

Lipopolysaccharide-induced tumor necrosis factor- α factor enhances inflammation and is associated with cancer (Review)

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Abstract. Lipopolysaccharide-induced tumor necrosis factor- α factor (LITAF) exerts transcription factor activity and is involved in protein quality control. LITAF activity is highly dependent on correct translocation from the endosome/lysosome to the nucleus, while certain LITAF mutants mislocalize to areas, such as the cytosol and mitochondria, resulting in developmental diseases. In addition, previous studies have proposed that LITAF functions as a tumor suppressor and is frequently under-represented in certain types of cancer. However, the mechanism of this phenomenon remains unclear. The present review summarizes the major advances in LITAF studies, and proposes that *LITAF* may serve as a switch in the balance between classical and alternative activation in tumor associated-inflammation. Thus, LITAF may be a promising therapeutic target with regard to the tumor microenvironment.

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1. Introduction

As first identified by Polyak *et al* in 1997 (1), the gene of lipopolysaccharide (LPS)-induced tumor necrosis factor (TNF)- α factor (*LITAF*) was initially termed *p53-inducible gene 7 (PIG7)*, due to the fact that it encodes for a protein that is positively regulated by the tumor suppressor protein, p53 (1). Two years later, Myokai *et al* (2) cloned an LPS-regulated gene with the same sequence as *PIG7*. This gene was subsequently termed *LITAF* as its encoded protein product, LITAF, translocated into the nucleus following cellular activation by LPS, which was followed by the upregulation of *TNF- α* transcription (2-4).

It is widely accepted that tumor-associated inflammation is a major contributor to cancer progression, and it has been recognized as the seventh hallmark of cancer (5,6). Numerous primary inflammatory mediators have been identified, including interleukin (IL)-4 (7), CCL18 (8) and granulocyte macrophage colony-stimulating factor (9). Previous observations suggest that *LITAF*, as a ubiquitously expressed gene (1-4), may be an enhancer of inflammatory diseases, as well as a suppressor of cancer-associated inflammation. In the current review, the above-mentioned observations are summarized, and *LITAF* is presented as a potential novel target for cancer therapy.

2. Structure and general features of LITAF

Human *LITAF* is located on chromosome 16 and it encodes a full length cDNA of 1,551 base pairs (bp), which contain three major structural components: A 5' untranslated region (UTR) of 1,001 bp, 3' UTR of 76 bp and an open reading frame of 474 bp (2,10). The C-terminal of the LITAF protein has enriched cysteine residues and includes a highly conserved C3H4 zinc finger region that is interrupted by 23 hydrophobic amino acids, called small integral membrane protein of lysosome/late endosome (SIMPLE)-like domain (SLD) (11). The SLD domain contains a YXX ϕ (ϕ is a hydrophobic amino acid) and double leucine motifs (12). It was reported that proteins containing the YXX ϕ motif interact with the clathrin adaptor compound and are, therefore, able to mediate the import and export of membrane proteins in the endosome, Golgi apparatus and lysosomes (13,14). Furthermore, proteins with double leucine motifs are able to target lysosomes and endosomes (15). However,

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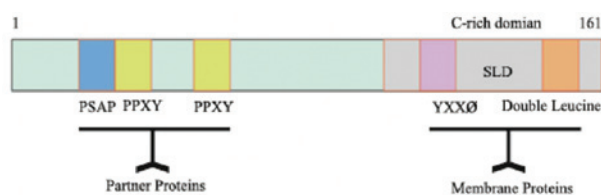


Figure 1. Structure of lipopolysaccharide-induced tumor necrosis factor- α factor.

the N-terminal of the LITAF protein is enriched with proline residues and has PPXY and PS/TAP motifs, which mediate the association of LITAF with partner proteins (16-18) (Fig. 1).

3. Trafficking of LITAF

The nuclear translocation and transcription factor activity of LITAF are critical for the activation of numerous immune cells via classical pathways (Fig. 2). While intracellular LITAF is located in the membranes of late endosomes and lysosomes under quiescent conditions, these processes require free LITAF to be released from these intracellular compartments. It has been proposed that such a process is orchestrated by the protein-protein interactions with ubiquitination-associated proteins, such as the E3 ligase NEDD4 (16). LITAF functions with the endosomal sorting complex required for transport components to control endosome-to-lysosome trafficking (17). As a negative control, previous studies have indicated that mutated LITAF proteins mislocalize to the cytosol (18) and/or mitochondria (19), where they cease their wild-type (WT) activities and serve as an etiological cause of Charcot-Marie-Tooth disease, a severe peripheral nervous system disorder (20,21).

4. LITAF and STAT6 (B) in inflammation

LITAF is known as a TNF- α inducer (22), therefore, it is notable that transient transfection of LITAF resulted in no significant elevation of TNF- α levels following LPS treatment (3). This indicates that LPS activates additional factors, other than LITAF, that also regulate the transcription of TNF- α and that these factors may be binding partners of LITAF. Using a yeast two-hybrid system, a transcription factor, signal transducer and activator of transcription (STAT)6 (B), has been identified as a functional binding partner of LITAF (3). LITAF and STAT6 (B) are activated by LPS, then associate with toll-like receptor-2/4 to form a complex, which is dependent on MyD88 and is phosphorylated by p38- α (3). Phosphorylated LITAF and STAT6 (B) consequently interact to form a protein complex prior to translocating into the nucleus, where LITAF binds specifically to the promoter sequence, thus activating the expression of downstream genes, such as TNF- α and IL-6 (4,23) (Fig. 3). Focusing on this pathway, LITAF has become a novel target for the treatment of endotoxic shock and inflammation (24), as implicated by Matsuno *et al* (25) who demonstrated that LITAF-knockout mice were more resistant to LPS-induced mortality.

5. LITAF and inflammatory diseases

As a significant disease associated with LITAF, inflammatory bowel disease (IBD) is a type of chronic intestinal

inflammatory disease with an unknown etiology, which includes ulcerative colitis (UC) and Crohn's disease (CD) (26). The typical pathogenesis of IBD includes aberrant expression of bowel-specific proinflammatory cytokines, including TNF- α (24,27,28). This indicates that LITAF may be involved in IBD and may be abnormally expressed in this disease. Stucchi *et al* (29) observed that the mRNA levels of LITAF in colon tissue samples from patients with CD were five times higher than those from healthy controls. In addition, within the same CD sample, the inflammatory areas presented with 60% more LITAF mRNA than the non-inflammatory areas (29). Similar phenomena have been observed in patients with UC. Colon tissues from patients with UC expressed LITAF mRNA levels 15 times greater than healthy individuals (26). However, in such patients, there was no significant difference in the mRNA level of LITAF between the inflammatory areas and the surrounding normal tissues. Immunohistochemistry has demonstrated that LITAF is predominantly expressed by lamina propria macrophages (LPM) (29). This was verified by Bushell *et al* (30) with a 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced mouse colon inflammation model. This study additionally indicated that mRNA and protein levels of LITAF were dramatically upregulated in TNBS-treated mice when compared with untreated mice. Furthermore, the expression of TNF- α in the LPM from LITAF *mac*^{-/-} mice was significantly lower than that of the WT mice (30). These results strongly suggest that LITAF upregulates expression of TNF- α in LPM and elevated expression of LITAF coincides with the progression of IBD.

Arthritis is an inflammatory disease occurring in the joints of the human body and surrounding tissues, which has a complex etiology. Causal factors include chronic inflammation, autoimmune reactions, infection, metabolic disorders, trauma and degenerative disorders (31). Patients with arthritis commonly exhibit vascular endothelial dysfunction with alterations in numerous inflammatory factors, including TNF- α , IL-6 and IL-8 (32,33). To investigate whether LITAF was involved in arthritis, Merrill *et al* (34) established an LITAF knockout mouse [tamLITAF(i)^{-/-}] through tamoxifen induction. LPS was used to treat WT and tamLITAF(i)^{-/-} mice and collagen-induced arthritis experiments were performed. The degree of disease severity was found to be dramatically higher in the WT mice than in the tamLITAF(i)^{-/-} mice, this observation was noted from 3 days post-treatment and the difference became more significant over time. In addition, pannus and synovitis inflammations were observed to be elevated in the tamLITAF(i)^{-/-} mice. Additionally, the degree of bone resorption was observed to be lower in tamLITAF(i)^{-/-} mice compared with the WT mice (34). These results suggest that *in vivo* depletion of LITAF effectively

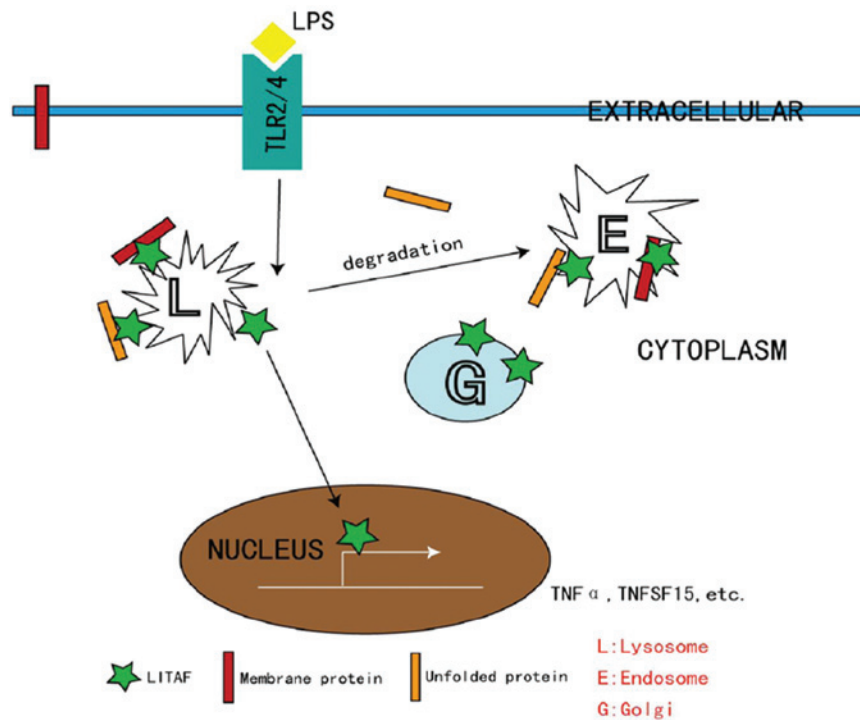


Figure 2. Schematic representation of subcellular localization of LITAF. LPS stimulation translocates LITAF from the cytoplasm into the nucleus to promote target gene expression. LITAF may target the lysosome or endosome to regulate protein degradation. LITAF, lipopolysaccharide-induced tumor necrosis factor- α factor; LPS, lipopolysaccharide; TLR2/4, toll-like receptor 2/4; TNF, tumor necrosis factor.

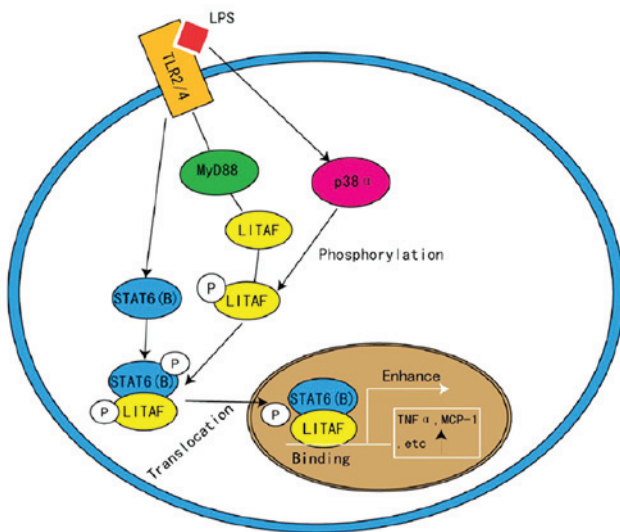


Figure 3. Mechanisms of inflammation regulation by LITAF. LITAF and its functional partner, STAT6 (B) can be activated by LPS/TLR2/4 signaling, which involves phosphorylated p38- α . Phosphorylated LITAF binds to STAT6 (B), which is followed by translocation into the nucleus and regulation of proinflammatory gene expression. LITAF, lipopolysaccharide-induced tumor necrosis factor- α factor; STAT6, signal transducer and activator of transcription 6; TLR2/4, toll-like receptor 2/4.

reduces the harmful effects of arthritis. Corroborating these results, Srinivasan *et al* (35) identified a connection between LITAF and arthritis, and proposed that it may involve extracellular-related kinase 1/2 and protein kinase B (35). These observations suggest that LITAF may promote the progression of arthritis, as well as additional associated whole body inflammation in mice.

6. LITAF and cancer

In addition to inflammation, *LITAF* has been identified as a potential tumor suppressor gene, due to the fact that its expression can be induced by p53 (1). Evidence from cohort studies has revealed that LITAF expression is significantly lower in tumor tissues when compared with isogenic normal tissues (36,37). However, the functional mechanisms of the action of LITAF in tumors remains unclear.

Zhou *et al* (38) used small hairpin (sh)RNA to disrupt gene expression in the adenosine monophosphate-activated protein kinase (AMPK)-LITAF-TNF superfamily member 15 (TNFSF15) signaling pathway in prostatic cancer cells and elucidated that shRNA targeting of *LITAF* (shRNA-*LITAF*) significantly enhanced the degree of malignancy of cancer cells. Notably, its effect was more marked than that of shRNA-p53 (38). Furthermore, Zhou *et al* (38) established an allograft prostatic tumor model by subcutaneous injection of prostatic cancer cells into nude mice. Following development of tumors, those analyzed from the shRNA-*LITAF* group were observed to be significantly larger in size and weight compared with the tumors from the shRNA-control group (38). These results suggest that LITAF inhibits the proliferation of prostatic cancer cells, which supports the assumption that *LITAF* functions as a tumor suppressor gene.

Furthermore, a breast cancer study analyzed the gene expression of normal breast tissues, ductal carcinoma *in situ* (DCIS) and invasive ductal carcinoma (IDC) using the Serial analysis of gene expression method. The study revealed that *LITAF* expression was 29 times lower in DCIS compared with that of normal tissues, while there was no clear alteration in the *LITAF* levels observed in IDC (36). Similarly,

Fernandez-Cobo *et al* (39) confirmed that *LITAF* expression in breast cancer cells was 37 times lower than that in normal breast epithelial cells. It was hypothesized that *LITAF* and other cytokines participate in the recovery process of breast tissues following pregnancy and lactation, during which extensive apoptotic events occur in breast tissues (40). Furthermore, lower expression of *LITAF* may promote the early transformation of breast tissues by slowing down the normal apoptotic process.

Wang *et al* (37) conducted qualitative polymerase chain reaction analysis and established that bone marrow *LITAF* expression in patients with acute leukemia (as well as refractory and relapsed acute leukemia) is significantly reduced, when compared with the expression levels in patients at initial diagnosis. In addition, Wang *et al* elucidated that the transient expression of *LITAF* has little apparent influence on the proliferation of acute leukemia cells. However, *LITAF* markedly enhances the inhibitory effects of etoposide and daunomycin on acute leukemia, suggesting that *LITAF* sensitizes leukemic cells to chemotherapeutic agents (37).

It should be noted that not all cancer cells exhibit low expression of *LITAF*. For example, Matsumura *et al* (41) examined a rare malignant skin tumor, extra-mammary Paget's disease (EMPD) and observed that EMPD tissues exhibited higher expression levels of *LITAF* in comparison with isogenic normal tissues, in three out of four individuals (41). This phenomenon may be relevant to somatic mutations. The study also identified *LITAF* site mutations in three out of 12 cases, among which two exhibited non-synonymous mutations and one exhibited synonymous mutations (41). The mechanism of this mutation and the associated expression remains unclear.

There are numerous mechanisms suggested to be involved in the tumor suppressor activity of *LITAF* (Fig. 4). Firstly, the two PPXY motifs at the N-terminal of *LITAF* associates with the WW domain containing proteins, such as NEDD4 and Itch, which are able to promote p53- and/or p72-mediated cell apoptosis and subsequently restrict tumor growth (40,42,43). Secondly, *LITAF* may promote the ubiquitin-proteasome system in mediating the degradation of pro-cancerous proteins (44). Thirdly, *LITAF* is able to stimulate the expression of TNFSF15 and then restrain angiogenesis to inhibit tumor growth, as it acts as a downstream target of the tumor suppressor factor, AMPK (38).

It is hypothesized that *LITAF* may serve as a switch in the balance between classical inflammation and alternative activation in cancer. Immune cell infiltration is a typical trigger of cancer-associated inflammation. Notably, studies using mouse models suggested that the alleviation of immune responses results in a decline in the quantity and size of tumors in the murine body (45,46). Alternative activation of various cell types, including tumor-associated macrophages (47), cancer-related fibroblasts (48) and aberrantly activated neutrophils (49) have been identified in numerous types of cancer, including breast (50) and colorectal cancer (51), and melanoma (52). In the context of these types of cancer, the regulators and determinants of classical and alternative immune activation remain unclear. It has been observed that *LITAF* is highly expressed in macrophages in various acute inflammatory tissues, and classically induces TNF- α , which

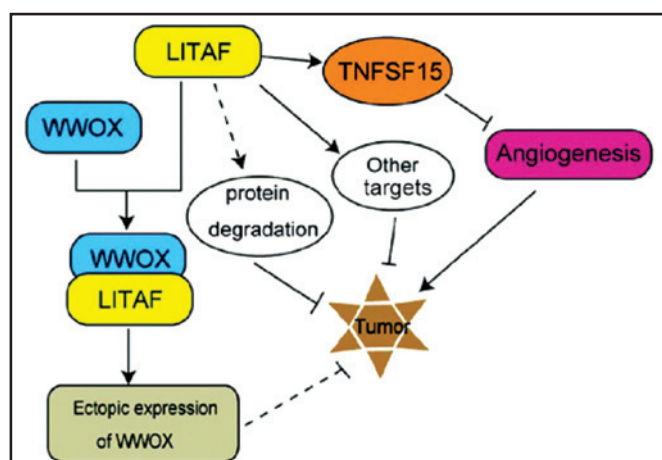


Figure 4. Possible mechanisms of the tumor suppressing role of *LITAF*. *LITAF*, lipopolysaccharide-induced tumor necrosis factor- α factor.

exerts antiviral, antitumor and proapoptotic activities when at sufficiently high *in situ* concentrations (53,54). Short-term activation of *LITAF* inhibits the growth of cancer cells potentially through proinflammatory effects that target the expansion of tumor-antigen specific T cells and the cancer cells themselves (55). During chronic inflammation, inflammatory factors overexpressed by the alternative activated immune cells may suppress the expression of *LITAF* via the negative feedback mechanism, for example via the nitric oxide pathway (56). However, the exact role of *LITAF* in the transition from inflammation to tumor suppression requires further investigation, which may elucidate the potential for *LITAF* manipulation to modulate early carcinogenesis and/or cancer progression.

7. Summary and prospect

LITAF may affect cellular functions by either acting as a transcription factor in mediating target gene expression, or by acting as a recruiting factor that targets partner proteins to the lysosome for degradation. Current evidence indicates that various possible mechanisms may explain the contribution of altered *LITAF* expression to the progression of diseases, such as inflammation or tumors: i) Cytokine levels are dysregulated; ii) p53-mediated cell apoptosis signaling is affected; iii) Protein degradation in the lysosome is interrupted. It is proposed that *LITAF* may serve as a switch in the balance of classical and alternative activation in the tumor microenvironment. It remains unclear whether *LITAF* is a cause or effect of tumor inflammation, thus it is an important focus for further investigation and may be a promising therapeutic target.

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