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Suppression of Chemotherapy-induced Cytokine/Eicosanoid Storm and Ovarian Tumor Growth by a Dual COX-2/sEH Inhibitor

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While chemotherapy remains a mainstay in cancer treatment, growing evidence indicates that it may stimulate tumor growth. Other cancer therapies including radiation, immunotherapy, and stem cell transplantation may also trigger the release of pro-inflammatory and pro-tumorigenic cytokines in the tumor stroma. We recently demonstrated that although cancer therapy reduces tumor burden by killing tumor cells, the resulting dead cells, or 'debris', can promote tumor growth by stimulating the release of cytokines. Chemotherapy fails to generate remission in over 70% of patients with ovarian cancer, is rarely curative, and simultaneously creates tumor cell debris. Thus, cancer therapy is inherently a double-edged sword and targeting a single cytokine or pathway may not prevent therapy-induced cancer. Soluble epoxide hydrolase (sEH) inhibitors have been shown to stimulate the resolution of inflammation by promoting the synthesis of pro-resolving mediators and counter-regulating pro-inflammatory cytokines. In this study, tumor cell debris was prepared *in vitro* by treating either murine or human ovarian tumor cells with first-line platinum or taxane-based cytotoxic chemotherapies used for treating ovarian cancer (e.g. cisplatin, carboplatin, or paclitaxel). Chemotherapy-generated tumor cell debris stimulated ovarian tumor growth in both immunocompetent and immunocompromised hosts. Debris triggered macrophage production of a series of pro-inflammatory and pro-angiogenic cytokines. Further, LC-MS-MS–based oxylipin profiling of tumor cell debris generated by chemotherapy revealed a pathological release of tumor-promoting bioactive lipids ('eicosanoid storm') including cyclooxygenase (COX)-derived prostaglandins, lipoxygenase-derived HETEs, CYP450-derived DiHOMEs and EpOMEs. We hypothesize that dual COX-2/sEH inhibition may be a novel modality in suppressing ovarian tumor growth by stimulating the natural debris-clearing process. A dual COX-2/sEH inhibitor, PTUPB, suppressed debris-induced cytokines (e.g. TNFα, CCL2, CCL4, CXCL2, G-CSF, ICAM-1, MMP-9, and PAI-1) and eicosanoids (e.g. PGF_{2a}, PGD_2, and PGJ_2). PTUPB also delayed the onset of debris-stimulated tumor growth in an ovarian cancer (ID8) model, achieving sustained survival over 80 days post-injection. It is imperative to overcome the predicament between killing tumor cells and the inherent tumor-promoting activity of the debris. Thus, dual inhibition of COX-2/sEH may be a novel approach in cancer therapy to suppress the therapy-induced cytokine/eicosanoid storm and debris-stimulated tumor growth.

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