PORTFOLIO SAMPLE

How This Document Came to Be

About this sample. A principal investigator at a university medical school came to us with a tight, deadline-bound commission: to produce a pre-manuscript survey of the literature and current thinking on their assigned review topic — Prostaglandins and Leukotrienes in Immuno-Oncology. Unlike an open-ended discovery question, this was a defined-scope synthesis problem. The field is large, fast-moving, and spread across decades of murine mechanism studies and a more recent — and often discordant — body of human trial data. The client needed it mapped, sourced, and structured quickly, without sacrificing rigour.

This topic is hard to review due to its internal tensions: the same lipid mediator can be immunosuppressive in one cell type and protective in another, and promising preclinical targets have repeatedly underdelivered in the clinic. Capturing those contradictions faithfully, rather than smoothing them over, was central to the brief.

We began by discussing the client's goals and assessing the available tools and public resources, including our own. We also considered systems developed by other teams. When another tool is better suited to a particular task, we recommend it.

In this case, our research-writing and data-mining system was a good fit. Working with the client, we turned the initial idea into a focused research brief and developed the prompt reproduced below. The system generated a "writing kit," which our specialists then checked and revised in consultation with the client. We verified the bibliographic references and performed an internal review tracing the quantitative and mechanistic claims to their cited sources.

The brief we developed with the client

> "Create a comprehensive and deep academic review on the following topic: 'Prostaglandins and Leukotrienes in Immuno-Oncology: Mechanisms and Measures in Murine Models and Human Trials.' Cover the arachidonic acid–COX/LOX network in the tumour microenvironment, including PGE_2 amplification and the pro-resolving mediators that oppose it. Detail receptor-level mechanisms — EP2/EP4, DP1/DP2, IP, BLT1/BLT2, and the cysteinyl leukotriene receptors — and how each reshapes myeloid, T cell, and NK cell function. Distinguish clearly between findings established in murine models and those tested in human trials, giving due weight to negative and contradictory results. Address therapeutic strategies (selective receptor antagonists, dual COX-2/5-LO blockade, and checkpoint-inhibitor combinations) and the measurement and biomarker approaches — including LC–MS/MS eicosanoid quantification and spatial immune mapping — used to assess pathway activity. Close with the open questions and translational gaps that should guide future work."

> **A note on deliverables.** This PDF document itself is a small part of our full research output. The client deliverables include PRISMA-compliant literature search strategies, PubMed retrievals, writing blocks the client may use for reconstruction and revision while catering to different reporting formats, a reference database compatible with major bibliographic software, Python code for data extraction and analysis, and more.

> Our team has verified the bibliographic references and checked the quantitative claims against their cited sources. This document is a literature synthesis intended to support manuscript development; it is not itself a peer-reviewed publication, and nothing in it constitutes medical advice.

Prostaglandins and Leukotrienes in Immuno-Oncology: Mechanisms and Measures in Murine Models and Human Trials

1. Introduction

1.1 Arachidonic Acid–COX/5-LO Network in Tumors

(See Figure 1: Arachidonic acid cascade in tumors: PGE_2 amplification vs pro-resolving brakes)

Chronic inflammation is a hallmark of the tumor microenvironment (TME), and the arachidonic acid (AA) cascade via cyclooxygenases (COX) and lipoxygenases (LOX) is a central driver of this process in cancer (Greene et al., 2011). AA is liberated from membrane phospholipids by phospholipase A_2 (PLA_2); in particular, the cytosolic $PLA_2\alpha$ isoform (PLA2G4A) is frequently activated by oncogenic MAPK signaling and inflammatory cytokines in tumor cells, leading to bursts of AA release (Dennis et al., 2011). This abundant AA fuels downstream COX-2 and 5-LOX pathways to generate eicosanoids that sustain chronic, smoldering inflammation within tumors (Greene et al., 2011).

COX-2–derived prostaglandin E_2 (PGE_2) is ubiquitous in many cancers and has pleiotropic pro-tumor effects, acting on immune cells to skew responses toward tolerance and suppression (Zelenay et al., 2015). Mechanistically, PGE_2 signals mainly through the G_s-coupled prostaglandin E (EP) receptors—especially EP2 and EP4—on immune cells, elevating intracellular cAMP and activating PKA–CREB pathways (Kalinski, 2012; Wang & DuBois, 2016). As discussed in Sections 2.1 and 2.2, these receptors are central to myeloid-mediated immunosuppression and the direct inhibition of T cell effector functions, driving the induction of immunoregulatory factors such as IL-10, arginase-1, and PD-L1 (Cuenca-Escalona et al., 2024; Prima et al., 2017).

1.2 Specialized Pro-resolving Mediators and Degradation Evasion

In parallel to these pro-inflammatory eicosanoids, LOX pathways can also generate specialized pro-resolving mediators (SPMs) that provide a natural brake on inflammation. Lipoxins and resolvins engage receptors such as ALX/FPR2 and ChemR23 to actively promote the resolution of inflammation (Chiang & Serhan, 2020). In cancer, lipoxin A_4 acting on ALX/FPR2 dampens the production of TNF-α and IL-6 and inhibits autocrine TGF-β_1 signaling, alleviating immunosuppressive pressure (Bai et al., 2015). Similarly, resolvins limit neutrophil recruitment and induce macrophages to adopt phenotypes geared toward debris clearance rather than immunosuppression, reducing tumor-promoting inflammation and metastasis (Sulciner et al., 2018).

Many tumors further amplify PGE_2 levels by evading its degradation. Under physiological conditions, PGE_2 is inactivated by 15-hydroxyprostaglandin dehydrogenase (15-PGDH), which oxidizes it to the less active 15-keto-PGE_2 (Lu et al., 2014). This enzyme is frequently downregulated in colorectal, lung, and pancreatic cancers, correlating with poorer patient outcomes (Myung et al., 2006; Pham et al., 2010); epigenetic silencing (including promoter methylation/HDAC–Snail repression) is one described mechanism. Additionally, cancers commonly suppress the transporter SLCO2A1 (PGT), which imports PGE_2 for catabolism (Nomura et al., 2017). The combined effect of 15-PGDH loss and PGT downregulation

reinforces a feed-forward loop of pathological PGE_2 accumulation and immune evasion (Wang & DuBois, 2016; Figure 1).

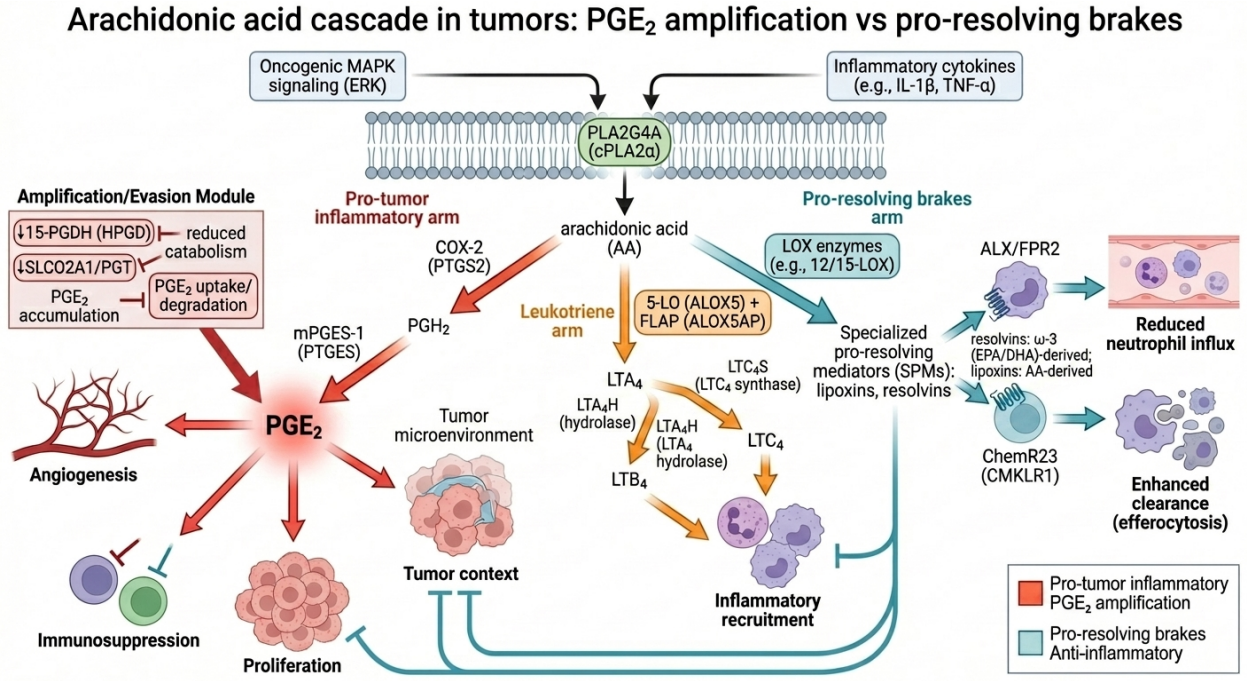

Figure 1. The arachidonic acid (AA) cascade in tumors, contrasting pro-tumor PGE_2 amplification (red/orange) with pro-resolving brakes (teal). Oncogenic MAPK/ERK signaling and inflammatory cytokines (e.g., IL-1β, TNF-α) activate cytosolic phospholipase $A_2α$ (PLA2G4A/cPLA2α), releasing AA from membrane phospholipids. In the pro-tumor arm, COX-2 (PTGS2) converts AA to PGH_2 and mPGES-1 (PTGES) generates PGE_2, which promotes angiogenesis, immunosuppression, and proliferation; tumors amplify PGE_2 by reducing its catabolism (↓ 15-PGDH/HPGD and ↓ SLCO2A1/PGT), producing feed-forward accumulation. In the leukotriene arm, 5-LO (ALOX5) with FLAP (ALOX5AP) converts AA to LTA_4, metabolized to LTB_4 (LTA_4 hydrolase) and, via LTC_4 synthase, to LTC_4, recruiting inflammatory cells. In the pro-resolving arm, 12/15-LOX generate AA-derived lipoxins, while resolvins derive from ω-3 (EPA/DHA) substrates; these SPMs act via ALX/FPR2 and ChemR23 (CMKLR1) to limit neutrophil influx and enhance efferocytosis. Solid arrows = enzymatic conversion; blunt lines = inhibition. (Refs: Dennis 2011; Greene 2011; Wang & DuBois 2016; Nomura 2017; Chiang & Serhan 2020; Sulciner 2018.)

2. Prostaglandin-Mediated Immunomodulation in the Tumor Microenvironment

2.1 COX-2/PGE_2 Axis Promotes MDSC and M2 TAM Accumulation and Regulatory T Cell Induction

(See Figure 2: COX-2/PGE_2 reshapes the tumor immune ecosystem: MDSCs, M2 TAMs, Tregs, and dysfunctional DCs)

The COX-2/PGE_2 axis strongly expands immunosuppressive myeloid populations in the TME, notably myeloid-derived suppressor cells (MDSCs). Tumor-derived PGE_2 can drive the differentiation of bone marrow myeloid precursors toward MDSCs at the expense of functional dendritic cells (Sinha et al., 2007). PGE_2/EP-receptor agonism drives differentiation of $CD11b^+Gr1^+$ MDSCs from bone-marrow precursors, and EP2-receptor–deficient (*Ptger2*−/−) hosts show reduced MDSC accumulation and slower tumor progression (Sinha et al., 2007). While MDSCs express all four EP receptors, EP2 signaling appears to be a

dominant driver of their expansion and suppressive activity in vivo (Sinha et al., 2007). PGE_2-conditioned MDSCs upregulate enzymes that impair T-cell function, including arginase-1, inducible nitric oxide synthase (NOS2), and indoleamine 2,3-dioxygenase (IDO1) (Obermajer et al., 2011). Notably, PGE_2 can induce COX-2 expression within MDSCs themselves, creating a positive feedback loop that sustains local PGE_2 production (Obermajer et al., 2011).

PGE_2 likewise skews macrophages toward an anti-inflammatory, pro-tumoral phenotype. In response to PGE_2, macrophages adopt an M2-like tumor-associated macrophage (TAM) phenotype characterized by high IL-10 production (MacKenzie et al., 2013). A pivotal receptor in this process is EP4: interference with EP4 signaling has been shown to shift TAM polarization toward the pro-inflammatory M1 state and enhance anti-tumor T cell activity (Na et al., 2013). In murine models of colon and lung cancer, genetic or pharmacologic EP4 blockade reduced the abundance of $IL\text{-}10^+$, $arginase\text{-}1^+$ M2 TAMs and concurrently increased intratumoral $CD8^+$ T cell infiltration (Chang et al., 2015; Chen et al., 2014; Zhao et al., 2024). Conversely, tumor-derived PGE_2 can directly reprogram infiltrating monocytes; for example, glioblastoma stem cells secrete PGE_2 that converts macrophages into an IL-10–secreting M2 phenotype supportive of tumor growth (Yin et al., 2020). The spatial distribution of these suppressive populations relative to eicosanoid gradients is further explored in Section 5.4.

An associated consequence of PGE_2-driven inflammation is the enrichment of $FoxP3^+$ regulatory T cells (Tregs). COX-2/PGE_2 activity promotes Treg differentiation and accumulation; in mouse lung cancer models, elevated PGE_2 levels correlate with increased $CD4^+CD25^+FoxP3^+$ Treg numbers, while COX-2 inhibition reduces their frequency (Sharma et al., 2005). Mechanistically, PGE_2 cooperates with transforming growth factor-β (TGF-β) to drive the de novo induction of Tregs from naive $CD4^+$ T cells. In human non-small cell lung cancer cultures, TGF-β stimulation induces COX-2–dependent PGE_2 production, and neutralization of PGE_2 impairs the generation and suppressive function of these Tregs (Baratelli et al., 2010). These pro-Treg effects are mediated chiefly through EP2 and EP4 receptors on T cells, where PGE_2-driven upregulation of FOXP3 is significantly blunted by EP4 blockade and abolished in the absence of EP2 (Sharma et al., 2005).

In addition to mobilizing suppressive cells, PGE_2 sabotages the priming of anti-tumor T cells by directly impairing dendritic cell (DC) maturation. Sustained PGE_2 exposure via EP2/EP4 on developing DCs inhibits the upregulation of MHC class II and co-stimulatory molecules while enhancing IL-10 and IDO1 production, resulting in diminished antigen-presenting capacity (Sharma et al., 2003; Wang & Dubois, 2018). PGE_2 also disrupts DC migratory behavior through a biological paradox: while it can induce the surface expression of the lymph node–homing receptor CCR7, it simultaneously suppresses the DC-mediated production of CCR7 ligands (such as CCL19) required to recruit and organize naive T cells (Muthuswamy et al., 2010). This results in "partially matured" DCs that may express homing receptors yet fail to effectively migrate or attract T cells, leading to poor priming of tumor-specific $CD8^+$ T cells (Chheda et al., 2016; Muthuswamy et al., 2010; Figure 2).

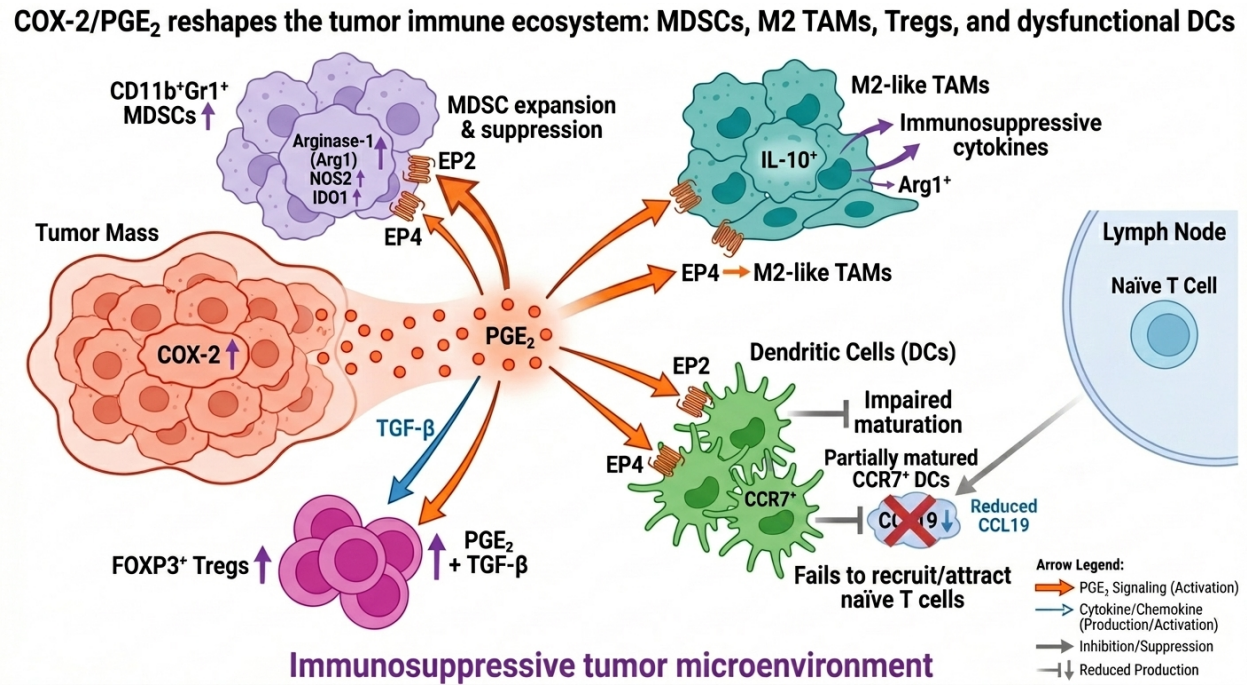

Figure 2. COX-2/PGE₂ remodeling of the tumor immune microenvironment. Tumor cells overexpressing COX-2 secrete PGE₂, signaling via EP2/EP4. PGE₂ expands CD11b⁺Gr1⁺ MDSCs upregulating Arg1, NOS2, and IDO1 (EP2 a dominant driver; Sinha 2007; Obermajer 2011); EP4 skews macrophages to an IL-10⁺Arg1⁺ M2-like TAM phenotype (MacKenzie 2013; Chang 2015). PGE₂ cooperating with TGF-β promotes FOXP3⁺ Treg induction (Baratelli 2010; Sharma 2005). PGE₂ impairs DC maturation and, although it can induce surface CCR7, suppresses DC CCL19 production, yielding "partially matured" CCR7⁺ DCs that fail to recruit/prime naive T cells (Muthuswamy 2010). Arrow legend: orange = PGE₂ signaling/activation; blue = cytokine/chemokine production; gray blunt = inhibition; gray ⊣ = reduced production. Net effect: an immunosuppressive tumor microenvironment.

2.2 EP2/EP4 Receptor Signaling Suppresses T Cell and NK Cell Effector Functions

(See Figure 3: PGE₂ as a metabolic checkpoint: EP2/EP4 signaling disables CD8 T cells and NK cells and promotes exhaustion)

The impairment of the priming phase is compounded by the direct inhibition of effector lymphocytes. Beyond its role in skewing myeloid differentiation, PGE₂ acts as a potent checkpoint for T cell and natural killer (NK) cell activity within the TME. Building on the cAMP–PKA signaling framework, PGE₂ effectively inhibits interleukin-2 (IL-2) synthesis—a critical autocrine growth factor for T cells—thereby curtailing clonal expansion and effector differentiation of anti-tumor T cells (Morotti et al., 2024). Mechanistically, the loss of IL-2 signaling deprives T cells of key metabolic cues: PGE₂ exposure dampens IL-2R–STAT5–mTORC1 signaling and inhibits mitochondrial oxidative metabolism in CD8⁺ T cells, resulting in insufficient metabolic reprogramming for sustained anti-tumor immunity (Lacher et al., 2024; Morotti et al., 2024). Consistently, single-cell transcriptomic analyses of human tumors have found that high EP4 receptor expression (*PTGER4*) in tumor-infiltrating T cells correlates with downregulation of IL-2–STAT5 target genes and reduced expression of nuclear-encoded oxidative phosphorylation genes, underscoring the link between PGE₂–EP4 activity and suppressed T cell metabolism in vivo (Punyawatthananukool et al., 2024).

In parallel to shared cAMP/PKA-mediated effects, EP4 receptor engagement can initiate a β-arrestin–dependent signaling cascade. Unlike EP2, EP4 can recruit β-arrestin adaptors and engage PI3K–AKT signaling in addition to Gs–cAMP signaling (Take et al., 2020); whether this β-arrestin arm directly drives inhibitory-receptor upregulation in tumor CD8⁺ T cells remains to be established. Chronic exposure to PGE_2 in the tumor milieu is associated with an exhausted CD8⁺ tumor-infiltrating lymphocyte phenotype; in microsatellite-stable colorectal cancer, tumor-associated macrophage–derived PGE_2 drives emergence of PD-1⁺ TIGIT⁺ exhausted CD8⁺ T cells and resistance to anti–PD-L1 therapy (Fumet et al., 2026). Notably, tumor-associated macrophages in microsatellite-stable colorectal cancer were recently shown to produce abundant PGE_2 that drives CD8⁺ T cell exhaustion and resistance to anti–PD-L1 therapy, directly linking elevated PGE_2 signaling to anti–PD-L1 resistance in microsatellite-stable colorectal cancer models and patient datasets (Fumet et al., 2026).

NK cells are likewise direct targets of PGE_2-mediated immunosuppression. NK cells express both EP2 and EP4 receptors, and PGE_2 signaling in these cells elevates cAMP levels, mirroring the suppressive effects observed in T cells (Martinet et al., 2010). The result is a profound reduction in NK cell cytolytic activity and cytokine secretion. For example, PGE_2-treated NK cells show markedly diminished release of interferon-γ (IFN-γ), an effect predominantly mediated through EP2/EP4 engagement (Holt et al., 2012). In addition to blunting effector functions, tumor-derived PGE_2 can directly impede NK cell persistence by suppressing proliferation and inducing apoptosis (Li et al., 2015). These deficits can be reversed by blocking PGE_2 receptors; pharmacologic antagonism or genetic ablation of EP4 restores NK cell IFN-γ production and cytotoxicity, leading to enhanced clearance of metastatic tumor cells in preclinical studies (Holt et al., 2012; Kundu et al., 2009; Figure 3).

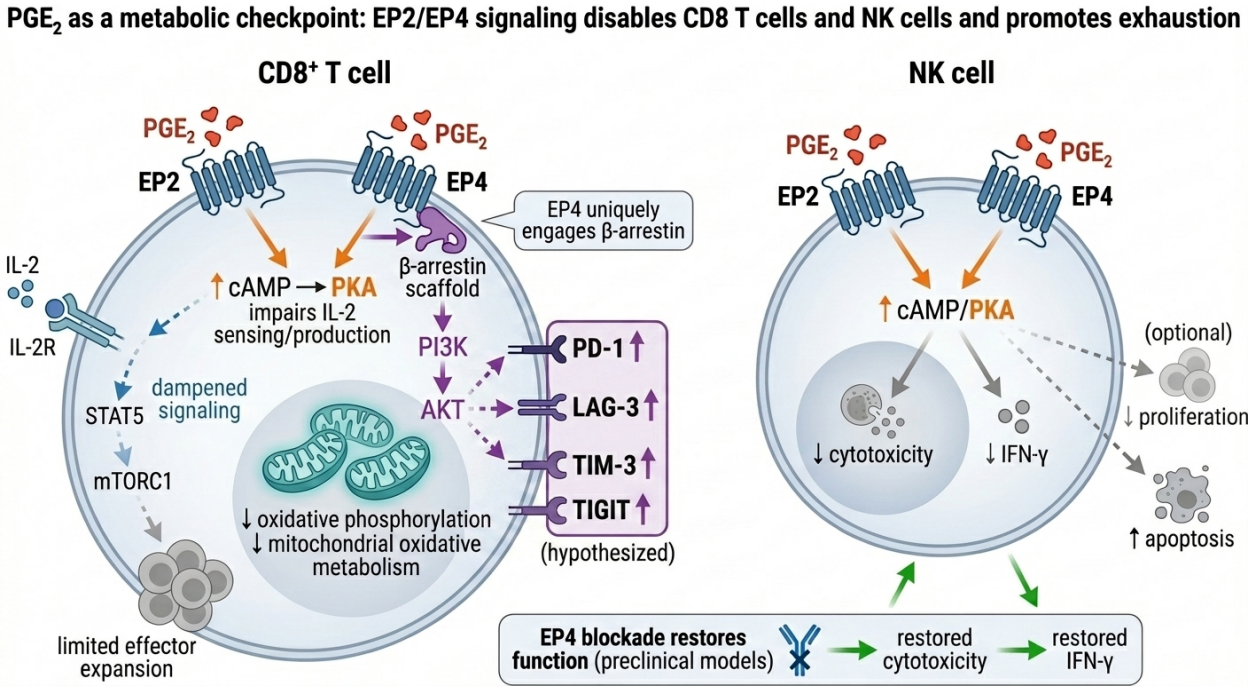

Figure 3. PGE_2 as a metabolic checkpoint on cytotoxic lymphocytes. In CD8⁺ T cells, PGE_2 engages EP2/EP4, raising cAMP and activating PKA; this impairs IL-2 sensing/production and dampens IL-2R–STAT5–mTORC1 signaling, reducing oxidative phosphorylation and limiting effector expansion (Morotti 2024; Lacher 2024; Punyawatthananukool 2024). EP4 additionally engages β-arrestin–PI3K–AKT signaling (Take 2020); a proposed (not yet established) consequence is upregulation of inhibitory

receptors (PD-1, LAG-3, TIM-3, TIGIT) associated with exhaustion (shown as hypothesized). In NK cells, PGE_2–EP2/EP4–cAMP/PKA reduces cytotoxicity and IFN-γ and can decrease proliferation and increase apoptosis (Martinet 2010; Holt 2012; Li 2015); EP4 blockade restores NK cytotoxicity and IFN-γ in preclinical models (Holt 2012; Kundu 2009). Orange = cAMP/PKA; purple = β-arrestin/PI3K–AKT (hypothesized exhaustion link); green = restoration by EP4 blockade.

2.3 Divergent Roles of Other Prostaglandins (PGD_2 and Prostacyclin) in Tumor Immunity

Aside from the broadly immunosuppressive PGE_2 axis, other prostaglandins such as PGD_2 and prostacyclin (PGI_2) exert complex and sometimes contrasting effects on tumor immunity. PGD_2 is produced in the TME by various cells, including TAMs, mast cells, and cancer cells, and mediates its effects through two receptors: DP1 and DP2 (also known as CRTH2). These receptors engage different signaling pathways: DP1 is a G_s-coupled receptor that elevates intracellular cAMP, whereas DP2 is G_i-coupled and triggers distinct downstream signals, such as calcium mobilization and chemotaxis (Wu et al., 2020; Sen et al., 2022).

Activation of the DP1 receptor on macrophages can attenuate certain immunosuppressive mechanisms. In interferon-γ–stimulated macrophage models, PGD_2 signaling through DP1 represses the induction of IDO1 (Bassal et al., 2016). By curbing IDO1 production—an enzyme previously noted for its role in MDSC-mediated T cell depletion (Obermajer et al., 2011)—DP1 activation may relieve a key immune brake, representing a non-canonical pro-immune role for a prostaglandin within the tumor milieu (Bassal et al., 2016). In contrast, engagement of the DP2/CRTH2 receptor by PGD_2 can orchestrate a pro-tumorigenic immune response by mobilizing type 2 immunity. DP2 is highly expressed on Th2-skewed $CD4^+$ T cells and group 2 innate lymphoid cells (ILC2s). In acute myeloid leukemia and breast cancer models, PGD_2–DP2 signaling drives the expansion of ILC2s, which in turn promotes the accumulation of Tregs and MDSCs and polarizes macrophages toward an M2-like phenotype (Wu et al., 2020; Zhao et al., 2021). Thus, PGD_2 emerges as a double-edged sword: through DP1 it can mitigate immunosuppression, but through DP2 it can reinforce it.

Prostacyclin (PGI_2) shows yet another facet of prostanoid influence, often aligning with enhanced immunosurveillance. PGI_2 signals primarily via the IP receptor, a G_s-coupled receptor that triggers cAMP/PKA signaling. In immunocompetent murine lung cancer models, elevating intratumoral prostacyclin via synthase overexpression significantly improved anti-tumor immune activity and increased the infiltration of $CD4^+$ T lymphocytes (Li et al., 2018). Mechanistically, PGI_2-rich tumors showed upregulated expression of the T cell–attracting chemokine CXCL9. This effect was contingent on tumor immunogenicity, as MHC II–negative tumors derived little benefit (Li et al., 2018).

3. Leukotriene-Mediated Immunomodulation in the Tumor Microenvironment

3.1 LTB_4–BLT1 Signaling: Neutrophil-Driven Tumor Progression vs T Cell–Mediated Tumor Control

(See Figure 4: Therapeutic trade-offs and crosstalk: LTB_4 duality and arachidonic acid shunting motivate dual COX-2/5-LO blockade)

Parallel to the prostaglandin branch, the 5-LO–leukotriene pathway provides another strategy for tumor subversion, though its influence is notably context-dependent. Leukotriene B_4 (LTB_4) in the tumor microenvironment exerts dual influences on cancer immunity, largely

dictated by which leukocyte population it engages and through which receptor (BLT1 or BLT2) (Jang et al., 2021).

On one hand, LTB_4 is a potent neutrophil chemoattractant (primarily via BLT1) that can fuel tumor progression. Neutrophils are well-equipped to synthesize LTB_4—they express 5-LO, 5-LO–activating protein (FLAP), and leukotriene A_4 hydrolase—but notably lack leukotriene C_4 synthase, thus funneling arachidonic acid metabolism predominantly into LTB_4 rather than cysteinyl leukotrienes (Tian et al., 2020; Peters-Golden & Henderson, 2007). The resulting high local levels of LTB_4 create an autocrine and paracrine loop that recruits additional neutrophils and amplifies inflammation (Cho et al., 2013; Subramanian et al., 2017). In pre-metastatic niches, inflammatory cues including LTB_4 attract neutrophils, which are then skewed by tumor-derived factors such as TGF-β toward a pro-tumor “N2” phenotype (Fridlender et al., 2009). These N2 neutrophils secrete pro-angiogenic and matrix-remodeling factors—vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), and neutrophil elastase—that promote tumor cell extravasation and seeding at distant sites (Fridlender et al., 2009; Coffelt et al., 2015). In breast cancer models, LTB_4-driven neutrophil recruitment to future metastatic sites creates a permissive niche for circulating tumor cells, markedly increasing metastatic burden (Wculek & Malanchi, 2015). Neutrophils in the pre-metastatic lung produce LTB_4 which selectively expands highly tumorigenic cancer cell subpopulations; genetic or pharmacologic ablation of neutrophil 5-LO significantly reduces metastatic colonization (Wculek & Malanchi, 2015).

Conversely, LTB_4 signaling can bolster protective anti-tumor immunity by recruiting and activating T lymphocyte subsets. Effector $CD8^+$ T cells and certain γδ T cells express BLT1 receptors, which guide their chemotaxis toward LTB_4 gradients (de Souza Costa et al., 2010; Sharma et al., 2013). Preclinical studies have demonstrated that BLT1 expression on $CD8^+$ T cells is required for efficient tumor infiltration and cytotoxic function: mice lacking BLT1 show significantly reduced intratumoral $CD8^+$ T cell and NK cell accumulation and fail to control tumor growth effectively (Sharma et al., 2013; Chheda et al., 2016). In immunogenic tumor settings, LTB_4 gradients help concentrate these cytotoxic cells within tumor tissue to promote clearance. Indeed, in lung cancer models, deletion of 5-LO in the host microenvironment led to impaired $CD8^+$ T cell recruitment accompanied by accelerated tumor progression, underscoring the importance of LTB_4 in sustaining anti-tumor T cell immunity (Poczobutt et al., 2016). This duality explains the clinical challenges observed with BLT1 antagonists (Bhatt et al., 2017), as detailed in Section 5.3.

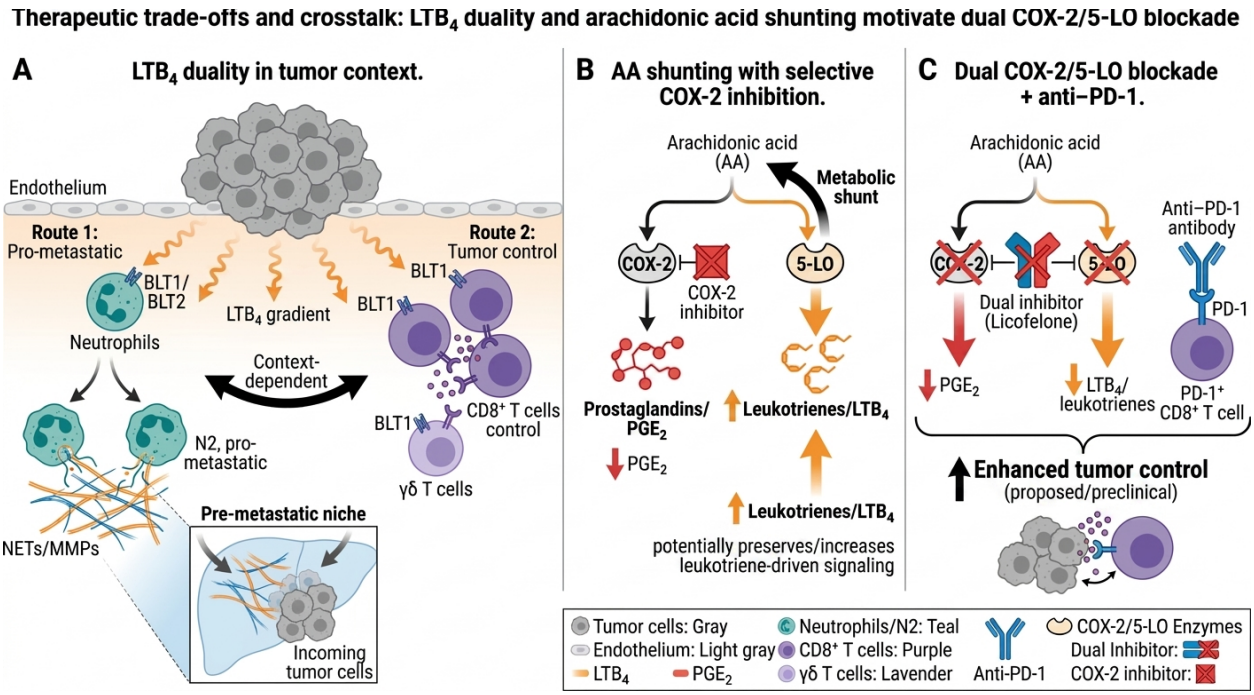

Figure 4. Therapeutic trade-offs and crosstalk in tumor eicosanoid metabolism. (A) LTB_4 duality: LTB_4–BLT1 (and BLT2) recruit neutrophils that, skewed by TGF-β toward a pro-tumor "N2" phenotype, release NETs and MMPs to build pre-metastatic niches (Fridlender 2009; Wculek & Malanchi 2015; Coffelt 2015); the same LTB_4–BLT1 axis recruits cytotoxic $CD8^+$ and γδ T cells mediating tumor control (de Souza Costa 2010; Sharma RK 2013; Chheda 2016) — a context-dependent balance. (B) Arachidonic-acid shunting: selective COX-2 inhibition lowers PGE_2 but redirects AA toward 5-LO, increasing leukotriene/LTB_4 output that can sustain immunosuppressive signaling (Park 2012; Ye 2005). (C) Dual COX-2/5-LO blockade (e.g., licofelone) lowers both PGE_2 and LTB_4/leukotrienes; combination with anti–PD-1 is a proposed/preclinical strategy hypothesized to enhance $CD8^+$ T-cell–mediated tumor control (Mohammed 2011; Pu 2021). Solid arrows = conversion/signaling; blunt ends = inhibition; the synergy bracket in (C) denotes a hypothesized, not yet clinically established, benefit.

3.2 Cysteinyl Leukotrienes Drive Th2 Immunity and M2 Macrophage Polarization

While the LTB_4–BLT1 axis often supports anti-tumor immunity, the cysteinyl leukotriene branch (LTC_4, LTD_4, and LTE_4) is increasingly recognized for driving a shift toward type 2 (Th2-skewed) immunity and immune evasion. These mediators originate from the 5-LOX pathway: various immune cells in tumors, including mast cells, eosinophils, and certain TAMs, express the requisite enzymes (5-LOX and LTC_4 synthase) to convert the intermediate LTA_4 into LTC_4, which is subsequently metabolized to LTD_4 and LTE_4 in situ (Peters-Golden & Henderson, 2007; Tian et al., 2020). Cysteinyl LTs signal through specific G-protein–coupled receptors—primarily $CysLT_1$ and $CysLT_2$—expressed on diverse leukocytes and stromal cells. A third receptor, GPR99/OXGR1, has also been identified with selectivity for LTE_4, potentially amplifying LTE_4-mediated inflammation (Kanaoka et al., 2013).

The accumulation of cysteinyl LTs in tumors has clear parallels to allergic inflammation (Laidlaw & Boyce, 2015). In Th2-polarized T cells, exposure to LTD_4 or LTE_4 triggers excessive release of hallmark Th2 cytokines, notably IL-13 (Xue et al., 2012). This suggests that CysLTs can activate Th2-skewed T cells or group 2 innate lymphoid cells (ILC2s) in the tumor milieu to secrete IL-4, IL-5, and IL-13 (Salimi et al., 2017), biasing the

microenvironment away from a cytotoxic Th1 orientation and toward a tumor-permissive Th2 profile (De Monte et al., 2011). A primary consequence of this skewing is the conditioning of macrophages toward an alternative (M2) activation state, mirroring the effects of the COX-2/PGE_2 axis. LTD_4 signaling through the high-affinity $CysLT_1$ receptor on monocytes/macrophages triggers intracellular MAPK/NF-κB pathways that induce immunoregulatory mediators such as CCL2 (Hashimoto et al., 2009). In the presence of Th2 cytokines, CysLT exposure reinforces macrophage differentiation into immunosuppressive phenotypes that upregulate IL-10 and arginase-1 (Noy & Pollard, 2014; Tsai et al., 2022). Notably, Th2 cytokines such as IL-13 feed back on myeloid cells by upregulating LTC_4 synthase expression, creating a feed-forward loop of local cysteinyl LT production (Tian et al., 2020).

4. Preclinical (Murine) Models Targeting Prostaglandin and Leukotriene Pathways in Cancer

4.1 COX-2/PGE_2 Pathway Blockade in Murine Tumor Models Enhances T Cell–Mediated Tumor Control

While the biochemical and cellular mechanisms of prostanoid-mediated suppression are well-characterized, their systemic impact is most clearly demonstrated in vivo. Multiple preclinical studies have demonstrated that inhibiting the COX-2/PGE_2 pathway can reinvigorate anti-tumor T cell activity in the mouse tumor microenvironment (Zelenay et al., 2015; Liu et al., 2015). By interrupting this pathway, the balance shifts in favor of immune-mediated tumor control. In B16 melanoma models, both pharmacological COX-2 inhibition and genetic ablation of tumor-cell PGE_2 synthesis result in significantly slower tumor growth and enhanced intratumoral T cell accumulation (Zelenay et al., 2015; Kim et al., 2019). These preclinical successes provided the rationale for the clinical trials and retrospective studies described in Section 5.1.

A central controversy in applying these findings is whether broad COX-2 inhibition or more selective mPGES-1/EP4 targeting best preserves beneficial eicosanoids while minimizing toxicity. Zelenay et al. (2015) found that $BRAF^{V600E}$ mouse melanoma cells rendered COX-deficient by CRISPR-mediated targeting of *Ptgs1*/*Ptgs2* were rejected or grew markedly more slowly in immunocompetent mice, in contrast to COX-expressing tumors that grew progressively. Similarly, Kim et al. (2019) reported that mPGES-1 (PTGES)-knockout B16 melanomas grew substantially more slowly than wild-type tumors in vivo, despite comparable proliferation in vitro.

Concomitantly, blocking COX-2/PGE_2 unleashes a more robust T cell infiltration into the tumor. In the mPGES-1–knockout B16 model, intratumoral $CD8^+$ T-cell infiltration was markedly increased relative to controls, as shown by both immunohistochemistry and flow cytometry of dissociated tumors (Kim et al., 2019). Notably, mPGES-1–knockout tumors proved significantly more responsive to checkpoint blockade therapy: anti–PD-1 treatment, which only modestly slowed the growth of PGE_2-producing B16 tumors, instead induced rapid and durable regressions in mice bearing *Ptges*-null melanomas (Kim et al., 2019).

4.2 5-LO/Leukotriene Pathway Inhibition: Effects on Myeloid Cell Infiltration and Metastasis

While COX-2 blockade consistently enhances T cell–mediated control, the 5-lipoxygenase (5-LO) leukotriene pathway presents a more complex target in preclinical models.

Interrupting this pathway can markedly alter the recruitment of leukocytes that shape the TME (Wang & Dubois, 2010). In syngeneic models such as 4T1 mammary carcinoma and Lewis lung carcinoma (LLC), both genetic ablation of 5-LO and pharmacological inhibition with agents like zileuton reduce the accumulation of pro-tumor myeloid cells. For example, in hypoxic ovarian tumor models, zileuton significantly decreased TAM infiltration, which correlated with slower tumor growth (Wen et al., 2015).

Leukotriene pathway inhibition has also shown a striking impact on metastatic progression. In the 4T1 model, neutrophils in the pre-metastatic niche secrete LTB_4 to facilitate the seeding and outgrowth of circulating tumor cells (Wculek & Malanchi, 2015). Genetic deletion of *Alox5* (encoding 5-LO) in bone marrow–derived cells or systemic zileuton treatment abrogated this neutrophil-driven metastasis, resulting in significantly fewer spontaneous lung metastases (Wculek & Malanchi, 2015). However, a critical countervailing observation highlights a paradigm tension: leukotrienes also guide effector T cells into tumors via the high-affinity LTB_4 receptor BLT1. Complete abrogation of 5-LO signaling can therefore compromise adaptive immune surveillance. BLT1-deficient mice challenged with syngeneic tumors exhibit accelerated tumor growth and reduced survival due to a profound deficit in intratumoral $CD8^+$ T cell accumulation (Sharma et al., 2013).

4.3 Combined COX-2 and 5-LO Inhibition to Overcome Compensatory Eicosanoid Signaling

The nuanced trade-offs and context-dependency observed in single-pathway targeting have led to the exploration of combination regimens. Tumor cells often exploit both the COX-2 and 5-LOX pathways, and these parallel circuits can compensate for each other when one is blocked. In inflammation-driven cancers, selective COX-2 inhibition alone can trigger a compensatory surge in leukotriene production via the 5-LOX pathway—a phenomenon termed “arachidonic acid shunting” (Park et al., 2012; Wikström et al., 2003; Ye et al., 2005; Figure 4). The biochemical basis for this shunting effect is introduced in Section 1.1 and its clinical implications are discussed in Section 5.3.

Given this crosstalk, concomitant inhibition of both COX-2 and 5-LOX has been hypothesized to more effectively collapse tumor-promoting inflammation. Murine cancer models and cell-based experiments strongly underscore the superior efficacy of dual COX-2/5-LOX inhibition (Che et al., 2016; Schroeder et al., 2007). In the $APC^{Min/+}$ genetic model of intestinal polyposis, the dual COX/5-LOX inhibitor licofelone produced a marked, dose-dependent reduction in intestinal tumor multiplicity and size (Bannwarth, 2004; Bias et al., 2004; Mohammed et al., 2011). Beyond impeding tumor cell proliferation, dual COX-2/5-LOX inhibition exerts pronounced immunomodulatory benefits. By simultaneously removing PGE_2-driven and leukotriene-driven immunosuppressive signals, combined blockade creates a more pro-inflammatory, anti-tumor milieu. Preclinical evidence suggests that neutralizing both PGE_2 and leukotriene signals can synergize with immune checkpoint inhibitors; in syngeneic mouse models, adding a dual COX/5-LOX blocker to anti–PD-1 therapy increased intratumoral $CD8^+$ T-cell accumulation and improved long-term tumor control relative to checkpoint inhibitor alone (Pu et al., 2021; Figure 4).

5. Clinical and Translational Investigations of Prostaglandin and Leukotriene Pathway Targeting in Cancer Immunotherapy

5.1 COX-2 Inhibitors (NSAIDs) as Immunotherapy Adjuncts: Trials and Clinical Observations

The potent immunosuppressive role of COX-2-derived PGE_2 in tumors has motivated investigations into cyclooxygenase-2 (COX-2) inhibitors (NSAIDs) as adjuncts to cancer immunotherapy. Retrospective analyses have reported that cancer patients on NSAIDs at the start of immune checkpoint blockade tend to experience improved therapeutic outcomes compared to those not using NSAIDs (Mahmud et al., 2021; Sharma et al., 2020). For example, in metastatic melanoma, patients taking NSAIDs at immunotherapy initiation showed significantly higher response rates and longer overall survival on anti–PD-1 ± CTLA-4 therapy than those not on NSAIDs (Wang et al., 2020).

Prospective studies have begun exploring these signals, with case reports documenting striking responses, such as a patient with refractory p16+ metastatic sinonasal undifferentiated carcinoma who responded when a COX-2 inhibitor (celecoxib) and ipilimumab were added to pembrolizumab after progression on pembrolizumab alone (Trinh et al., 2024). Furthermore, the Phase II *PCOX* trial in China indicated that PD-1 blockade plus COX inhibitors in metastatic dMMR (MSI-H) colorectal cancer upregulated antigen presentation pathways and induced a more inflamed gene expression profile (Li et al., 2022; Wu et al., 2024; Rousseau & Johannet, 2024). Importantly, not all tumor contexts have shown a benefit. A retrospective cohort study in metastatic renal cell carcinoma (RCC) found that patients receiving concomitant NSAIDs during anti–PD-1 therapy did not experience significant improvements in treatment outcomes (Zhang et al., 2022).

5.2 EP Receptor Antagonists: Clinical Development and Immune Impact

While broad COX-2 inhibition via NSAIDs offers a systemic approach to reducing PGE_2 levels, the associated cardiovascular and gastrointestinal risks have spurred the development of more precise interventions (Antman et al., 2005; Desai et al., 2023; Wallace, 2012). Direct targeting of prostaglandin receptors has thus reached clinical evaluation, focusing on the specific pathways through which PGE_2 exerts its immunosuppressive effects. Among the four E-prostanoid receptors (EP1–EP4), EP4 and EP2 signal through cyclic AMP and are most strongly linked to the immunosuppressive deviations discussed in Section 2 (Cuenca-Escalona et al., 2024).

The first-in-human trial of E7046 demonstrated evidence of immune modulation in patients but only modest clinical activity. In this Phase I study involving heavily pretreated solid tumor patients, oral E7046 was well tolerated (Hong et al., 2020). On-treatment tumor biopsies indicated increased expression of $CD8^+$ T-cell markers, yet these immune changes did not translate into tumor regressions; no objective responses were achieved (ORR 0%) (Hong et al., 2020). Subsequent clinical studies have focused on combining EP4 antagonists with checkpoint inhibitors. For example, the oral EP4 antagonist vorbipiprant (CR6086) was evaluated with PD-1 blockade in refractory MSS metastatic colorectal cancer. In a Phase Ib/IIa trial, approximately half of the treated patients achieved disease control, an uncommon outcome for MSS tumors (Pietrantonio et al., 2025).

5.3 Leukotriene Pathway Modulators in Cancer Patients: Trials and Challenges

Leukotriene-pathway inhibitors have thus far yielded disappointing results in cancer patients (Nakamichi et al., 2024; Zhao et al., 2019). For example, a randomized phase II trial of the BLT1 antagonist LY293111 (etalocib) added to first-line chemotherapy in advanced NSCLC

showed no improvement in outcomes (Bhatt et al., 2017; Jänne et al., 2014). This counterintuitive result aligns with emerging evidence that LTB_4 signaling can sometimes support anti-tumor immunity by recruiting effector leukocytes (Sharma et al., 2013). Efforts to repurpose cysteinyl leukotriene (CysLT) receptor antagonists in oncology have likewise met with little clinical success. Montelukast, a $CysLT_1$ receptor blocker, showed encouraging anti-cancer activity in preclinical studies (Tsai et al., 2017). Epidemiological data have even hinted that long-term use of leukotriene antagonists might reduce cancer incidence (Tsai et al., 2016; Jang et al., 2022). However, no prospective clinical trial to date has demonstrated meaningful therapeutic efficacy of montelukast in patients with established malignancies (Jang et al., 2022).

5.4 LC–MS/MS Tumor PGE_2/LTB_4 Quantification and Spatial $CD8^+$/Treg/MDSC Mapping as Immunotherapy Correlates

The clinical setbacks observed with single-pathway inhibitors underscore the necessity of more sophisticated biomarker strategies. The intratumoral activity of the COX-2/PGE_2 and 5-LO/leukotriene pathways has clear translational relevance. Tumors with elevated COX-2 (*PTGS2*) expression tend to exhibit a highly immunosuppressive milieu and resistance to T cell–based immunotherapies (Boumelha et al., 2024; Markosyan et al., 2019). Liquid chromatography–tandem mass spectrometry (LC–MS/MS) permits precise quantification of these metabolites directly in resected tissues (Jiang et al., 2022); complementary non-invasive readouts, such as urinary PGE-M, also track systemic PGE_2-pathway activity (Wang & DuBois, 2013). Tumors with high intratumoral PGE_2 levels are often “immune-cold,” characterized by an abundance of $FoxP3^+$ Tregs and $CD11b^+$ MDSCs (Veglia et al., 2018; Wang & DuBois, 2016).

Spatial mapping studies using multiplex immunofluorescence have shown that regions with high ALOX5 expression often coincide with dense $CD8^+$ T cell aggregates, indicating that 5-LO activity can actively orchestrate lymphocyte trafficking (Gao et al., 2025; Zhao et al., 2023). Implementing eicosanoid quantification as an immunotherapy correlate demands careful methodological standardization. Biopsies must be processed rapidly—snap-frozen or homogenized in cold solvent with enzyme inhibitors—to arrest metabolism (Liakh et al., 2019). Analysis by LC–MS/MS is typically performed in negative electrospray ionization mode using multiple reaction monitoring (MRM) and stable-isotope internal standards (Brose et al., 2011).

6. Future Directions and Unanswered Questions

Future research must prioritize the spatial and cellular deconvolution of the arachidonic acid (AA) network within the tumor microenvironment (TME). While this review highlights the roles of tumor-derived PGE_2 and leukotrienes, the relative contributions of cancer-associated fibroblasts (CAFs) and specific myeloid subsets to the total intratumoral eicosanoid flux remain poorly defined (Gong et al., 2022). A critical unanswered question is how localized gradients of PGE_2 and LTB_4 dictate the spatial architecture of immune exclusion, particularly the positioning of $CD8^+$ T cells relative to $FoxP3^+$ Tregs and MDSCs (Section 5.4). Emerging technologies, such as MALDI-imaging and spatial single-cell lipidomics, will be essential to map these metabolite microdomains and determine whether the loss of catabolic enzymes like 15-PGDH and the transporter SLCO2A1 represents an active, targetable immune-evasion program rather than a passive bystander event (Section 1.2).

A central challenge in therapeutic development remains the functional pleiotropy of eicosanoid receptors, most notably the LTB_4–BLT1 axis. Future studies must determine the contextual cues—such as hypoxia, microbiome-derived signals, or TGF-β levels—that flip this axis from a pro-tumorigenic driver of neutrophil recruitment to a requisite pathway for $CD8^+$ T-cell homing (Section 3.1, 4.2). Similarly, resolving the distinct signaling outputs of EP2 and EP4 receptors is paramount for overcoming the modest efficacy seen in early trials. It remains unclear whether the clinical failure of certain EP4 antagonists stems from redundant EP2 signaling or a failure to address EP4-exclusive β-arrestin scaffolding that may drive T-cell exhaustion (Section 2.2, 5.2). Investigating "arachidonic acid shunting," where the inhibition of COX-2 triggers a compensatory rise in immunosuppressive leukotrienes, is also critical. Research should evaluate whether dual COX-2/5-LO blockade or receptor-selective combinations (e.g., EP4 plus $CysLT_1$ antagonists) can achieve superior myeloid reprogramming without the systemic toxicities associated with global enzyme inhibition.

7. Conclusion

The arachidonic acid–COX/LOX network represents a fundamental metabolic axis that tumors co-opt to enforce immune evasion and sustain chronic inflammation. This review has synthesized the multifaceted roles of prostaglandins and leukotrienes, illustrating how their dysregulation—characterized by elevated PGE_2 and cysteinyl leukotrienes alongside impaired catabolism via 15-PGDH—shapes a profoundly suppressive tumor microenvironment (TME). By engaging specific G-protein–coupled receptors such as EP2, EP4, and $CysLT_1$, these lipid mediators orchestrate a systemic shift toward myeloid-derived suppressor cell (MDSC) expansion and M2 macrophage polarization. Simultaneously, they act as potent metabolic checkpoints that blunt the bioenergetic fitness and effector functions of $CD8^+$ T cells and NK cells, effectively shielding the tumor from cytotoxic clearance.

Integration of findings across murine models and human clinical data reveals both the promise and the intricate challenges of targeting these pathways. Preclinical studies have provided definitive proof-of-concept that interrupting the COX-2/PGE_2 axis can "heat up" immunologically cold tumors, restoring dendritic cell function and sensitizing otherwise resistant models to PD-1/PD-L1 blockade (Zelenay et al., 2015; Kim et al., 2019). However, the transition to human trials has underscored a more complex landscape defined by pathway redundancy and biochemical crosstalk. The phenomenon of "arachidonic acid shunting," wherein the inhibition of one enzymatic arm fuels a compensatory rise in other immunosuppressive eicosanoids, remains a significant hurdle. Furthermore, the dichotomous role of LTB_4—which facilitates both pro-metastatic neutrophil recruitment and essential T-cell homing—exemplifies the need for context-specific therapeutic strategies rather than broad systemic inhibition.

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