Modification and Regulation during IFNβ Expression

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Abstract: IFNβ is encoded by a single-copy gene without introns. It is only expressed when the body needs or is stimulated, and causes a series of response mechanisms. At present, the transcriptional regulation of IFNβ is still a research hotspot, and the expression of IFNβ is regulated by the corresponding transcriptional regulators transmitted and activated by different signaling pathways. With the further exploration in recent years, a large number of new regulatory mechanisms have been discovered, especially the research on the modification of the entire regulatory process, but there is currently a lack of a comprehensive overview of this complex modification network. This review focuses on this, and provides a comprehensive and systematic overview of the modification and regulation of IFNβ expression, and integrates the latest research results so that readers can have a comprehensive understanding of the regulation and modification of IFNβ in this review.
***Keywords*:** IFNβ, transcriptional regulator, signaling pathway, epigenetic modification, transcriptional regulation

1. Introduction

Three types of interferon have been discovered so far, IFN I-III [1, 2], type I interferon (IFN -I) aggregates on human chromosome 9 and mouse chromosome 4, composed of I FNα, IFNβ, IFNε, IFNκ and IFNω composition [3]. IFNβ is a single-copy gene with a single and conserved sequence and no introns. Normally, it is in a suppressed state of no expression or low expression in the body. IFNβ is a highly conserved key player in innate and adaptive antiviral immune responses [4, 5], and is also closely related to the occurrence of various immune diseases and even tumors [6]. In addition, IFNβ also plays a huge role in growth and development, inflammation and immunity, disease and cancer.

The expression of IFNβ often begins with endogenous and exogenous stimuli, such as virus invasion, exogenous or endogenous DNA. When these stimuli are detected by the corresponding receptors, they will pass through various signaling pathways, such as the P PR s-related pathway, the Cgas -STING pathway, the MAVS - RIG pathway, the J AK-STAT pathway, etc., and then the signal is transmitted to the IRFs through the pathway, NF -kB, AP-1 and other transcription factors [7], after a series of modifications, such as phosphorylation, ubiquitination, dimerization, palmitization, etc., they are translocated to the nucleus. Then the transcription factor binds to the relevant sequence on the promoter of IFNβ, leading to the initiation of IFNβ transcription.

Multiple levels of cellular and molecular events regulate IFNβ expression in a coordinated manner, in particular post-translational modification (PTM) of signaling molecules and epigenetic modification of gene expression processes are two important mechanisms, including phosphorylation and polyubiquitination, acetylation, methylation, sumoylation and ISGylation, etc., have been shown to effectively regulate type I IFN signaling by targeting different signaling steps or components.

2. Methylation

Methylation plays an important role in regulating the innate immune response, and is one of the hot topics in the study of IFNβ expression regulation in recent years. At present, DNA methylation, mRNA methylation, and protein methylation have been found in three forms of methylation Directly or indirectly involved in the regulation of IFNβ [8]. DNA methylation is a heritable DNA modification that refers to the addition of a methyl group to 5-cytosine (C) to form 5-methylcytosine under the action of DNA methyltransferases such as DNMT3a and DNMT3b (5mC) [9]. Gao [10] et al. found a CpG single nucleotide methylation, which disrupted the recruitment of IRF3 to the IFNβ promoter and inhibited the binding of IRF3 to PRDIII and PRDI, thereby inhibiting the expression of IFNβ. In addition to inhibition, Wang et al. [11] found that protein arginine methyltransferase (PRMT2) and protein arginine methylation can enhance IFN-β expression through the TLR4/IRF3 signaling pathway. m6A is mainly distributed in the mRNA coding sequence [12, 13], and in response, Rubio [13] et al. determined that the coding sequence and 3' untranslated region (UTR) of IFNβ mRNA were modified by m6A, This is also evidence for a direct regulation of IFNβ. However, the IFNβ regulatory network is so huge that it is obviously

impossible for m 6A modification to only act on it. Indeed, the presence of m6A methylation on viral and cellular RNA during viral infection has profound effects on the outcome of infection, and its impact on cellular RNA and pathways during infection has only recently begun to be elucidated [14]. For example: Chen [15] et al. demonstrated that stimulating signals can activate METTL3 through TBK1, and METTL3-mediated m6A modification ensures antiviral immunity by promoting mRNA stability (such as I RF3) and protein translation [15]. What's more, RNA modification is used as a molecular marker to distinguish self from non-self RNA. McFadden [14] et al. found that m6A modification can regulate the cell's perception of viral RNA. Protein methylation first begins with the methylation of histones, however, it has recently been found that methylation also occurs on non-histone proteins to regulate cell signaling and function. It has been reported that Arg31 of STAT1 protein is replaced by protein arginine methyl Methylation of PRMT1 promotes the translocation of STAT1 into the nucleus and prevents the STAT1 inhibitor PIAS1 from interacting with STAT1, resulting in increased DNA-binding activity of STAT1 [16]. In addition to arginine methylation, there are various types of protein methylation, such as lysine methylation, whether it has an impact on the regulation of IFNβ remains to be further studied.

3. Non-coding RNA regulation (Non-Coding RNAs)

Similar to m6A, the effect of non-coding RNA on IFNβ spreads throughout the entire regulatory network, playing the basic role of inducer or repressor in almost every step. The currently discovered non-coding RNAs involved in regulation are mainly MicroRNA (miRNA) and LncRNA. microRNA (miRNA) is a small non-coding RNA of approximately 22 nucleotides in length, and the main function of miRNA is to silence RNA by targeting protein-coding transcripts [16]. Transcripts generally longer than 200 base pairs are called long ncRNAs (lncRNAs) [17, 18]. Lnc-MxA is one of the few non-coding RNAs that directly interact with the IFNβ promoter. It forms an RNA-DNA triplex (triplex formed) with the IFNβ promoter, thereby hindering the combination of IRF3 and NF-κB, effectively It inhibits the activation of type I IFN [19]. Indirect regulation is achieved through pathways, such as: L ncRNA SOX2 can inhibit cGAS transcription [20], hsa-miR-146a-5p targets and degrades TRAF6 and destroys RIG-I/MDA5-mediated IFN-I signaling conduction [21]. lncRNA-155 enhances IFN synthesis and signaling pathways [19]. lncRNA-GM and MaIL1 promote the activity of TBK1 [22]. It is also achieved by interacting with transcription factors, such as the IRF family: Malat1 selectively promotes the production of antiviral IFN-I by increasing the nuclear IRF3 protein level [23]. And MALAT1 is further involved in type I IFNs-mediated SLE by up-regulating OAS2, OAS3 and OASL [24]. lncRNA ITPRIP-1 (inositol 1,4,5-triphosphate receptor interacting protein) can increase the expression of MDA5, MA VS and the activation of IRF3, and affect HCV replication [19]. lncLrrc55-AS increases the activity and demethylation of phosphatase methylesterase 1 (PME-1) and mediates the inactivation of protein phosphatase 2A (PP2A) and IRF3. IRF-1 has been shown to have functional interactions with miR-301a, miR-195, miR-19a, miR-18a, miR4295, miR-124 and miR-155. Meanwhile, IRF-2 interacts with miR-1290, miR-664 and miR-221-3p [22, 25]. Another example is the NF -kB family: lncRNA (NKILA) directly blocks IκB phosphorylation, interacts with NF-κB to form a stable ternary complex NF-κB/IκB/NKILA, a pseudogene Lethe, which binds to the NF-κB p65/RelA subunit and blocks DNA binding, thereby reducing inflammation. Lnc-EPA V plays a role by competitively binding to RelA and displacing its transcriptional repressor SFPQ, resulting in increased levels of RelA and its pro-inflammatory targets [19].

4. Phosphorylation and acetylation

Cross-regulation between phosphorylation and acetylation precisely controls IFNβ responses as well as downstream events. The modification of early IFNβ signaling pathway regulation has been mentioned in many places above, and the modification of the positive feedback pathway of IFNβ can be divided into canonical and non-classical two pathways. When IFNβ binds to IFNA R, the body rapidly phosphorylates T YK2 and JAK1 [26, 27], then activated JAK1 phosphorylates STAT1 on Tyrosine 701 (Y701), and STAT2 also has a phosphorylation site Threonine 387 (T387), but the specific mechanism of action is not clear. IKK-associated kinase-IKKε, under IFNβ signaling, can also phosphorylate STAT1 on S708, promoting the DNA-binding activity of STAT1. Thus, it can be seen that the phosphorylation of JAK1, TYK2, STAT1 and STAT2 is a key modification to activate canonical IFNβ expression as well as induce ISG expression. In addition to the canonical pathway, STAT1 is also phosphorylated at Serine 727 (S727) in response to IFNβ expression through the MAPK pathway. Protein acetylation occurs before and after phosphorylation [28]. During viral infection, histone deacetylase 9 (HDAC9) deacetylates TANK-binding kinase 1 (TBK1) to activate TBK1 phosphorylation, thereby Leads to increased induction of type I IFN. IRF9 is also acetylated by CBP on K81, which is required for IRF9 binding to STAT1. The latest study found that Liu [29] et al. proved that ASF1a promoted the production of IFNβ by promoting the acetylation of H3K56 mediated by CBP.

5. Ubiquitination and SUMOylation

Protein ubiquitination is a common form of post -translational modification. It refers to the process in which ubiquitin molecules classify intracellular proteins, select target protein molecules and perform specific modification under the action of a series of special enzymes. Three enzymes: activating enzyme (E1), conjugating enzyme (E2) and ligase (E3), among which E3 ligase determines the specificity of the substrate [30]. In eukaryotes, ubiquitin (Ub) is a ubiquitously distributed highly conserved protein consisting of 76 amino acids, Ub itself has 7 internal lysine residues (K6, K11, K27, K29, K33, K48 and K63), each of which can act as a Ub target to link another Ub. According to the number of connections of U b on the substrate, it can be divided into monoubiquitination and polyubiquitination. If the substrate is Ub itself, polyubiquitin chains will be formed on the substrate. In addition to lysine sites, non-canonical ubiquitination patterns at serine, threonine and cysteine sites were newly discovered [31]. The tripartite motif (TRIM) family is an important ubiquitination-mediating protein comprising at least 80 members in humans, most of which have ubiquitin or SUMO E3 ligase activity conferred by their N-terminal RING domain. TRIMs tend to broadly regulate various biological processes of IFNβ expression in an ubiquitination- or SUMOylation - dependent manner [32]. As mentioned earlier the IKK1/α subunit mediates ubiquitination of p100 for processing into mature p52. Production of IFNβ can be controlled by inducing protein degradation (via K48-linked ubiquitination) or affecting signal transduction (via other types of ubiquitination, such as K63 and K27). SUMO is a ubiquitin-like protein that can covalently bind to lysine residues of target proteins to affect many biological processes in the form of regulating protein-protein interactions, such as protein subcellular localization or stability, RNA transcription, DNA repair, innate immunity or antiviral defense, etc. [33, 34]. Humans were found to encode four SUMO proteins, SUMO1-4, all approximately 10 kD in size [35]. The SUMO precursor needs to be processed to function. The precursor SUMO protein is hydrolyzed by sentrin /SUMO-specific proteases (SENPs) to reveal its C-terminal diglycine motif, and at the same time, the E1 enzyme (SAE1/SAE2) is activated to process the mature form of SUMO. SUMO. Then, the SUMO molecules are transferred to the E2-binding enzyme Ubc9, the only E2 SUMOylase discovered so far. Finally, with the assistance of SUMO E3 ligase, the carboxyl group of the glycine residue at the carboxy-terminal of SUMO forms an isopeptide bond with the ε-amino group of the lysine residue on the target protein. However, SUMOylation is a dynamic and reversible process, S UMOylation can be removed by the SENP family of proteins. Studies have found that there is a consensus sequence ψKxE in the target protein of SUMOylation, where ψ corresponds to a large hydrophobic amino acid, K is a modified lysine residue, x is any amino acid, and E is a glutamic acid residue [33, 35]. SUMO plays a key role in signaling pathways that control type I interferon (IFN) production, such as: Binding of SUMO1 to RIG-I inhibits its K48-linked polyubiquitination and degradation and promotes its interaction with MAVS, thereby Induces activation of the IFNβ promoter. TRIM can target most components of the PRR and Jak-STAT1 pathways, such as cGAS, DDX41, MyD88, TRIF, STING, IRF3/7, NF- kB, etc. [31]

6. ISGylation and other modifications

ISGylation is also a PTM, the ubiquitin-like protein ISG15, stimulated by IFNβ, is initially expressed as a 17 kDa precursor protein, which is processed into a 15 kDa mature protein by protease cleavage, exposing the carboxy-terminal LRLRGG motif [36], this motif can covalently bind to lysine residues of certain substrates. ISGylation has many similarities with SUMOylation, for example: UbcH8 is the only specific E2 ISGase found so far [37], ISGylation ADDIN EN.CITE is also reversible and is removed by the de- ISGase UBP43 (USP18), also involved in Various regulatory activities in signal transduction, protein stability, intracellular trafficking and antiviral defense, ISG15 can also non-covalently bind to proteins and regulate their functions. In addition to ISG modification, there are many newly discovered modifications, such as: glutamylation, deamidation, neddylation, palmitoylation (palmitoylation) and UFMylation) etc. [31]. However, there are relatively few studies at present, and the role of these post-translational modifications (PTMs) in cellular processes such as immune response and inflammation, DNA damage response, autophagy and cell death cannot be ignored, so researchers still need to actively explore.

7. Discussion

Through this review, we can see that the entire modification and regulation process of IFNβ expression from signal generation to signal transmission and final protein production is a very large and complex network. Because of this, IFNβ can participate in and be regulated in a variety of biological processes, and is crucial to life activities. Now many researchers are using the IFNβ regulatory network as the target of agonists or inhibitors in scientific research and related biological processes. Therapeutic targets of diseases [38, 39].

This review has achieved a relatively comprehensive summary of the modification and regulation network of IFNβ in

this limited space by consulting a large number of articles in various aspects. Generally speaking, although the regulation of IFNβ has made a lot of progress, this does not mean that humans have fully grasped the regulation and modification mechanism of IFNβ, but there are many unsolved mysteries that need to be explored, and the existing regulation mechanism will also be There are new discoveries to further refine. However, most of the current research on IFNβ focuses on pre-transcriptional regulation, post-translational modification, and downstream regulation. There are few or no research reports on post-transcriptional modification, translation initiation, and translation initiation. More attention is needed.

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