THE COX-2 PATHWAY AS A MEDIATOR OF RESISTANCE TO ANTI-PD-1 THERAPY

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Background We previously found upregulation of the cyclooxygenase-2/prostaglandin E2 (COX-2/PGE2) pathway in the tumor microenvironment (TME) of cancers that respond poorly to anti-PD-1 therapy.1–2 The potential functional role of this pathway in anti-PD-1 resistance is unknown. We therefore studied modulation of COX-2 expression in cultured human tumor and immune cells, PGE2-mediated effects on myeloid cells and their reversal with prostaglandin (EP) receptor inhibitors.

Methods Nineteen tumor lines representing 6 histologies were treated with cytokines reported to induce COX-2 (IL-1β, IL-17A, TNF-α). Peripheral blood monocytes (Monos) were treated with toll-like receptor (TLR) agonists or TME-resident cytokines associated with high PD-L1 expression (IL-1A, IL-10, IL-27, IL-32g, IFN-γ).3–4 COX-2 protein was detected by Western blotting and flow cytometry. In some experiments, Monos were pre-incubated with EP2i (PF-04418948) and/or EP4i (ONO-AE3-208), then treated with PGE2 ± TLR4 (LPS) or TLR7 (imiquimod) agonists. IL-6, IL-10, TNF-α, and VEGF secretion were detected by ELISA. Monocytic DCs generated with GM-CSF+IL-4 were matured with CD40L, ± PGE2, then phenotyped.

Results Among 19 tumor cell lines, 6 expressed COX-2 constitutively, and 13 were induced to express COX-2 by 1-day exposure to IL-1B, IL-17A, TNF-a. Peripheral blood monocytes (Monos) were treated with toll-like receptor (TLR) agonists or TME-resident cytokines associated with high PD-L1 expression (IL-1A, IL-10, IL-27, IL-32g, IFN-γ).3–4 COX-2 protein was detected by Western blotting and flow cytometry. In some experiments, Monos were pre-incubated with EP2i (PF-04418948) and/or EP4i (ONO-AE3-208), then treated with PGE2 ± TLR4 (LPS) or TLR7 (imiquimod) agonists. IL-6, IL-10, TNF-α, and VEGF secretion were detected by ELISA. Monocytic DCs generated with GM-CSF+IL-4 were matured with CD40L, ± PGE2, then phenotyped.

Conclusions Understanding and preventing anti-PD-1 treatment resistance is a critical goal. Our results suggest that the COX-2/PGE2 pathway is expressed in tumor and immune cells, and modulates myeloid cell functions in a context-dependent manner. COX-2 expression is non-redundant with PD-L1 expression, providing a rationale to test COX-2 pathway inhibition in conjunction with anti-PD-1. Available drugs targeting this pathway, including IL-1R and IL-1B inhibitors, NSAIDs, and EP2 and EP4 inhibitors, will enable the clinical development of combination treatment regimens.

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