

Anti-Cancer Therapy: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in Combination with Immunotherapy

Abstract

Advances in cellular and molecular immunology have provided enormous insights into the nature and consequences of interactions between tumors and immune cells. This knowledge continues to lead to strategies that marshal the immune system to treat established malignancies. The most heralded class of immunoncology drugs are the immune checkpoint inhibitors, which work by blocking the molecules that switch off immune cells, thus increasing tumor immunogenicity. While monoclonal antibodies, cytokines, and vaccines have shown promise individually, it is likely that the best strategy to combat cancer will be to utilize a combinatorial approach. Varying combination strategies demonstrate benefit in different patient populations. One such strategy that has received little attention is the use of non-steroidal anti-inflammatory drugs (NSAIDs), in combination with immunotherapy. This editorial briefly discusses the potential for such a strategy.

Editorial

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Joseph Murphy*

Charles River Laboratories, USA

***Corresponding author:** Joseph Murphy, Charles River Laboratories, Discovery Research Services 251 Ballardvale Street, Wilmington, MA 01887, USA, Tel: 9784301729; Email: joseph.murphy@crl.com

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Editorial

Over the past three decades, a deeper understanding of the mechanisms underlying the generation of tumor immunity has provided a framework for developing more potent immunotherapies [1]. One major insight is that combinatorial approaches addressing the multiplicity of defects in the host response are likely to be required for clinical efficacy. Until recently, several immunosuppressive factors, including immune regulatory pathways/cells and tumor derived factors, have been identified that impede an effective antitumor immunotherapeutic responses [2]. Strategies to break these immunosuppressive mechanisms responsible for tumor immune escape is a key goal for an effective anticancer immunotherapy. One such strategy involves using anti-inflammatory drugs (NSAIDs). The main therapeutic target of NSAIDs is the enzyme cyclooxygenase (COX), the rate limiting enzyme in the formation of prostaglandins from arachidonic acid, which is released from cell membrane stores in response to a range of stimuli. There are two isoforms of COX: COX-1 is implicated in homeostasis while COX-2 is implicated in several physiological responses including angiogenesis and metastasis [3]. COX-2 is over expressed in most solid tumors, and selective COX-2 inhibitors can inhibit cell proliferation, tumor invasiveness, and angiogenesis, while simultaneously overcoming apoptosis and drug resistance as well as suppressing immune responses [4].

The impact of NSAIDs, particularly COX-2 inhibitors, on reducing cancer and cancer risk, in addition to improving survival rate in several types of cancer, is well established [5]. This impact is observed either alone or in combination with other therapies. Although the underlying mechanisms of these chemo-preventive effects have not yet been fully elucidated, some studies have shown that specific COX-2 inhibitors can increase the infiltration of CD4⁺ and CD8⁺ T cells to tumor sites, thus positively regulating the tumor specific host immune response. Moreover, by inhibiting

prostaglandin E2 (PGE₂), a key immuno-suppressor, they can also modulate the activity of T-regulatory cells, tumor-associated macrophages, and myeloid-derived suppressor cells [2].

In spite of the positive results obtained with COX inhibitors alone, very few studies address the potential for NSAIDs in combination with cancer immunotherapy. One recent study reported that administering aspirin in combination with immunotherapy could enhance the efficacy of treatment [6]. Researchers reported that skin, colorectal and breast cancer can produce large amounts of PGE₂, resulting in a diminution of the immune system's ability to attack aberrant cells and allowing cancers to hide from immuno-surveillance. Pre-clinical data demonstrate that inhibiting COX synergizes with anti-PD-1 blockade in inducing eradication of tumors. This implies that COX inhibitors could be useful adjuvants for immune-based therapies in cancer.

Although relatively few studies to date have addressed the utility of using checkpoint inhibitor therapy in conjunction with NSAIDs, preliminary data suggests that this modality warrants further investigation. As combination strategies are rapidly emerging as a new paradigm for cancer therapy, utilizing COX-2 inhibition thus offers a nontoxic, readily available approach that can potentially be used in conjunction with a wide variety of other immunotherapeutic approaches.

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