

REPURPOSING NSAIDS FOR CANCER IMMUNOTHERAPY: MECHANISMS BEYOND COX INHIBITION

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Background Adoptive cell therapy (ACT) using genetically modified T cells has evolved into a promising treatment option for patients with cancer. However, even for the best-studied and clinically validated CD19-targeted chimeric antigen receptor (CAR) T-cell therapy, many patients face the challenge of lack of response or disease relapse. There is increasing need to improve the efficacy of ACT so that durable, curative outcomes can be achieved in a broad patient population.

Methods Here we investigated the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on the efficacy of ACT in multiple preclinical models. Mice with established B-cell lymphoma received various combinations of preconditioning chemotherapy, infusion of suboptimal dose of tumor-reactive T cells, and administration of either indomethacin (indo, a COX-inhibitory NSAID) or ADT-030 (a non-COX-inhibitory novel NSAID). Donor T cells used in the ACT models included CD4+ T cells expressing a tumor-specific T cell receptor (TCR) and T cells engineered to express CD19CAR. Mice were monitored for tumor growth and survival. The effects of indo on donor T cell phenotype and function were evaluated. The molecular mechanisms by which the selected NSAID shapes the outcome of ACT were investigated.

Results ACT coupled with indo administration led to improved tumor growth control and prolonged mouse survival. Indo did not affect the activation status and tumor infiltration of the donor T cells. Moreover, the beneficial effect of indo in ACT did not rely on its inhibitory effect on the immunosuppressive COX2/PGE2 axis. Instead, indo-induced oxidative stress boosted the expression of death receptor 5 (DR5) in tumor cells, rendering them susceptible to donor T cells expressing TNF-related apoptosis-inducing ligand (TRAIL). Furthermore, the ACT-potentiating effect of indo was diminished against DR5-deficient tumors, but was amplified by donor T cells engineered to overexpress TRAIL.

Conclusions Our results demonstrate that the pro-oxidative property of NSAIDs can be exploited to enhance death receptor signaling in cancer cells, providing rationale for combining NSAIDs with genetically modified T cells to intensify tumor cell killing through the TRAIL-DR5 axis.

Ethics Approval All animal experiments and procedures were performed in accordance with the institutional protocol and were approved by the Institutional Animal Care and Use Committee (IACUC) of Augusta University.

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