Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2020.32.005206

Molecular Mechanisms Underlying Il-1β Production in Macrophages: MTOR and C/EBPβ Pathways

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ARTICLE INFO

Received: November 18, 2020

Published: November 24, 2020

ABSTRACT

Citation: Xuelian Hu, Qianqian Gao, Yang Gao, Wenhong Hou, Yuhui Miao, Wei Zhou, Linnan Zhu. Molecular Mechanisms Underlying Il-1β Production in Macrophages: MTOR and C/EBPβ Pathways. Biomed J Sci & Tech Res 32(1)-2020. BJSTR. MS.ID.005206.

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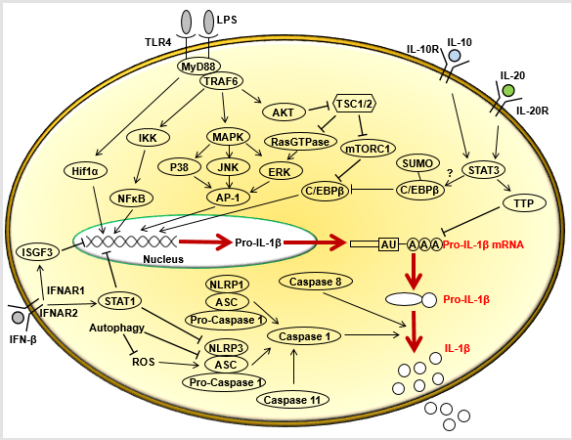

Note: In response to LPS, pro-IL-1β transcription is activated and then is cleaved to produce the biologically active IL-1β. NF-κB and MAPK pathways are critical for the regulation of IL-1β transcription. LPS-induced phosphorylation of AKT leads to the phosphorylation and activation of CREB that binds to C/EBPβ promoter and mediates C/EBPβ expression. STAT3 pathway activated by IL-20 leads to SUMO-mediated inactivation of C/EBPβ. C/EBPβ protein is required for the activation of IL-1β gene expression. IL-10 initiates TTP expression, which could bind to IL-1β 3'UTR and facilitate its degradation. Intracellular succinate acts as an endogenous danger signal to stabilize HIF-1α, which in turn promotes IL-1β expression. The maturation of pro-IL-1β into the active form of IL-1β is thought to be mainly mediated by caspase-1, which could be activated from pro-caspase-1 by NLRP1 and NLRP3 inflammasomes. Besides, caspase-11 and caspase-8 also play important roles for the IL-1β processing and activation. TSC1/2 is an endogenous negative regulator of mTORC1. Over-activated mTORC1 caused by TSC1/2 deficiency leads to decreased pro-IL-1β expression by inhibiting C/EBPβ expression. However, the absence of TSC1/2 increases the activity of RasGTPase, which leads to the activation of ERK and then potentially induces IL-1β transcription. Therefore, TSC1/2 controls IL-1β transcription through multiple pathways.

Figure 1: Multiple pathways regulating IL-1β production in macrophages.

As an important pro-inflammatory cytokine, IL-1β exerts its pro-inflammatory function by promoting inflammatory cytokines production and recruiting inflammatory cells to the site of injury or infection from the circulation.IL-1β is implicated in many pathological conditions, including acute inflammation, chronic inflammation and autoimmune diseases. Blocking IL-1β has been applied to cure patient with a class of inflammatory syndromes such as aphthous stomatitis, pharyngitis, rheumatoid arthritis, type 2 diabetes, urticarial vasculitis and so on [1]. Therefore, it is important to study the signaling pathways that regulate IL-1β production. In response to an exogenous stimulus such as LPS, IL-1β transcription is first activated. Then IL-1β is translated as an inactive precursor protein pro-IL-1β, which need to be further cleaved at the N-terminal 116 amino acids to produce the biologically active IL-1β. The regulation of IL-1β production is mainly processed on these two aspects (Figure 1). It is well known that NF-κB and Mitogen-Activated Protein Kinase (MAPK) signaling pathways are important for the regulation of IL-1β transcription [2,3]. LPS-TLR4 phosphorylates IKK through a Myeloid Differentiation Primary Resposnse Gene 88 (MyD88) dependent pathway, which releases NF-κB into the nucleus to regulate IL-1β transcription. In addition, MyD88 signaling also participates in the activation of Transforming growth factor-β-Activated Kinase 1 (TAK1), which results in the activation of MAPK cascades. MAPK can active downstream signals including P38, ERK and JNK, which activates transcription factor activator protein 1 (AP-1). Blocking any of P38, ERK and JNK activity could inhibit IL-1β transcription significantly [3,4].

CCAAT/enhancer-binding protein β (C/EBPβ) protein is required for the activation of mouse and human IL-1β gene expression [5]. C/EBPβ expression could be induced by LPS. LPS-induced phosphorylation of AKT can lead to the phosphorylation and activation of cAMP response element B (CREB) that binds to C/EBPβ promoter and mediates C/EBPβ expression. STAT3 pathway activated by IL-20 could lead to SUMO-mediated inactivation of C/EBPβ, which interferes with the induction of IL-1β expression in keratinocytes [6]. In macrophages, IL-10 initiates an STAT3-dependent increase of RNA-destabilizing factor tristetraprolin (TTP) expression. TTP could bind to IL-1β 3'UTR and facilitate its degradation by initiating the assembly of RNA decay machinery [7]. In addition, macrophages activated by LPS switch their core metabolism from oxidative phosphorylation to glycolysis. Chronic activation of macrophages by LPS causes an accumulation of intracellular succinate by a glutamine-dependent pathway. Succinate acts as an endogenous danger signal to stabilize hypoxia-inducible factor-1α (HIF-1α), which in turn binds to the -300 position of the IL-1β promoter and specifically promotes IL-1β expression [8]. Besides the regulation of IL-1β expression at the transcriptional level, protein maturation step is also important to produce the functional IL-1β. The maturation of pro-IL-1β into the active form of IL-1β is thought to be executed by canonicalcysteine protease caspase-1. Therefore, the regulation of IL-1β activity is also influenced by the regulation of caspase-1 activity. Caspase-1 could be activated from pro-caspase-1 by NACHT, LRR and PYD domains-containing protein 1(NLRP1) and NLRP3 inflammasomes [9]. ASC is one component of both NLRP1 and NLRP3 inflammasomes.

Autophagy could recognize ubiquitinated ASC and induce selective degradation of inflammasomes and thereby suppress the production of IL-1β [10]. NLRP3 inflammasome can be activated by ROS stimulation. Autophagy can decrease ROS level through the turnover of old and dysfunctional mitochondria. Accumulated old and dysfunctional mitochondria produce an excess of ROS upon stimulation [11]. Besides, it is reported that caspase-11 is also necessary for the activation of caspase-1. Caspase-11 can physically interact with caspase-1 to promote its activation [12]. It has been reported that type I interferon (IFN) could inhibit caspase-1 activity. IFN-β signaling, via the transcription factor STAT1, represses the activity of the NLRP1 and NLRP3 inflammasomes, thus suppressing caspase-1-dependent IL-1β maturation [13]. Moreover, IFN-β could also inhibit IL-1β transcription through STAT1 homodimers and the ISGF3 complex which consists of STAT1, STAT2, and IRF9 [14]. In addition to caspase-1, one additional factor that can mediate IL-1β processing and activation is proapoptotic enzyme caspase-8. Caspase-8 is the major protease that cleaves pro-IL-1β during infection with fungal pathogens. Fungal components activate dectin-1 receptor signaling to induce a noncanonical CARD9–BCL-10–MALT1–ASC–caspase-8 complex. Activated caspase-8 then cleaves pro-IL-1β independent of the inflammasome complex [15]. The mammalian target of rapamycin (mTOR) is a conserved serine–threonine kinase that is essential for the regulation of macrophage inflammatory response.

Actually, mTOR complex consists of two complexes, rapamycin-sensitive mTORC1 and relatively rapamycin-insensitive mTORC2. Tuberous sclerosis 1 (TSC1) and TSC2 are endogenous negative regulators of mTORC1. Over-activation of mTORC1 through TSC1 deficiency could lead to decreased pro-IL-1β expression by inhibiting C/EBPβ expression [4]. However, in the absence of TSC1/2, the activity of RasGTPase is increased, which leads to the activation of ERK [16] and then induces IL-1β transcription. Therefore, in TSC1 KO macrophage, the final IL-1β transcription is decreased as a result of the antagonistic effect of these two pathways. The mTOR is a key component to regulate the autophagy under cellular physiological conditions and environmental stress. The inhibitory function of mTORC1 in autophagy is well studied as mTORC1 activity reflects cellular nutritional status. TSC1 deficient macrophages exhibit the enhanced basal and mycobacterial infection-induced autophagy [17]. In Yang's paper, the activity of caspase-1 is suppressed by over-activated mTORC1, which facilitates the decreased production of active IL-1β [4]. However, the detailed molecular basis of mTOR-mediated regulation of caspase-1 activation is yet unclear. It would be interesting to investigate whether the altered autophagy contributes to the reduced IL-1β expression in TSC1 deficient macrophages.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2020.32.005206

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