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Editorial

The multi-functional roles of the cGAS–STING signaling pathway in health and diseases

The innate immune system provides an important first line of defense against invading pathogens or harmful damages. Over the past decade, our understanding on the recognition of pathogenic nucleic acids by innate immunity has advanced considerably by the discovery of the DNA-sensing receptor cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) synthase (cGAS) and its downstream effector stimulator of interferon genes (STING). The cGAS–STING signaling pathway is activated by various DNA microbes, leading to increased cytokine production and upregulation of type I interferon (IFN) gene expression. Subsequent studies reveal that the cGAS–STING signaling pathway is also activated by host DNAs such as mitochondrial and nuclear DNAs aberrantly localized in the cytosol, which has become an important mechanism triggering chronic inflammatory diseases, e.g. type 2 diabetes, non-alcoholic fatty liver diseases, and kidney diseases. To help researchers better understand the mechanisms regulating cGAS/STING activities and the roles of the cGAS–STING signaling pathway in various immune- and non-immune-related biological events, *Journal of Molecular Cell Biology* is pleased to present a collection entitled 'cGAS–STING signaling in health and diseases' that reviews recent advances in the field.

The discovery of the cGAS–STING pathway: a brief look back

In a search of proteins regulating double-stranded DNA-induced type I IFN response, several laboratories independently identified an endoplasmic reticulum (ER)-localized protein STING. STING does not bind directly to DNA and the ligand to activate cGAS, which remained unknown until 2013, when Dr Zhijian James Chen's group identified cGAMP as an endogenous second messenger that interacts with STING to initiate the type I IFN response (Sun et al., 2013; Wu et al., 2013; Zhang et al., 2013). Dr Chen's team also identified cGAS as the enzyme that catalyzes the synthesis of cGAMP (Sun et al., 2013). These milestone discoveries, which are summarized by Zhong and Shu (2021) and Hong et al. (2022) in this collection, open a new door in the study of innate immune activation and shed light on cGAS–STING signaling-related therapeutic implications.

Regulation of STING and cGAS

Various regulatory mechanisms operating at different levels in the innate immunity are used to control the expression and activities of STING and cGAS. As summarized by Yu et al. (2022) in this collection, STING is activated by binding not only to cGAMP but also to other cyclic dinucleotides from invaded bacteria, which triggers a conformational change and translocation of the protein from the ER to the Golgi apparatus to induce type I IFN response. At the Golgi, the activity of STING is also promoted by other ligands, such as the sulfated glycosaminoglycans, but suppressed by high cGAMP level-induced ER membranous condensation (Yu et al., 2022). Similar to STING, the activity of cGAS is also regulated at multiple levels. cGAS is activated by binding not only to DNA but also to RNA and metal ions such as Mn^{2+} and Zn^{2+} (Yu et al., 2022). The activity of cGAS is also regulated by its distinct cellular localization such as at the plasma membrane (Barnett et al., 2019) or in the nucleus (Bai and Liu, 2022). Other mechanisms regulating cGAS–STING signaling include chromatin tethering, caspase interaction, phosphorylation, and phase separation, which are comprehensively evaluated by several reviews in this collection (Xiong et al., 2021; Zhong and Shu, 2021; Yu et al., 2022).

The multi-functional roles of cGAS–STING beyond immune surveillance

As a critical innate immune DNA sensor, the cGAS–STING signaling pathway plays a critical role in innate immune regulation against infection by pathogens including SARS-CoV-2

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(Yang et al., 2020), malignancies, and autoimmune disorders (Xiong et al., 2021). While early studies on cGAS mainly focused on its classical function in innate immunity, recent studies reveal that this molecule also plays a broader role in the regulation of many non-innate immune-relevant biological events such as cellular senescence, cell stemness, apoptosis, inhibition of angiogenesis, cell proliferation, DNA replication, and damage repair process (Hong, et al., 2022; Li and Bakhoum, 2022; Liu et al., 2022). cGAS is not only highly expressed in immune-relevant tissues/organs but also in many non-immune-related tissues such as the brain, pancreas, prostate, bladder, kidney, liver, and adipose tissue. In addition, dysregulation of the cGAS–STING pathway in adipocytes, hepatocytes, and renal proximal tubule epithelial cells are associated with metabolic dysfunction, impaired energy homeostasis, and kidney diseases (Bai and Liu, 2019, 2021, 2022), as well as tumorigenesis (Hong et al., 2022; Li and Bakhoum, 2022). These findings strongly suggest that the cGAS–STING signaling pathway has functions beyond DNA sensing in innate immunity. Understanding the tissue/cell-specific roles of the cGAS–STING pathway may shed new light on the mechanistic link between immunity and other biological systems. This can also promote the development of precision therapeutic interventions for various sterile inflammatory diseases, such as metabolic disorders, neurodegenerative diseases, autoimmune diseases, and cardiovascular diseases (Hong et al., 2022).

In summary, extensive progress has been made on our understanding of the multifaced roles of the cGAS–STING signaling pathway in both immune and non-immune activities. Indeed, several antagonists or inhibitors have been developed and showed promise for the treatment of cGAS–STING signaling-related inflammatory diseases (Hong et al., 2022). However, while targeting this pathway holds therapeutic potential, a deeper mechanistic understanding of the pleiotropic functions of cGAS and STING would be critical for developing new solutions to unanswered basic research questions and unsolved clinical needs in the era of precision medicine.

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