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The regulation of leukemia inhibitory factor

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Abstract

Leukemia inhibitory factor (LIF), a secreted cytokine, plays an important role in a wide array of biological processes including inducing differentiation of leukemia cell, inflammatory response, neuronal development, embryonic implantation, stem cell self-renewal and cancer progression, etc. LIF exerts its biological functions mainly through the activation and regulation of JAK/STAT3, AKT, EKR1/2 and mTOR signal pathways. The expression levels of LIF are regulated by many different factors under different conditions in different tissue/cell types. For example, estrogen and p53 are important regulators for the high LIF production in uterine tissues at the implantation stage. Hypoxia plays a critical role in LIF overexpression in solid tumors. Many cytokines, including IL-6, IL-1β, can also induce the LIF expression and production. In this review, we summarize the current understanding on the transcriptional regulation of LIF under various conditions.

Leukemia inhibitory factor (LIF) is a multi-functional cytokine which belongs to the IL-6 superfamily. Other members in the IL-6 superfamily include oncostatin M (OSM), IL-6, IL-11, ciliary neurotrophic factor (CNTF), and cardiotrophin-1 (CT-1)[1, 2]. *LIF* gene is highly conserved between humans and mice; the homology between the human and murine *LIF* gene is 75%[3]. LIF protein is a monomeric glycoprotein which is often modified by glycosylation[3]. The molecular weight of the unglycosylated LIF protein is 20–25 kDa, while the molecular weight of the glycosylated protein is in the range of 37–63 kDa[3, 4].

LIF functions through both autocrine and paracrine manners. LIF binds to its specific receptor LIFR, then recruits gp130 to form a high affinity receptor complex to induce the activation of the downstream signal pathways including JAK/STAT3, PI3K/AKT, ERK1/2 and mTOR signaling[5–8]. Early studies on LIF uncovered the function of LIF in inducing the differentiation of murine M1 myeloid leukemia and macrophage maturation to suppress leukemia proliferation[9]. That's how LIF got its name. Further studies have clearly proven that LIF is a multifunctional protein which has a broad biological functions in neuronal, hepatic, endocrine, inflammatory and immune systems[10]. LIF regulates the embryonic stem cell self-renewal and is an indispensable factor to maintain mouse embryonic stem cell pluripotency[11]. Furthermore, LIF plays an important role in embryonic implantation. LIF

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regulates several events during implantation, which include the receptive state of endometrial, the interaction between endometrial and embryo, stromal decidualization, the invasion of blastocyst, blastocyst development, and the infiltration of uterine leukocyte[12]. In addition, LIF can regulate the synthesis of prostaglandins (PGs), which is an important mediator in implantation and decidualization[13]. LIF knockout in female mice causes infertility due to the defect in the implantation[14].

LIF has a complex role in tumor development and progression. In contrast to its role in inhibiting the growth of leukemia cells, LIF often promotes the development and progression of many types of solid tumors. Overexpression of LIF promotes the proliferation of cultured human cancer cells and increases the growth of xenograft tumors formed by many human tumor cells[7, 15]. Further, LIF increases the migration and invasion abilities of tumor cells, and promotes metastasis of breast cancers and rhabdomyosarcomas[7, 16]. LIF promotes tumor metastasis through multiple mechanisms. We reported that LIF activates the mTOR signaling in breast cancer cells to promote metastasis. Another recent report showed that transforming growth factor β (TGF-β) can induce LIF production in carcinoma-associated fibroblasts which leads to proinvasive activation of fibroblasts and increased invasion of carcinoma cells[17]. LIF also increases the resistance towards cancer therapy, including chemotherapy and radiotherapy[8, 18]. The overexpression of LIF is frequently observed in many human tumors, including breast cancer, bladder cancer, colorectal cancer, lung cancer, melanoma and nasopharyngeal carcinoma[7, 8, 18, 19]. Furthermore, LIF overexpression is frequently associated with poor prognosis on recurrent free survival in many human tumors, including colorectal cancers, breast cancers and nasopharyngeal carcinoma[7, 8, 18].

Considering the critical role of LIF in such a wide array of biological functions, it is important to understand the regulation of LIF expression. LIF expression levels can be induced at the mRNA levels under the inflammatory stress, in uterine tissues at the embryonic implantation stage. LIF is also frequently overexpressed at both the mRNA and protein levels in many tumor tissues and tumor environments. The transcriptional regulation of LIF is through different mechanisms under different conditions.

In tumors, LIF is frequently overexpressed. The amplification of the *LIF* gene is not a common event in human tumors[20]. Instead, our recent study showed that hypoxia is an important factor which induces the expression of LIF mRNA. Hypoxia induces the stabilization of hypoxia inducible factors (HIFs) to mediate majority of the hypoxia responses in cells. HIFs are transcriptional factors that are composed of an α-subunit and a β-subunit protein[21]. HIFs can regulate the transcription of their target genes through binding to DNA containing a hypoxia-responsive element (HRE; 5'-G/ACGTG-3'). HIF-1α and HIF-2α are two major α-subunit HIF proteins. A number of target genes of HIF-1α and HIF-2α are overlapping, while each transcription factor has their unique target genes as well. The LIF promoter region contains two HREs which can be transcriptionally activated by hypoxia. Furthermore, the induction of LIF by hypoxia is mediated mainly by HIF-2α instead of HIF-1α[20]. In human colorectal tumor samples, there is a strong association of increased HIF-2α levels and high LIF levels. Consistently, a recent study observed that hypoxia induces the LIF expression in malignant melanoma[19]. Taken together, these

findings demonstrate that hypoxia, a condition often existed in solid tumors, is an important factor to induce LIF overexpression in human tumors. In addition to hypoxia, TGF-β has been reported to induce the expression of LIF mRNA in both tumor cells and fibroblasts, and increase the production and secretion of LIF protein. In turn, LIF promotes proinvasive fibroblast activation and creates an invasive tumor microenvironment that leads to the progression and metastasis of primary tumors[17]. In addition, TGF-β can induce LIF in a Smad-dependent manner in glioma-initiating cells (GICs) which are responsible for the initiation and recurrence of gliomas. The induction of LIF is important to maintain the self-renewal capacity of GICs and prevent their differentiation[22].

The expression of LIF is also regulated by estrogen, especially for the induction of LIF in the uterine tissue at the embryonic implantation stage. The estrogen levels increase significantly at the implantation stage in both mice and humans to induce LIF mRNA levels in the uterine tissues, which is critical for the embryonic implantation[23]. In addition, LIF is a transcriptional target gene of p53, a well-known tumor suppressor. The *LIF* gene contains a consensus p53-binding element in the first intron. p53 binds to the p53-bidning element in the *LIF* gene to regulate basal LIF expression levels in various tissues, including uterine tissues. In fact, the induction of LIF at the implantation stage requires both estrogen and p53. In the absence of p53, the expression levels of uterine LIF at the implantation stage reduce significantly, which in turn leads to impaired implantation and decreased fertility in the p53 deficient female mice. As a p53-regulated gene, the expression levels of LIF are also increased under various stressed conditions, such as ionization irradiation, hypoxia, etc., when the p53 protein is activated[24].

The expression of LIF is induced under inflammatory stress. Lipopolysaccharide (LPS) injection into the trachea of rats induces the expression and secretion of LIF into bronchoalveolar lavage fluid to play an important role in anti-inflammation[25]. The expression of LIF is also regulated by many cytokines. In the cultured normal human bone marrow stromal cells, IL-1α, IL-1β, TGF-β and tumor necrosis factor-α (TNF-α) can all increase the transcription of LIF mRNA[26]. The induction of LIF by IL-1β and TNF-α was also observed in gingival fibroblasts and several cell types in human airways[27, 28]. In addition, the induction of LIF expression by other cytokines, including IL-6, IL-2 has been observed in different cell types, including airway smooth-muscles and MT-2 cells[28, 29]. The expression of LIF can also be inhibited by some factors, including 1α, 25-dihydroxyvitamin D3 and dexamethasone[29]. The analysis of the LIF promoter revealed that transcription factor STAT5 can bind to the LIF promoter and induce its expression in myeloid cell lines[30]. In addition, LIF promoter region contains several ETS binding sites. The binding of ETS transcription factors to the LIF promoter is critical for the induction of LIF in response to T cell activators[31].

While the transcriptional regulation of LIF has been extensively studied, some interesting questions on the regulation of LIF still remain. It is clear that the LIF expression is induced under many conditions and is regulated by many different transcription factors. It is unclear why the induction of LIF requires different transcriptional regulation mechanisms. One possibility is the availability of different transcriptional factors in different cell/tissue types and development stages. Another possibility is that the induction of LIF by different

transcription factors may have different kinetics in inducing LIF which will lead to either quick and transient increase of LIF or sustained increase of LIF. It will be also interesting to investigate the regulation of LIF at the protein levels. The secreted LIF protein has very short half-life due to the serum protease. However, the post-translational regulation of LIF is still largely unclear, which needs further studying.

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