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Mini Review

Frontiers of Research on cGAS-STING Signaling Pathway Activation by Mitochondrial DNA

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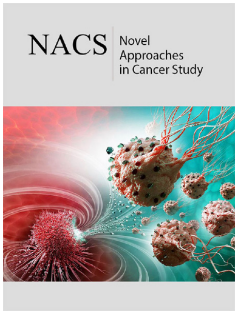

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Abstract

In addition to their role in cellular metabolism, mitochondria regulate a range of biological processes such as cell death and inflammation. Mitochondrial DNA (mitochondrial DNA, mtDNA) is the genome of the mitochondria themselves, and when leaked from stressed mitochondria into the cytosol, is able to activate the cyclized GMP-AMP synthase (cGAS)-stimulator of interferon genes STING innate immune signaling pathway, leading to the production of type I interferons and inflammatory cytokines. These products are capable of not only resisting invasion by pathogenic microorganisms but also leading to the development of inflammatory diseases. In this review, we review the role of mtDNA in the activation of the cGAS-STING innate immune signaling pathway.

Keywords: mtDNA; Innate immune; cGAS-STING signaling pathway

Introduction

As the first line of defense, the innate immune system protects the body from the invasion of pathogenic microorganisms. The host recognizes pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) in cells through pattern recognition receptors (PRRs), and then starts a series of innate immune signal pathways to induce the production of type I interferon, pro-inflammatory chemokines and cytokines. Current research shows that PRRs include NOD-like receptor (NLR), Toll-like receptor (TLR), retinoic acid inducible gene I (RIG-I)-like receptor (RLR) and C-type lectin receptor (CLR) [1]. Immune stimulation products such as protein, RNA and DNA released by damaged tissues or necrotic cells can activate the innate immune signal pathway [2]. In recent years, the cyclized GMP-AMP synthetase (cGAS)-interferon stimulating gene (STING) signal pathway is a newly discovered and hotly studied innate immune signal pathway. The cGAS-STING signaling pathway plays an important role in many pathophysiological processes such as autoimmune diseases, metabolic diseases, tumors and inflammatory diseases [3-5]. About 2 billion years ago, mitochondria were first thought to exist in eukaryotic cells in the form of symbiosis within bacteria [6,7]. Mitochondria not only provide energy for cells, but also play a vital role in regulating cell apoptosis, participating in heme and cholesterol biosynthesis, maintaining calcium homeostasis and producing intracellular reactive oxygen species (ROS). In the past few years, mitochondria have been widely studied in the field of immunology. One of the important reasons is that mitochondria play a direct role in the activation of immune signal pathways. Various mitochondrial matrix contents released from mitochondria, can directly trigger the innate immune response [8]. Among these mitochondrial matrix contents, mtDNA has been widely confirmed as a danger signal, sending an alarm signal to the body and activating the innate immune response program in the target cells. In this review, we focus on the relationship between mtDNA and cGAS-STING innate immune signaling pathway. It is expected to provide new reference materials for the prevention and treatment of related inflammatory diseases by targeting mtDNA.

mtDNA

Mammalian mtDNA is a circular DNA of about 16.5kbp, composed of guanine-rich heavy (H) and light (L) chains mtDNA encodes 37 genes, including 13 genes encoding polypeptides required for electronic transport chain (ETC) [9], 22 tRNAs and 2 rRNAs [10]. In cells with higher energy requirements, such as human skeletal muscle and cardiac muscle cells, the abundance of mtDNA is also higher [11]. Research shows that under the stimulation of various PAMPs such as lipopolysaccharide (LPS), mouse macrophages begin to replicate mtDNA and further produce pro-inflammatory cytokines to trigger inflammation [12]. mtDNA is not naked, but consists of mitochondrial transcription factor A (TFAM), mitochondrial single-stranded DNA binding protein (mtSSB) and DNA polymerase γ. Such auxiliary proteins are packaged into "nuclear like" structure [13]. TFAM also acts as a "protective layer" and agglomerates mtDNA to protect it from oxidative damage of mitochondrial reactive oxygen species (mtROS), thus avoiding being recognized by the innate immune system and activating inflammatory reaction [14]. Compared with nDNA, the DNA repair mechanism of mtDNA is not comprehensive [13]. Mitochondria lack nucleotide-excision repair and other nuclear repair mechanisms [15,16]. Therefore, mutated or damaged mtDNA can be detected by the innate immune sensor in the cell and activate the inflammatory reaction. From the perspective of energy and metabolism, there are multiple copies of wild-type mtDNA in the same cell at the same time to tolerate mtDNA mutations [15,16]. Only when the mtDNA mutations are as high as 80% can clinical pathological changes occur. Excessive mtDNA exists in most tissues, including liver. Therefore, the small or moderate loss of mitochondrial DNA copy has no harmful effect on mitochondrial function. Research shows that the copy number of mtDNA must be lower than 20-40% of the basic level to induce serious mitochondrial dysfunction and adverse events [17]. In this case, the few mtDNA copies remaining in each mitochondrial cannot provide enough MRC polypeptides, resulting in oxidative phosphorylation damage. Compared with nDNA, mtDNA is hypomethylated, and changes in mtDNA methylation are related to cancer, obesity, diabetes and cardiovascular and neurodegenerative diseases [18].

At present, the relationship between mtDNA methylation and demethylation and activation of the innate immune system is still poorly understood, and more research is needed for clarification. In addition to mtDNA, intermediate nucleic acids such as double-stranded RNA and TFAM protein produced during mtDNA transcription can also activate the immune response [19-21].

mtDNA and cGAS-STING signaling pathway

Cyclic GMP-AMP synthase (cGAS) is a cytoplasmic nucleotide synthase capable of recognizing DNA and catalyzing the synthesis of cyclic GMP-AMP (cGAMP) from ATP and GTP. cGAMP acts as a second messenger capable of binding STING and ultimately mediating through phosphorylation of TANK-binding kinase 1 (TBK1) and the transcription factor IFN regulatory factor 3 (IRF3) IFN-stimulated gene (ISG) and type I IFN transcription [22-24]. Not only that, STING can also induce the expression of inflammatory factors such as TNF and IL-1β by phosphorylating IκB and allowing NF-κB to enter the nucleus [25]. In recent years, an increasing number of studies have demonstrated that mtDNA released into the cytoplasm can be recognized by cGAS and thus activate the STING pathway [26,27]. It was shown that during apoptosis, the Bcl-2 family of pro-apoptotic proteins Bax and Bak oligomerize at the outer mitochondrial membrane, inducing mitochondrial outer membrane permeabilization (MOMP), which in turn leads to the release of mtDNA, which can be recognized by the cGAS-STING pathway and subsequently triggers type I IFN production [28]. It was demonstrated that in embryonic fibroblasts (MEF) in a transgenic mouse model, TFAM deficiency promotes mitochondrial stress and mtDNA mispackaging, leading to its ejection into the cytoplasm, where it binds and activates cGAS, triggers the STING signaling pathway, and ultimately mediates ISG and type I IFN expression [26]. Notably, mtDNA-mediated type I IFN can promote antiviral immune responses following DNA virus infection in addition to inducing sterile inflammation [26,29].

Concluding Remarks

Although there is a relatively large body of research on mtDNA-induced activation of the cGAS-STING signaling pathway in the development of pathogenic microbial infections and inflammatory diseases, there are many questions that need to be explored in greater depth. For example, how mtDNA is released from the mitochondria?. Although it has been shown that mtDNA can be released from the mitochondrial outer membrane into the cytoplasm via BAX and BAK, mitochondrial outer membrane permeabilization (MOMP), mitochondrial permeability transition pore (mPTP), or mitochondrial VDAC-mediated pore channels, these mechanisms are still controversial and more experimental data are needed to investigate this issue in depth. In addition to the cGAS-STING signaling pathway, there are also intracellular innate immune signaling pathways such as TLR9 and NLRP3. Which mtDNA recognition pathway is activated by damaged mitochondria under different stressors remains to be further explored, and whether there is crosstalk between the mtDNA-cGAS-STING pathway and other innate immune pathways is still poorly understood. The answers to these questions will help guide the development of targeted drugs.

Author Contributions

Writing original draft preparation, Guangwei Tao; review and editing, Wenyan Liao, Guodong Chen, Chengming Ding, Shuo Qi, Jiafeng Hou, Jun Qiu, Xinmiao Jiang, Xin Deng. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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