ESTABLISHMENT OF A NOVEL PRECLINICAL MODEL FOR EVALUATING IMMUNE CHECKPOINT BLOCKADE-INDUCED ANTITUMOR IMMUNOLOGICAL MEMORY IN LUNG CANCER

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Background Immune checkpoint blockade (ICB) has been shown to elicit long-term, durable responses in patients with metastatic or unresectable lung cancer. Similar to immunity against pathogens, memory-like antitumor T cell response may be pivotal in these patients. Nonetheless, due to the absence of suitable clinic-to-bench preclinical animal models, the mechanisms behind the generation of beneficial T cells following ICB in lung cancer remain largely unexplored.

Methods Subclones were obtained from a syngeneic murine lung cancer cell line. Alongside confirming their genomic oncogenicity through whole exome sequencing, MHC class I and class II neoantigens within the subclones were computationally identified. The subclones were subsequently tested in vivo for their sensitivity to ICB, including anti-PD-1 monotherapy and a combination of anti-PD-1 and anti-CTLA-4, both of which are the standard of care for lung cancer. Additionally, we assessed the role of memory-like antitumor T cell response in wild-type and Batf3 knockout (KO) mice that had previously rejected the lung tumor cells post-ICB treatment.

Results Three subclones, huL1, huL2, and huL3, were established. These retained oncogenic driver mutations, such as Kras, Nras, and Trp53, present in the parental cells, and also shared immunogenic MHC class I and class II neoantigens. Wild-type mice were subcutaneously challenged with 1x10⁶ tumor cells, followed by ICB treatment on days 3, 6, and 9. Upon anti-PD-1 monotherapy, tumor rejection rates in mice bearing huL1, huL2, and huL3 were 30%, 0%, and 50%, respectively. Treatment with a combination of anti-PD-1 and anti-CTLA-4 improved rejection rates to 20% for huL1, 36% for huL2, and 100% for huL3. Following a minimum interval of three weeks after the rejection of huL3 tumors, mice were re-challenged with 5x10⁶ huL3 tumor cells on the opposite flank. Despite remaining untreated, these mice spontaneously rejected the secondary-challenged tumor cells. The same approach was replicated with Batf3 KO mice, which also rejected huL3 tumor cells when treated with the ICB combination, albeit at a rate of 50%. Interestingly, these tumor-free Batf3 KO mice could not spontaneously reject re-challenged huL3 tumor cells, unlike their wild-type counterparts.

Conclusions We have developed a novel preclinical lung cancer model that assesses antitumor immunological memory through tumor rejection. Our research findings suggest that Batf3 is crucial for the development of memory-like antitumor T cells following ICB.

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