Something Old and Something New to Unleash the Power of Natural Killer Cells against Metastases

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Single-agent immunotherapy has improved outcomes for patients with cancer, but only a minority of patients respond, necessitating investigation of combinations of immunotherapy agents. In this issue of *Cancer Immunology Research*, Milling and colleagues show that neoadjuvant therapy with an intratumoral stimulator of interferon genes agonist combined with systemic IL2 and anti–PD-1 results in clearance of lung metastases mediated by natural killer cells in mouse models of triple-negative breast cancer.

See related article by Milling et al., p. 26 (4).

IL2, a cytokine discovered more than 40 years ago for its ability to sustain the activation and proliferation of T and natural killer (NK) cells, was the first immunotherapy approved by the FDA for patients with cancer (1). This preceded the approval of immune checkpoint inhibitors by two decades. Although clinical use of IL2 has remained limited, engineered derivatives with improved therapeutic index are being pursued for specific indications. One such derivative is an albumin–IL2 fusion (Alb–IL2) with extended half-life (2).

Stimulator of interferon genes (STING) agonists are a new class of immunotherapy agents under investigation for their ability to induce type I IFN (IFN-I) leading to antigen-presenting cell activation and development of antitumor T-cell responses. STING is activated by cyclic dinucleotides (CDN) produced by GMP–AMP synthase (CGAS), the sensor for DNA displaced to the cytosol due to viral infection, genomic instability, or DNA-damaging therapies such as radiation. So far, early clinical testing of STING agonists has not fulfilled expectations, with modest activity as single agents and in combination with anti–PD-1, suggesting the need for new combinations that optimally leverage STING activity (3).

Milling and colleagues test a triple combination of an old immunotherapy, IL2, given as Alb–IL2, a new immunotherapy, a STING agonist, and anti–PD-1 (hereafter referred to as CIP) in the 4T1 and EO771 preclinical models of metastatic triple-negative breast cancer (TNBC; ref. 4). Similar to the results of clinical trials, they found that intratumoral delivery of a STING agonist is minimally effective by itself, and the addition of systemic anti–PD-1 did not improve the response. However, long-term survival is achieved in 60% of mice treated with the neoadjuvant CIP triple combination. The long-term survival is due to clearance of lung metastases, and all three therapies are required for best results. Importantly, the CIP triple combination is effective only when given before but not after resection of the primary tumor, and long-term survival is lost if the primary tumor is not excised.

The authors chose the CIP triple combination rationally to leverage both innate and adaptive immunity. Analysis of immune cells in the treated tumor and in the lungs confirms this expectation. Surprisingly, although tumor-specific T cells are expanded and activated by CIP, they are dispensable for the clearance of lung metastases and long-term survival of the animals. It is NK cells that are the chief effectors responsible for metastases clearance. Mechanistically, NK cells are expanded and activated in the lungs, expressing the effector cytotoxic molecules granzyme B and perforin, as well as IFNγ and TNFα. This strong effector phenotype of NK cells is driven by IFN-I acting in synergy with IL2. The primary tumor receiving the STING agonist is the main source of IFN-I, but the latter is also elevated in the circulation and produced by lung-resident dendritic cells.

Overall, the work of Milling and colleagues highlights the importance of testing rational combinations of immunotherapy agents and investigating the mechanisms of response or resistance, as there are surprises. The combination of STING agonists and IL2 used in the neoadjuvant setting of TNBC or other early cancers with high risk for metastasis holds promise but awaits clinical testing. Interestingly, the activated NK cells also express PD-1, possibly explaining the added benefits of anti–PD-1, but more work is needed to dissect the role of NK cells in response to anti–PD-1 in patients.

Author's Disclosures

S. Demaria reports grants and personal fees from Lytix Biopharma and personal fees from AstraZeneca, EMD Serono, Ono Pharmaceuticals, and Genentech outside the submitted work.

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Cancer Immunol Res 2022;10:3

doi: 10.1158/2326-6066.CIR-21-0948

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