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Commentary

Significance of Type-I Interferon Signaling Pathway

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DESCRIPTION

In the fight against pathogen invasion, the type-I Interferon (IFN-I) signalling pathway is vital. Exogenous dsRNA and ssRNA may trigger an immune response. This pathway's improper operation causes autoimmune disorders or the effects of microbial invasion. All processes are monitored by intricate feedbacks and regulators, from receptors' distinction of "self" and "non-self" molecules to the fine-tune modulations in downstream cascades. Long Noncoding RNAs (lncRNAs) are playing new roles in signalling control, according to studies published recently. LncRNAs can have complicated and specialised modes of action since they attach to targets through their structure and sequence.

Here, we have an overview of the lncRNAs that affect the RNA-activated IFN-I signalling pathway, sorted by the signalling events. This review should make it clearer how lncRNAs are involved in controlling IFN-I signalling. The Interferon (IFN) signalling system is one of the most crucial internal defence mechanisms used by cells to fend off pathogen invasion. According to their activities and amino acid sequences, IFNs can be divided into three categories. There are three types of Type III IFNs: IFN-1, IFN-2 and IFN-3. Of them, IFN-I and IFN-III are directly antagonistic to invasions and are triggered by "non-self" stimuli like infections. The immune system is modulated by IFN-II.

Further effects of IFN-I signalling activation include global translational inhibition, cell apoptosis, and even cell proliferation halt. Exogenous ssRNA and dsRNA can stimulate IFN-I signalling and have immunogenic effects. It may result from bacterial invasion, viral infection, or occasionally *in vitro* produced RNAs. Melanoma differentiation-associated protein 5 (MDA5), Cytosolic Retinoic Acid-Inducible Gene I (RIG-I), endosomal toll-like receptor 3 (TLR3), TLR7, and TLR8 are examples of host-encoded sensors for non-self RNA (will be discussed in more detail below). Double-stranded RNAs (dsRNAs) that have triphosphates (ppp) or diphosphates (pp) and are 2'-O-unmethylated at the 5' end are recognized by RIG-I. Such a request disqualifies as its ligands endogenous mRNAs, rRNAs, and tRNAs. Long dsRNA with a flawless duplex structure is preferred by MDA5.

The host-Encoded Adenosine Deaminase, RNA-Specific 1 (ADAR1), which is a dsRNA binding protein and performs A-to-I editing on duplex, further edits the defective endogenous duplex structures. Endogenous duplexes lose their structural integrity as a result of such an occurrence, and MDA5 no longer recognizes them. Cytosolic RNAs are typically prevented from interacting with TLRs because they face the interior of the endosome. Studies on type-I interferonopathies showed that when RNA metabolisms are altered as a result of gene abnormalities, even endogenous RNA molecules can be immunogenic. For instance, the absence of editing on endogenous inverted-repeat Alu duplexes, which are then recognized by MDA5 as non-self, results in abnormal IFN-I signalling because of the Loss-of-Function (LOF) mutation (P193A or G1007R) or shortage of ADAR1.

As a result, it was shown that the proper metabolism of cellular nucleic acids was essential for the suppression of IFN-I signalling in non-infectious circumstances. Non-Coding RNAs (ncRNAs) are now being implicated in the regulation of IFN-I signalling, according to a growing body of research. Transcripts with a length of more than 200 Base Pairs (bp), which are known as long ncRNAs (lncRNAs), have recently received attention for their role in controlling IFN-I signalling. In this review, we will concentrate on nucleic acid-mediated IFN-I signalling and provide an update on our knowledge of the lncRNAs that control this pathway.

The cell-encoded Pattern Recognition Receptors (PRRs) activate IFN-I signalling in response to various "non-self" stimuli known as Pathogen-Associated Molecular Patterns (PAMPs) or Damage-Associated Molecular Patterns (DAMPs). Despite having diverse origins, they are equally perceptible when exposed to PRRs. Each PRR has a distinct subcellular location and substrate; the TLR3 senses double-stranded RNAs (dsRNAs) in the endosome, the TLR7 and TLR8 sense single-stranded RNAs (ssRNAs), and the TLR9 attaches to DNA. RIG-I and MDA5 recognize dsRNAs in the cytoplasm, and Cyclic GMP-AMP Synthase (cGAS) binds to DNA. Different PRR-PAMP binding stimulates various downstream adaptor proteins, which then set off comparable cascades for the production of the IFN gene. For instance, cGAS creates cyclic GMP-AMP (cGAMP) to activate STING for a

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downstream cascade of interferon genes. RIG-I and MDA5 both require Mitochondrial Antiviral-Signaling Protein (MAVS) as the adaptor to build protein filament on dsRNAs after identifying their respective dsRNA substrates. Although the other TLRs interact with MyD88 for the activation of IFN signalling, TLR3 recruits TIR-domain-containing adapter-inducing interferon.

Through the recruitment of kinases such as TANK Binding Kinase 1 (TBK1) and NF-B essential modulator/I-B kinases and NF-kappa-B Essential Modulator/IKappaB Kinase (NEMO/IKK) adaptors mediated the phosphorylation of interferon regulatory factor 3 (IRF3) or IRF7. IRF3 or IRF7 that have been phosphorylated then dimerize, move into the nucleus, and function as transcription factors for the synthesis of type-I IFNs like IFN- and IFN-. It also has to work in concert with other proteins including p300, the cyclic AMP response element-binding protein (p300/CBP), and c-jun/ATF-2. IFN-/-Receptor (IFNAR), which is made up of the subunits IFNAR1 and IFNAR2, is where secreted IFNs like IFN- bind. These receptors activate the Janus Kinase upon binding (JAK). Signal Transduction Factors and Transcription Activators (STATs) are phosphorylated in the cytoplasm by these tyrosine kinases, which phosphate one another to activate them. IFN-stimulated gene factor 3 is a trimeric complex made up of STAT1, STAT2, and transcription factor IRF9. (ISGF3). It moves into the nucleus, interacts with genes that include IFN Stimulatory Response Elements (ISREs), and promotes the transcription of IFN-Stimulated Genes (ISGs), including the Tripartite Motif-Containing 5 Alpha Isoenzyme (TRIM5), Oligoadenylate Synthases (OASes), and Mx GTPase family.