CLINICAL IMPLICATIONS OF BASIC RESEARCH

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How DNA Sensing Drives Inflammation

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The 2024 Albert Lasker Award for Basic Medical Research is awarded to Zhijian (James) Chen for his landmark discoveries that explain how DNA stimulates immune responses.

DNA is best known as genetic material, but befitting its central role in biology, DNA can also be a potent stimulator of inflammation. Our cells detect foreign DNA as a means to initiate immune responses to DNA viruses. These immune responses involve the production and secretion of type I interferons, which are proteins that orchestrate antiviral immunity. Responses to DNA are now known to play central roles in many diseases, including autoimmune diseases and cancer. Chen's key contribution was to identify a DNA-activated enzyme called cyclic GMP–AMP synthase (cGAS), which binds DNA and initiates inflammation.[1,2]

As with all great discoveries, the discovery of cGAS was built on a foundation of previous work. Efforts that began in the late 1990s established that a transmembrane receptor for DNA called toll-like receptor 9 (TLR9) acts in cells to initiate inflammatory responses after binding to engulfed DNA derived from extracellular sources. It soon became apparent, however, that TLR9 did not fully account for the ability of the immune system to respond to DNA. Indeed, two important studies published in 2006 from the laboratories of Ruslan Medzhitov[3] and Shizuo Akira[4] showed that cytosolic or intracellular DNA can also elicit interferon responses independent of TLR9. What followed was a confusing 7-year race to find the "cytosolic" DNA sensor. At least a half dozen such sensors were proclaimed in the pages of prominent journals, only to be subsequently debunked.

Although not apparent at the time, a key advance turned out to be the discovery of a potent interferon-inducing protein that we now call STING (stimulator of interferon genes). This protein was discovered by several groups, and each group gave it a different name and ascribed to it distinct functions. Genetic evidence that STING was essential for the interferon response to intracellular DNA was eventually provided by Glen Barber and colleagues,[5] but the identity of the DNA sensor acting upstream of STING and the biochemical mechanism of STING activation remained mysterious.

In parallel, bacteriologists were studying how mammalian cells respond to bacterial signaling molecules called cyclic dinucleotides. Like RNA and DNA, cyclic dinucleotides are composed of nucleotide building blocks joined by phosphodiester bonds. Unlike RNA and DNA, which are long linear polymers, cyclic dinucleotides consist of only two nucleotides, which are linked in a tight loop. Cyclic dinucleotides were first discovered in bacteria, in which they play diverse roles as second messengers that regulate bacterial physiology. These bacterial molecules were shown by several groups to elicit interferon responses in mammalian cells. Then, in my laboratory in 2011, Dara Burdette discovered that cyclic dinucleotides stimulate the synthesis of interferons by acting as agonists that bind directly to STING.[6] Although this finding was ultimately important in understanding the cGAS signaling pathway, its relevance at the time was murky at best.

The fog finally lifted in late 2012, when — in two monumental back-to-back papers[1,2] — Chen's group reported the discovery of cGAS and its unique enzymatic product. These papers showed that cGAS is an enzyme that is activated upon binding to DNA. Once activated, cGAS combines GTP and ATP to form a cyclic dinucleotide called cyclic GMP–AMP (cGAMP) (Fig. 1). Unlike bacterial cyclic dinucleotides, cGAMP produced by cGAS is formed by an unusual combination of one con-

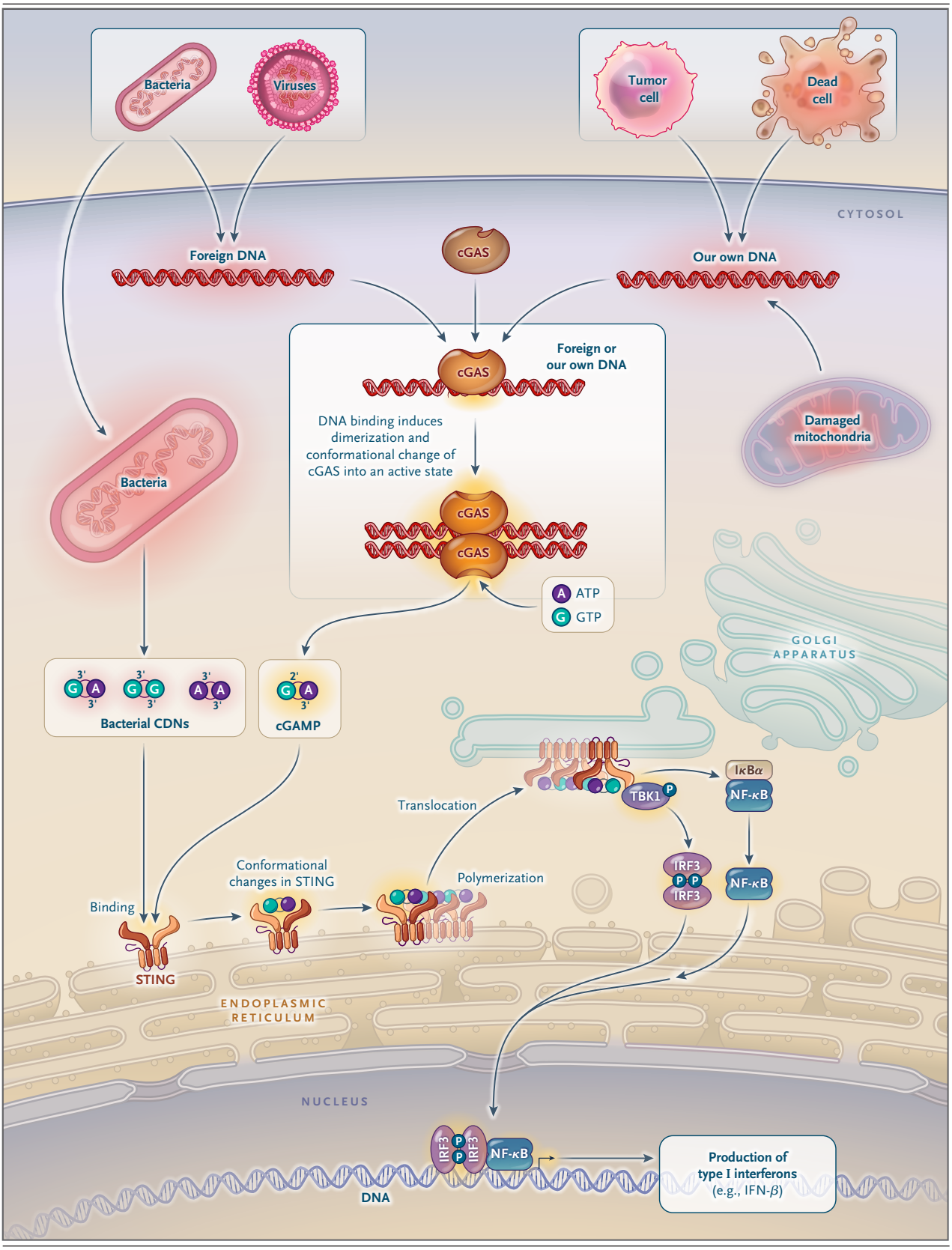

Figure 1 (facing page). The cGAS–STING DNA Sensing Pathway.

The cyclic GMP–AMP synthase (cGAS) enzyme binds to viral DNA, tumor DNA, or our own aberrant DNA. DNA binding activates cGAS to synthesize cyclic GMP–AMP (cGAMP) from ATP and GTP nucleotides. Bacteria also produce cyclic dinucleotides (CDNs). Bacterial cyclic dinucleotides and cGAMP bind to STING, a protein of the endoplasmic reticulum, which results in activation of a signaling pathway that stimulates the production of type I interferons. IRF3 denotes interferon regulatory factor 3, IκBα nuclear factor of κ light polypeptide gene enhancer in B cells inhibitor alpha, NF-κB nuclear factor κB, and TBK1 TANK binding kinase 1.

ventional 3′ to 5′ phosphodiester bond, similar to the bonds found in DNA and RNA, and one unusual 2′ to 5′ phosphodiester bond. Nevertheless, Chen showed that cGAMP binds to STING in a manner similar to that of bacterial cyclic dinucleotides to elicit interferon responses, thereby linking DNA sensing by cGAS to STING signaling and interferon induction.

Chen's 2012 papers were quickly followed by a tsunami of papers from many laboratories that showed that cGAS is important for defense against viruses and other infectious agents. A fascinating but still not fully resolved question is how cGAS is able to respond to pathogen DNA without being activated by the abundant DNA naturally present in our cells. One hypothesis is that pathogen DNA is detected in compartments such as the cytosol, whereas our own DNA is relegated safely to the nucleus. Regardless, it is clear that our own DNA can aberrantly activate cGAS in many biologic contexts, and thus the role of cGAS extends beyond infections. Rare genetic diseases, such as Aicardi–Goutières syndrome, are now understood to arise from a pathological accumulation of DNA that induces a cGAS-dependent disorder. Loss of DNA integrity and cGAS activation also occur in tumor cells and can elicit antitumor immunity. Even autoimmune conditions and aging may involve cGAS-induced inflammation. Thus, cGAS has emerged as a central player in both protective and harmful immune responses. Numerous pharmaceutical companies are now targeting cGAS–STING, generating inhibitors to block autoimmunity and agonists to promote antitumor immunity.

Chen's work has illuminated how our cells detect foreign or aberrant DNA to protect our own DNA. One particularly surprising aspect of the story has been recent work showing that cGAS-like and STING-like proteins are also present in bacteria, where they function to provide a defense against the viruses that infect bacteria.[7] Thus, cGAS–STING is an ancient feature of our biology, dating back more than a billion years. We are fortunate to have lived in the brief few years when the work of Chen has led the field to understand how it all works.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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