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COMMENTARY

Repositioning Ku70 unlocks cGAS−STING immunity in colorectal cancer

KEY WORDS

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The cyclic GMP−AMP synthase (cGAS)−stimulator of interferon genes (STING) pathway provides a central link between genomic instability and antitumor immunity. Cytosolic double-stranded DNA activates cGAS to generate 2′,3′-cyclic GMP−AMP (cGAMP), which engages STING and initiates TBK1−IRF3 signaling, type I interferon production, and immune-cell recruitment. Translating this pathway into effective cancer immunotherapies, however, has proved challenging: tumor cells can limit the generation or cytosolic exposure of immunostimulatory DNA, retain cGAS in an inactive state, or attenuate downstream signaling[1-3].

In this issue, Huang et al.[4] identify a pharmacologically actionable mechanism that couples DNA repair failure to innate immune activation in colorectal cancer. Through limited proteolysis−small-molecule mapping, cellular thermal shift assays, molecular docking, and microscale thermophoresis, the authors nominate Ku70 as a direct target of Bruceine A (BA), a natural compound derived from *Brucea javanica*. BA promotes the nuclear-to-cytoplasmic redistribution of Ku70 together with cGAS, compromises non-homologous end joining, increases damaged and mislocalized DNA, and amplifies STING-dependent antitumor immunity. The study therefore places protein localization—not simply protein abundance—at the center of a therapeutically exploitable DNA damage−immunity circuit.

Ku70, encoded by XRCC6, is best known as the DNA end-binding component of the DNA-dependent protein kinase complex. Together with Ku80 and DNA−PKcs, Ku70 recognizes DNA double-strand breaks and initiates non-homologous end joining[5]. Yet Ku70 is not confined to genome maintenance. Cytoplasmic Ku70 can sense microbial or aberrantly localized DNA and induce interferon responses, while the DNA−PK−Ku70−Ku80 complex can activate IRF3 through a cGAS-independent route[6,7]. Against this background, the conceptual advance of Huang et al.[4] is not the designation of Ku70 as a previously unknown DNA sensor. Rather, it is the demonstration that pharmacologically redirecting Ku70 between cellular compartments can simultaneously weaken nuclear DNA repair and enhance cGAS-dependent immune sensing.

This spatial model is particularly relevant because cGAS activity is tightly governed by subcellular context. Although cGAS is present in the nucleus, its interaction with nucleosomes restrains productive activation, whereas damaged DNA, micronuclei, and cytosolic DNA can provide accessible ligands[8-10]. Notably, cGAS contains a functional nuclear export signal, and disruption of its nuclear export impairs interferon responses to cytosolic DNA. Moreover, the nuclear cGAS−Ku80 complex has recently been shown to regulate the balance between canonical and alternative NHEJ[11,12], suggesting that BA-induced redistribution of cGAS and Ku70 may influence not only immune sensing but also DNA-repair pathway choice. Huang et al.[4] show that BA enhances the Ku70−cGAS interaction and promotes their accumulation outside the nucleus. Ku70 depletion attenuates BA-induced cGAS redistribution and downstream signaling, and purified Ku70 and cGAS interact directly. These observations support a model in which Ku70 acts as a molecular escort or scaffold that links the release of cGAS from a chromatin-restrained state to its encounter with immunostimulatory DNA.

The resulting feed-forward mechanism is the most compelling aspect of the work. Loss of nuclear Ku70 activity suppresses non-homologous end joining and increases γH2AX and cytosolic or extracellular dsDNA. Concurrently, cytoplasmic Ku70 associates

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with cGAS and promotes its oligomerization and activation. Thus, BA appears to increase both sides of the sensing equation—the abundance of accessible DNA ligands and the competence of the sensor—converting Ku70 from a predominantly genome-protective factor into a mediator of immunogenic DNA damage. This dual action provides a mechanistic rationale for the enhanced responses to oxaliplatin, irradiation, and anti-PD-1 therapy observed in the MC38 model.

The findings also suggest a potentially useful alternative to conventional STING agonism. Direct STING agonists can be constrained by limited tumor delivery, systemic inflammatory toxicity, species-specific pharmacology, and heterogeneous pathway competence across tumors. Consistent with these challenges, an early-phase clinical study of the intratumoral STING agonist MIW815 demonstrated systemic immune activation but limited single-agent antitumor activity[13]. Rewiring an endogenous DNA damage−sensing module could, in principle, generate immunostimulatory DNA within the tumor while lowering the threshold for its recognition. Consistent with this idea, BA lost most of its antitumor activity in Sting1-deficient or CD8-deficient hosts, whereas combination treatment increased intratumoral $CD8^+$ T-cell infiltration and effector activity. These results connect the tumor-cell stress response to host adaptive immunity rather than attributing tumor control solely to direct cytotoxicity.

Important questions nevertheless remain. First, although Ku70 depletion and STING loss establish essential nodes in the proposed pathway, direct genetic evidence that cGAS itself is indispensable for BA-induced signaling and tumor control would further distinguish this mechanism from cGAS-independent DNA−PK signaling. Second, the molecular basis of Ku70−cGAS nuclear export remains unresolved: whether BA exposes an export determinant, disrupts nuclear retention, recruits a transport factor, or alters post-translational modification of either protein is unknown. Third, tumor-cell-intrinsic and host-cell STING may make distinct contributions that will require compartment-specific genetic models. Finally, because Ku70 is essential for genome maintenance and BA may engage additional proteins, pharmacokinetics, target selectivity, normal-tissue genotoxicity, and the consequences of sustained treatment will be central to defining a therapeutic window. Validation in orthotopic, genetically engineered, and patient-derived colorectal cancer models will also be important.

Overall, Huang et al.[4] reveal Ku70 localization as a druggable interface between DNA repair and innate immunity. Their work broadens the therapeutic logic of cGAS−STING activation from administering an exogenous agonist to spatially reprogramming endogenous DNA-sensing machinery. If its selectivity and safety can be established, this strategy may offer a way to convert otherwise repair-proficient, immune-refractory tumors into lesions that generate-and respond to-their own immunostimulatory DNA.

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