Constitutively Active cGAS for Enhanced Immune Response

This technology involves the design of constitutively active cyclic GMP-AMP synthase (cGAS) mutants that stimulate a robust immune response without the need for DNA binding.

What is the Problem?

The innate immune system relies on pattern recognition receptors like cGAS to detect intracellular pathogens, DNA damage, and tumorigenesis. However, the activation of cGAS typically requires binding to double-stranded DNA (dsDNA), which can limit its effectiveness in certain therapeutic applications. The cGAS-stimulator of interferon genes (STING) pathway regulates the innate and adaptive immune responses and elicits type I interferon immunity against viral infections. As a result, it is a promising therapeutic target for cancers and infectious diseases. Current small-molecule STING agonists, which aim to activate the cGAS-STING pathway, often suffer from low efficacy or adverse reactions.

What is the Solution?

Researchers have developed constitutively active cGAS (CA-cGAS) mutants that do not require dsDNA binding to activate. These mutants were created using a combination of two-state computational design and informatics-guided design. The CA-cGAS mutants exhibit interferon-stimulating activity comparable to dsDNA-stimulated wild-type cGAS. X-ray crystallography confirmed the DNA-independent adoption of the active conformation. Additionally, in vivo studies demonstrated that expressing CA-cGAS in tumor cells led to STING-dependent tumor regression, highlighting its therapeutic potential.

What is the Competitive Advantage?

DNA-Independent Activation: CA-cGAS mutants do not require dsDNA for activation, making them more versatile in various therapeutic contexts.

Enhanced Immune Response: These mutants stimulate a robust interferon response, which is crucial for effective immune activation.

Therapeutic Potential: In vivo studies show that CA-cGAS can induce tumor regression, indicating its potential as a cancer therapy.

Genetically Encoded: As a biologic, CA-cGAS can be engineered for specific activity, localization, and regulation, offering advantages over small-molecule drugs.

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