clarify the importance of JAK-STAT signals in ESCs.

Regulation of ESC Pluripotency by TRIM Proteins

TRIM8 is highly expressed in a variety of cancers including anaplastic oligodendroglioma and its gene maps to human

chromosome 10q24.3.[88] The region has frequent deletions or loss of heterozygosity in glioblastomas. Hence, TRIM8 is also called glioblastoma-expressed RING finger protein (GERP). It has been reported that TRIM8 is induced by IFN-γ and acts as a SOCS1-interacting protein.[89] We showed that TRIM8 interacts with PIAS3, which inhibits IL-6-dependent activation of STAT3. TRIM8 overexpression suppresses the negative effect of PIAS3 on STAT3, either by degradation of PIAS3 via the ubiquitin-proteasome pathway or exclusion of PIAS3 from the nucleus.[90] Although we checked more than 30 different types of cancer cell lines, we failed to detect endogenous TRIM8 in those cell lines. Finally, we checked ESCs because TRIM8 regulates PIAS3 and STAT3 is a crucial regulator for the LIF-dependent signaling pathway. We found that endogenous TRIM8 is highly expressed in mouse undifferentiated ESCs and that differentiated ESCs cultured without LIF do not express endogenous TRIM8, suggesting that TRIM8 is necessary for maintenance of pluripotency and self-renewal of ESCs. Actually, we showed that TRIM8 interacts with Hsp90β, which interacts with STAT3 and selectively downregulates transcription of *Nanog* in ESCs (**Fig. 1**).[13,15,16] TRIM8 inhibits translocation of STAT3 into the nucleus through interaction with Hsp90β and consequently inhibits transcription of *Nanog* in ESCs, suggesting that TRIM8 regulates self-renewal or differentiation of ESCs.

Recently, we found that TRIM6, another of the TRIM family ubiquitin ligases, is also highly expressed in ESCs and binds to c-Myc and that TRIM6 overexpression causes decrease in c-Myc-mediated transcription.[91] The proto-oncogene product c-Myc is known to be a master regulator of cell proliferation by specific binding to the *E-box* motif in promoter regions of target genes.[92] It has also been reported that c-Myc plays an important role in the proliferation and maintenance of pluripotency of ESCs and that the transcriptional activity of c-Myc is regulated by several post-translational modifications including phosphorylation and ubiquitination.[93] It has been reported that c-Myc overexpression maintains the pluripotency of mouse ESCs even without LIF, but sustained activation of c-Myc induces differentiation of human ESCs, suggesting that c-Myc has different functions in mouse and

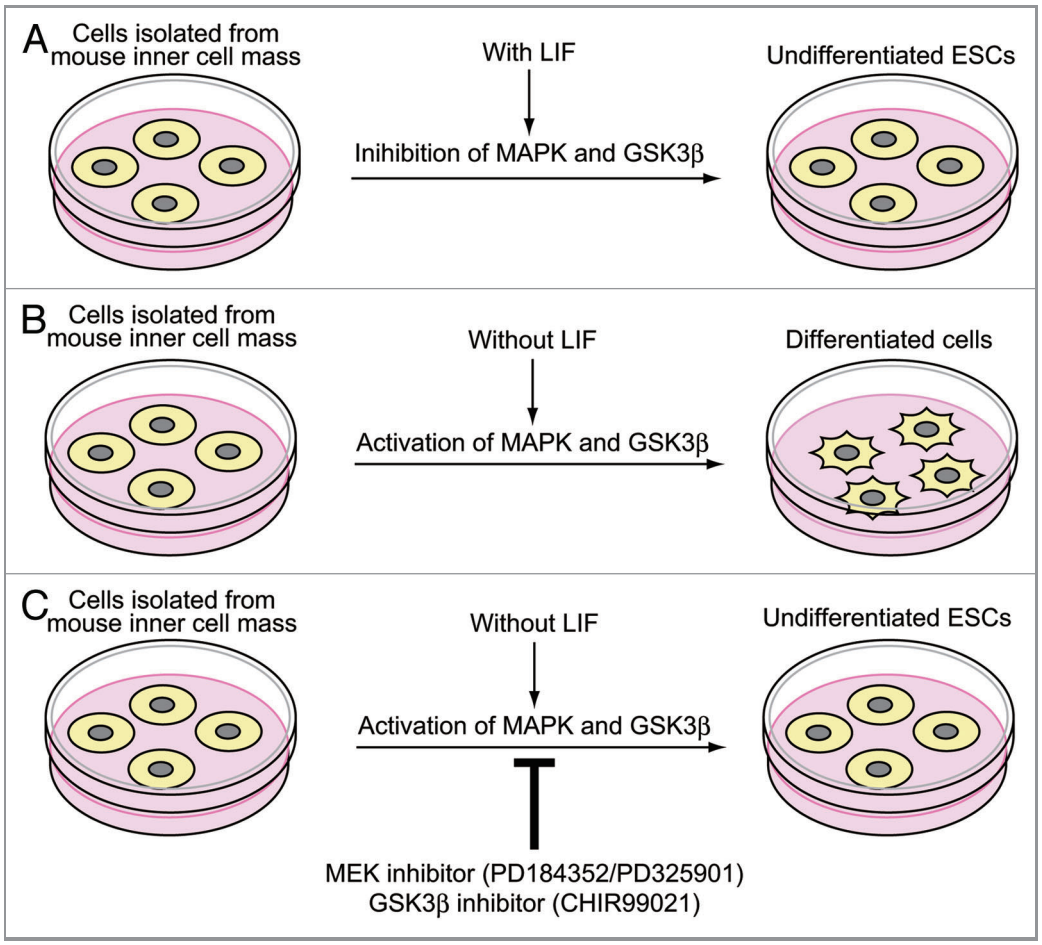

Figure 3. Maintenance of self-renewal and pluripotency of mouse ESCs by chemical inhibitors. FGF4 autocrined by ESCs likely causes activation of SHP2-Ras-MAPK. Activation of the SHP2-Ras-MAPK cascade including MEK induces differentiation of ESCs. Moreover, activation of GSK3β causes phosphorylation of c-Myc followed by degradation of c-Myc and also inhibits Nanog expression, resulting in the differentiation of ESCs. LIF-mediated AKT activation causes phosphorylation of GSK3β, followed by inactivation of GSK3β (A). Without LIF, mouse ESCs are differentiated through unphosphorylated GSK3β and MAPK activated by autocrine FGF4 (B). The combination (2i) of a MEK inhibitor (PD184352/PD325901) and GSK3β inhibitor (CHIR99021) is sufficient for maintaining self-renewal and pluripotency of mouse ESCs without LIF (C).

human ESCs.[93,94] We showed that TRIM6 overexpression in mouse ESCs inhibits c-Myc-mediated transcription, resulting in induction of the differentiation of ESCs (**Fig. 1**). These findings suggest that TRIM6 controls the transcriptional activity of c-Myc for maintaining self-renewal and pluripotency of ESCs. In addition to ESCs, induced pluripotent stem cells (iPSCs) are established by the expression of four genes, Oct3/4, Sox2, Klf4 and c-Myc, into several cell lineages of mice and humans.[95] However, the carcinogenic potential of c-myc inhibits its use in iPSCs for clinical application. However, the efficiency of iPSC establishment without c-Myc expression is very low.[96] Therefore, appropriate regulation of the expression level of c-Myc at an inducing stage of stem cells should be important to establish iPSCs. TRIM6 is expressed at higher level in undifferentiated ESCs than in differentiated cells, and c-Myc expression level is robustly elevated in TRIM6-knockdown ESCs.[91] Once ESCs enter the differentiation stage, the expression of TRIM6 is rapidly decreased.[91] TRIM6-knockdown ESCs are rapidly differentiated even in the presence of LIF.[91] Taken together, the findings indicate that TRIM6 may regulate c-Myc expression level within optimal ranges to maintain pluripotency of ESCs. It is likely that TRIM6 strictly modulates the expression level or activity of c-Myc to prevent dysregulation of cell proliferation by c-Myc in ESCs.

Concluding Remarks

Mouse ESCs are usually maintained by using LIF and feeder cells to inhibit differentiation. Recently, it has been reported that LIF can be replaced by chemical compounds to inhibit several signaling pathways. The cocktail of three inhibitors, a FGF-R tyrosine kinase inhibitor (SU5402), MEK inhibitor (PD184352) and GSK3β inhibitor (CHIR99021), is called 3i.[97] This cocktail is sufficient to maintain mouse ESCs even in the absence of LIF. If a more potent MEK inhibitor (PD325901) is used, the cocktail (2i) including PD325901 and CHIR99021 is sufficient for maintaining self-renewal of mouse ESCs without LIF (**Fig. 3**).[97] This recent technology has been established on the basis of results of studies on the LIF-mediated signal pathway at the detailed molecular level. Further studies to clarify related molecules and signal networks should lead to novel technologies for developmental engineering and tissue engineering.

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