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The PGE_2–NK-cell Axis in Tumor Immune Escape: Mechanisms and Therapeutic Targeting

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Abstract. Natural killer (NK) cells sit at the center of tumor immune surveillance. Their contribution goes beyond direct killing—they produce cytokines, release chemokines, and help recruit dendritic cells. Yet solid tumors often contain high local levels of prostaglandin E2 (PGE_2) , generated by cyclooxygenase-2 (COX-2) and microsomal prostaglandin E synthase-1 (mPGES-1) , and this PGE_2-rich environment dampens NK-cell responses at several points. This review examines how tumor-derived PGE_2 signals through EP2/EP4 (E-prostanoid receptors 2 and 4) and the downstream cAMP (cyclic adenosine monophosphate)/PKA (protein kinase A) cascade. The consequences include altered NK-cell activation, cytokine output, receptor expression, immune-synapse organization, cytotoxicity, migration, and antimetastatic activity. We also compare ways to interrupt this axis: pharmacological inhibitors of PGE_2 synthesis, selective or dual EP2/EP4 blockade, and cell-intrinsic engineering approaches aimed at making NK cells less sensitive to PGE_2. Attention is paid to inconsistencies among experimental models and to whether interventions restore NK-cell function directly or act more broadly on the tumor. Biomarkers that might support patient selection are discussed as well. Current evidence suggests the PGE_2–NK-cell axis is a druggable immunosuppressive circuit, although clinical translation will likely require pathway-based stratification and prospective pharmacodynamic assessment.

Keywords: PGE_2, natural killer cells, tumor immune escape, EP2/EP4, cancer immunotherapy

1. Introduction

Natural killer (NK) cells are innate lymphocytes that arise from common lymphoid progenitors. They do not require classical antigen presentation or prior clonal sensitization to respond rapidly to cellular stress. Instead, their behavior is shaped by the balance of signals coming from activating and inhibitory receptors. Malignant transformation can reduce major histocompatibility complex class I expression, induce ligands for stress receptors, or change the density of antibody-coated targets. Recognition of these changes permits NK cells to trigger apoptosis through perforin–granzyme release, Fas ligand, and TNF-related apoptosis-including ligand (TRAIL). Cluster of differentiation 16 (CD16) additionally enables antibody-dependent cellular cytotoxicity, positioning NK cells as important effectors of therapeutic antibodies [1-4]. It is also worth noting that an activated NK cell

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is not a single-use cytotoxic compartment; it can serially engage targets and adjust its response to cytokine and metabolic cues within the tumor microenvironment.

The antitumor contribution of NK cells goes beyond direct target-cell lysis. Activated NK cells produce interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) , which can constrain tumor growth and shape the inflammatory state of the lesion. Alongside this, they release XCL1 (X-C motif chemokine ligand 1) , XCL2 (X-C motif chemokine ligand 2) , and CCL5 (C-C motif chemokine ligand 5) ; these chemokines recruit conventional type 1 dendritic cells (cDC1) into tumors. cDC1 then support antigen cross-presentation and the development of CD8+ T-cell responses, creating a functional link between innate cytotoxicity and adaptive immune control [5-8]. In other words, effective NK-cell surveillance depends on a chain of coordinated events: recognition of abnormal cells, activation, migration into the tumor, survival under metabolic stress, formation of a productive immune synapse, repeated killing, and communication with other immune populations.

Solid tumors frequently disrupt this chain at several points. Hypoxia, nutrient competition, abnormal extracellular acidity, suppressive cytokines, adenosine, transforming growth factor-β (TGF-β) , and prostaglandins can reduce activating-receptor expression and increase the threshold required for degranulation. As a result, tumor-infiltrating NK cells may retain a recognizable phenotype while displaying weak cytotoxicity, reduced cytokine production, impaired motility, or poor persistence. The functional state is also heterogeneous: circulating NK cells, tissue-resident populations, and tumor-adapted subsets can differ in receptor expression, metabolic fitness, and sensitivity to suppressive signals [9]. For mechanistic work, it matters whether cell numbers drop or function is lost, and whether NK cells fail to reach the tumor or fail to kill after contact.

Prostaglandin E_2 (PGE_2) is a lipid mediator produced from arachidonic acid. In normal physiology it contributes to vascular, inflammatory, and tissue-repair processes. In cancer, however, persistent induction of COX-2 and mPGES-1 can increase local PGE_2 production and establish a soluble immunosuppressive field. PGE_2 acts through four E-prostanoid receptors. Among them, EP2 and EP4, both coupled predominantly to Gαs, are especially relevant to immune regulation. Their activation increases adenylyl cyclase activity and intracellular cyclic AMP (cAMP), which can interfere with receptor-proximal signaling in cytotoxic lymphocytes [10-13].

The NK-cell consequences of tumor-derived PGE_2 have been demonstrated across complementary systems. In thyroid cancer models, tumor-cell PGE_2 reduced expression of NKp30, NKp44 (natural cytotoxicity receptors), and TRAIL, weakened nuclear factor kappa-B (NF-κB)- and mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK)-associated responses, and impaired maturation as well as killing of K562 targets [14]. Work with primary human NK cells points in a similar direction: PGE_2 affects receptor expression, IFN-γ production, degranulation, the kinetics of target-cell killing, and chemotaxis through C-X-C chemokine receptor type 3 (CXCR3) and C-X-C chemokine receptor type 4 (CXCR4) [15]. Taken together, these findings position PGE_2 at the intersection of tumor metabolism and immune escape rather than as a narrow inhibitor of one effector pathway.

This review follows the mechanistic path from tumor-associated PGE_2 generation and accumulation, through EP2/EP4 signaling in NK cells, to disruption of activation and trafficking, and then to therapeutic intervention at the level of ligand production, receptor engagement, or NK-cell intrinsic resistance. We keep the focus on the PGE_2–NK-cell axis; effects on other immune populations are mentioned only when they clarify NK-cell recruitment, cooperation, or treatment response. Because this is a narrative review, the discussion is organized around the tumor PGE_2 source, EP2/EP4 signaling, NK-cell functional consequences, and therapeutic intervention points. It is not intended to replace a systematic review or meta-analysis.

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2. PGE_2 production and signaling in NK cells

2.1. Production and accumulation of PGE_2 in tumors

The synthesis of PGE_2 begins with the release of arachidonic acid from membrane phospholipids by phospholipases. Cyclooxygenases then convert this fatty acid into PGH_2, a shared precursor that prostaglandin E synthases subsequently isomerize to PGE_2. While COX-1 tends to maintain baseline prostanoid levels, COX-2 is induced by a range of signals—inflammatory cytokines, oncogenic pathways, hypoxia, tissue injury, and mitogenic stimulation. mPGES-1 often works in tandem with COX-2, receiving PGH_2 and channeling it toward PGE_2 [10, 12, 16-18]. This functional coupling may explain why local PGE_2 can remain elevated even as individual tumor cells encounter changing stimuli.

Tumor cells are not the only source. Cancer-associated fibroblasts, tumor-associated macrophages, and other myeloid cells can also express COX-2 or prostaglandin synthases and add to the extracellular pool. The concentration sensed by NK cells depends on synthesis, but secretion, diffusion, binding to extracellular structures, and enzymatic inactivation all matter as well. Production and degradation are not evenly balanced across a tumor; gradients are likely, meaning PGE_2 levels at the tumor margin, stromal compartment, and hypoxic core may differ considerably. For NK cells, this matters because migration, synapse formation, and killing could be exposed to different local concentrations.

Evidence from melanoma links mPGES-1 activity to an immunosuppressive state. High mPGES-1 expression has been associated with reduced lymphocyte infiltration and adverse clinical features, and genetic deletion of Ptges in syngeneic models increased dendritic-cell and CD8+ T-cell infiltration while restraining tumor growth [16, 19]. In pancreatic cancer, tumor-intrinsic EPHA2–TGF-β signaling can upregulate PTGS2, the gene for COX-2; loss of Ptgs2 or pharmacological inhibition has been reported to partially reverse immune exclusion [20]. These findings suggest that PGE_2 supply is not merely a downstream metabolic byproduct. It can be continuously reinforced by oncogenic signaling, thereby translating tumor-intrinsic biology into an immune-suppressive microenvironment.

The cellular origin of PGE_2 also affects how one interprets therapeutic results. A COX-2 inhibitor that reduces secretion from tumor cells may not act the same way as an EP4 antagonist that blocks signaling simultaneously in NK cells, myeloid cells, and tumor cells. Moreover, a high PGE_2 measurement in bulk tumor tissue does not identify which cells produced the mediator or which compartment was exposed to the highest concentration. Future work should combine tissue PGE_2 measurements with spatial expression of PTGS2 and PTGES, EP2/EP4 expression on NK cells, and functional readouts such as CD107a mobilization and IFN-γ production.

2.2. EP2/EP4 signaling in NK cells

PGE_2 binds to EP1–EP4, a family of G-protein-coupled receptors, but the dominant inhibitory route in NK cells is generally attributed to EP2 and EP4. Both receptors couple mainly to Gαs and stimulate adenylyl cyclase, which raises cAMP and activates protein kinase A (PKA). cAMP-dependent PKA signaling can inhibit early signaling proteins downstream of natural cytotoxicity receptors, NKG2D, and CD16, so receptor engagement is less efficiently converted into calcium flux, actin remodeling, polarization, degranulation, and cytokine transcription [10, 11, 21, 22]. In effect, one soluble mediator is able to dampen several activating receptors at once.

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It would be a mistake to treat EP2 and EP4 as interchangeable in every context. The apparent contribution of each receptor depends on relative receptor abundance, maturation state, previous cytokine exposure, species, and the duration and intensity of PGE_2 exposure. Human and murine NK cells may differ in receptor transcription, receptor trafficking, and downstream cAMP handling. In thyroid cancer-conditioned systems, antagonism of either EP2 or EP4 partially restored cytotoxicity and was accompanied by improvement of NF-κB- and MAPK/ERK-related responses [14]. The partial rescue points to parallel signaling and receptor compensation rather than a single dominant receptor.

Experiments with primary human NK cells give a more dynamic picture. PGE_2 has been shown to reduce ERK1/2 phosphorylation after target-cell stimulation, delay microtubule-organizing-center polarization toward the immune synapse, and lower the expression of activating receptors such as NKG2D, NKp30, and NKp44. At the same time, it can reduce CXCR3 and increase CXCR4, shifting chemotactic responses away from CXCL10-rich inflammatory sites and toward CXCL12-associated niches [11, 15, 23]. This points to a signaling route—PGE_2–EP2/EP4–Gαs–adenylyl cyclase–cAMP/PKA—with downstream branches affecting early activation, receptor abundance, synapse organization, granule release, and tissue positioning.

Functional rescue, then, needs to be assessed with more than one endpoint. A treatment may restore IFN-γ without restoring target-cell killing, or increase tumor-associated NK-cell numbers without improving their per-cell cytotoxicity. Conversely, a receptor antagonist may improve migration and cell accumulation while its direct effect on tumor-cell growth contributes substantially to the observed tumor response. Mechanistic studies should therefore pair cell-intrinsic assays with tumor-level measurements and distinguish changes in NK-cell frequency, phenotype, localization, and function.

3. Effects of PGE_2 on NK-Cell antitumor function

3.1. Suppression of activation and cytokine production

PGE_2 often begins by raising the activation threshold in NK cells. In human NK cells, exposure to 0.1–1 μM PGE_2 suppressed IFN-γ synthesis induced by interleukin-12 (IL-12) and interleukin-18 (IL-18); under combined stimulation, the average reduction was about 41.5% [24]. A similar pattern appears in murine splenic NK-cell systems, where PGE_2 dampened interleukin-2 (IL-2)-induced IFN-γ and TNF-α production, and an EP4 agonist mimicked the inhibitory profile of PGE_2 [14]. What these data indicate is that PGE_2 can interfere with both receptor-mediated target recognition and cytokine-driven activation, in line with broader accounts of NK-cell signaling integration [25]. That said, the relative contribution of EP2 and EP4 differs across models.

Reduced IFN-γ matters for more than one reason. It weakens a direct antitumor effector program and may limit the ability of NK cells to influence tumor-cell growth and local antigen presentation. At the same time, it disrupts communication between NK cells and other immune populations. NK-cell-derived IFN-γ and chemokines help recruit and activate cDC1 and other antigen-presenting cells; losing these mediators could amplify the original NK-cell defect by weakening the broader immune network. This is not to say that every PGE_2-associated change in adaptive immunity runs through NK cells. Still, NK-cell cytokine loss represents one plausible connecting event.

How much cytokine suppression occurs depends heavily on the experimental setup. Short pulses of PGE_2, continuous exposure, and conditioning during expansion can yield different phenotypes. Cytokine concentration, cell density, target-cell ratio, and the presence of accessory cells further shape the response. Because of this, the percentage reduction in IFN-γ should not be read as a fixed

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clinical effect size. It may be more useful to ask whether PGE_2 shifts the activation threshold, the maximal response, or the persistence of cytokine production after repeated stimulation.

At the transcriptional level, cAMP/PKA signaling intersects with pathways controlling NF-κB, MAPK, and cytokine-responsive transcription factors. The result is not always complete silencing. Some NK cells may continue producing cytokines but fail to coordinate this with cytotoxicity; others show a broader loss of activation receptors and effector cytokines. This heterogeneity matters for the design of combination therapies: an intervention that restores PGE_2-sensitive signaling may work best when residual NK cells are present but functionally restrained, rather than when the tumor has eliminated or profoundly reprogrammed the NK-cell compartment.

3.2. Impairment of receptor expression, degranulation, and cytotoxicity

PGE_2 does not stop at suppressing activation signals; it also interferes with target-cell recognition and the execution of killing. When primary human NK cells were exposed to 221 or K562 targets, PGE_2 lowered CD107a surface mobilization by 15.0% ± 5.9% and 26.4% ± 14.9%, respectively, while cell viability remained largely intact [15]. It is worth noting that degranulation dropped even though viability was mostly unchanged, so the defect looks like functional inhibition rather than NK-cell depletion. The same study also found lower expression of NKG2D (natural killer group 2 member D), CD16, NKp30, and NKp44. PGE_2 therefore appears to reduce both the input signals and the chance that these signals will lead to productive granule release.

Live-cell imaging added another layer: after contacting target cells, PGE_2-treated NK cells were slower to initiate killing and less likely to complete it successfully [15]. This kinetic picture is informative because cytotoxicity is not just about how much perforin or granzyme a cell stores. To kill productively, an NK cell must recognize the target, adhere, assemble an immune synapse, polarize the centrosome, converge granules, undergo exocytosis, and push the target cell toward death. Even when intracellular cytotoxic proteins are still detectable, a delay at any one of these steps can cut down serial killing.

Reports on perforin and granzyme B do not always agree across experimental models. In poly(I:C)-stimulated murine splenocyte systems, PGE_2 lowered perforin and granzyme B messenger RNA; blocking this effect improved NK-cell activity in melanoma models [26]. Primary human NK cells, on the other hand, did not always show the same drop in intracellular perforin or granzyme B. In some settings, these markers were preserved or even slightly increased even though degranulation and killing were impaired [11, 15]. Taken together, these findings make a simple "granule-deficiency" explanation unlikely. A more plausible view is that PGE_2 acts at multiple levels—receptor downregulation, proximal signaling inhibition, defective polarization, delayed exocytosis, and altered target-cell engagement.

The difference between having the capacity to kill and actually performing the kill has practical consequences. For example, a treatment might restore degranulation but not serial killing, or boost granzyme expression while immune-synapse dynamics remain poor. Preclinical assessment should therefore include not just chromium-release or flow-based cytotoxicity assays, but also CD107a, live-cell imaging, conjugate formation, and target-cell death kinetics. This is especially relevant for engineered NK cells. A construct that keeps cells alive but does not fix PGE_2-sensitive signaling may look good in expansion assays, yet fail inside a PGE_2-rich tumor.

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3.3. Reduced migration and antimetastatic activity

PGE_2 doesn't just suppress NK-cell effector functions; it also changes where these cells go. CXCR3 and its ligands, including CXCL10, normally steer NK cells toward inflamed or tumor-bearing regions. CXCR4–CXCL12 signaling, by contrast, tends to promote tissue homing and retention in particular anatomical niches. PGE_2 lowers surface CXCR3 and raises CXCR4, so NK cells migrate less toward CXCL10 and more toward CXCL12 [15]. Under stable chemokine gradients, PGE_2-treated NK cells also show reduced velocity, directionality, and forward migration efficiency toward CXCL10. What emerges is not simply a smaller number of NK cells, but a redistribution away from sites where target recognition and killing would be most useful.

This trafficking defect works together with the functional inhibition described earlier. An NK cell that reaches the tumor with weakened cytotoxicity may fail to kill, while an NK cell with intact killing but poor chemotaxis may never encounter malignant cells at all. The combined outcome is a spatially constrained immune response—the most active cells can be excluded from the tumor core or diverted toward nonproductive niches. Because chemokine gradients are shaped by tumor cells, stromal cells, and immune cells themselves, PGE_2-driven changes in NK-cell migration may also feed back into the local balance between innate and adaptive immune recruitment.

In a breast cancer mouse model, the EP4 antagonist RQ-15986 restored tumor-associated NK-cell migration and cytokine production, and it reduced primary tumor growth and spontaneous lung metastasis [11, 27]. Depleting NK cells weakened or abolished the antimetastatic effect, which points to a meaningful NK-cell contribution. That said, EP4 antagonism does not act only on NK cells; it can also directly affect tumor cells and other stromal or myeloid populations. The study therefore supports NK-cell participation, but it cannot assign the entire antimetastatic effect to NK-cell rescue. Future work would benefit from combining NK-cell depletion with tumor-cell EP4 manipulation, spatial imaging, and adoptive transfer of PGE_2-resistant NK cells.

Migration deserves to be treated as a pharmacodynamic endpoint rather than a secondary descriptive variable. Measuring tumor-infiltrating NK-cell density alone is not enough; it should be paired with localization relative to tumor nests, vasculature, and hypoxic areas. The phenotype of infiltrating cells matters as well, because increased numbers of poorly functional NK cells may not represent successful immune restoration. A fuller picture would integrate location, receptor expression, degranulation, and cytokine production to judge whether a PGE_2-targeting intervention has genuinely restored antimetastatic immunity.

3.4. Integrated immune-escape mechanism

What emerges across these studies is that PGE_2 does not hit a single checkpoint; instead, it disrupts several linked steps in the NK-cell antitumor response. Through EP2/EP4–cAMP/PKA signaling, the activation threshold is raised, activating-receptor expression is brought down, cytokine output is weakened, and early cytotoxic signaling is interfered with. Degranulation drops and killing is delayed, cutting effector output, while CXCR3/CXCR4 remodeling keeps NK cells away from the tumor. The immune-escape phenotype that results is better understood as a mix of functional insufficiency and spatial inaccessibility than as the product of one molecular lesion.

The evidence, though, has limits. Many mechanistic studies use exogenous PGE_2 concentrations that may not match the free mediator levels actually present in human tumors. Primary NK cells from healthy donors cannot fully capture the exhaustion, differentiation, or metabolic adaptation seen in tumor-infiltrating NK cells. Mouse models differ in receptor expression and tumor architecture, and pharmacological antagonists can also affect malignant and non-NK compartments

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[28]. These caveats do not necessarily invalidate the mechanism, but they do warrant caution when interpreting effect sizes, and they point toward validation in patient-derived samples, spatially resolved tumor models, and treatment-response cohorts.

4. Therapeutic targeting of the PGE_2–NK-cell axis

4.1. Inhibition of PGE_2 synthesis and upstream regulation

One obvious place to intervene is PGE_2 production itself—cutting the supply of the mediator rather than blocking its receptors. In thyroid cancer-conditioned systems, the COX-2 inhibitor NS398 reduced tumor-cell PGE_2 secretion, restored NK-cell killing of K562 targets, and partially recovered NKp30 and NKp44 expression [14]. What these data suggest is that upstream inhibition may improve both target recognition and effector execution at the same time, rather than producing a narrow change in a single cytokine. A somewhat different setting—high-grade serous ovarian cancer—points in the same direction: increased COX-2 expression in circulating NK cells was associated with functional impairment, and celecoxib pretreatment improved degranulation and cytotoxic responses against ovarian cancer cells [29, 30].

Caution is needed, though, when interpreting COX inhibition. COX enzymes sit in a shared metabolic branch and regulate prostanoids with distinct physiological roles. Systemic or nonselective inhibition may affect gastrointestinal integrity, platelet biology, vascular tone, and tissue repair. There is also the question of attribution: an apparent antitumor response could reflect direct inhibition of tumor proliferation, vascular effects, or changes in myeloid cells rather than a genuine restoration of NK-cell function. A rational development program would therefore measure tumor PGE_2, COX-2/mPGES-1 expression, NK-cell receptor status, CD107a mobilization, and cytokine production before and during treatment, rather than relying on tumor size alone.

mPGES-1 offers a more downstream target than COX-2 and may provide greater pathway selectivity in tumors where PGE_2 dominates the prostanoid output [31]. Even so, the biological consequences of mPGES-1 inhibition may still depend on substrate redistribution and compensatory prostanoid pathways. One should also consider tumor-cell genotype, stromal composition, and the relative contribution of tumor versus immune-cell PGE_2 production when choosing between COX-2 and mPGES-1 inhibition. Biomarker-enriched trials seem more likely to reveal a therapeutic window than giving these agents to unselected patients across all tumor types.

4.2. EP2/EP4 blockade and receptor selectivity

Blocking the receptors operates closer to the NK-cell response, so it offers a more direct route to interrupt PGE_2 signaling. In thyroid cancer-conditioned media, AH6809 and AH23848—commonly used EP2 and EP4 antagonists—partially reversed the loss of NK-cell cytotoxicity [14]. Since both receptors can feed into cAMP signaling, inhibiting one alone may leave residual activity through the other. That makes it hard to assume a single dominant receptor in every tumor; whether to block selectively or block both becomes an empirical question rather than a theoretical one.

Dual EP2/EP4 blockade has shown activity in PGE_2-rich preclinical settings. TPST-1495 restored immune function more effectively than single-receptor inhibition under high PGE_2 conditions and displayed antitumor activity in several tumor models [11, 32]. Other dual-antagonist programs have also been developed to reverse PGE_2-mediated immune suppression. Collectively, these programs suggest dual blockade may be especially useful when both receptors are expressed or when receptor compensation limits single-agent activity [23, 33].

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That said, selective inhibition may still be preferable when one receptor clearly dominates or when broader EP2/EP4 blockade raises tolerability concerns. EP4-directed agents have entered early clinical testing, including the first-in-human study of E7046 in advanced solid tumors [34]. Whether receptor blockade proves clinically valuable will likely depend on identifying tumors with a high PGE_2 burden, preserved but restrained NK-cell populations, and a receptor state that remains accessible to drugs. A practical biomarker panel might include tumor PGE_2 concentration, PTGS2/PTGES expression, NK-cell EP2/EP4 abundance, and baseline functional reserve.

Drug-response assessment needs to go beyond tumor volume. Receptor blockade may increase NK-cell infiltration without improving per-cell function, or it may restore cytokine production without fully correcting cytotoxic kinetics. Serial blood and tumor sampling could therefore measure NK-cell frequency, EP2/EP4 expression, activating receptors, CD107a, IFN-γ, and spatial localization. Combining these readouts with pharmacokinetic exposure and tumor-cell response would help separate direct antitumor effects from immune-mediated effects.

4.3. Engineering NK cells with intrinsic PGE_2 resistance

Adoptive NK-cell therapies open a different possibility: instead of depending only on systemic drug exposure, PGE_2 sensitivity can be addressed while the cells are being manufactured. When NK cells are conditioned with IL-15 rather than IL-2, the resulting population tends to be enriched for CD25+/CD54+ cells and shows higher mTOR activity and PDE4A expression. Because cAMP is hydrolyzed more efficiently, these cells retain cytotoxicity, perforin, TRAIL, and IFN-γ responses even in the presence of PGE_2 [35]. What this suggests is that PGE_2 resistance is not simply a receptor-level property; it is connected to metabolic fitness, adhesion, and tissue entry.

A more direct route is genetic engineering. Deleting EP2 or EP4 alone gives only partial recovery, but disrupting both receptors can maintain IFN-γ and TNF production as well as IL-15-induced proliferation in PGE_2-containing environments [36]. Membrane-anchored IL-15/IL-15Rα trans-presentation adds another layer by supporting survival, expansion, and persistence. These approaches could be built into chimeric antigen receptor NK (CAR-NK) products, or they might simply improve the performance of unmodified expanded NK cells once inside solid tumors.

But each engineering choice carries drawbacks. Removing EP2/EP4 could alter physiological responses, migration, or interactions with other cells, and complete receptor disruption may also create selective pressure during manufacturing. Boosting PDE4A might affect signaling pathways beyond PGE_2, while strong cytokine support can push cells toward activation-induced stress or exhaustion. For product development, it would therefore be important to look beyond expansion and short-term killing. Serial cytotoxicity, metabolic stability, persistence, tumor penetration, and off-target inflammatory effects all need attention.

There is also the question of whether PGE_2 resistance alone is enough. Tumors often contain TGF-β, adenosine, hypoxia, and nutrient deprivation at the same time. An NK cell modified only at the PGE_2 receptor could still struggle in a metabolically hostile tumor. A more rational design might combine EP2/EP4 disruption with cytokine trans-presentation, improved homing, or checkpoint-resistant signaling. Yet every additional modification adds manufacturing complexity and safety-testing burden.

4.4. Combination therapy and translational limitations

It may be more useful to think of PGE_2-axis inhibition as a sensitizing strategy—one that raises the functional ceiling for NK-cell therapy and immune-checkpoint blockade. In mouse tumor models,

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combining EP4 inhibition with anti-programmed cell death protein 1 (anti-PD-1) gave better tumor control than either agent alone, and both NK-cell and myeloid compartments were affected [37-39]. A similar sequence appears in ovarian cancer models, where celecoxib improved NK-cell function and subsequent cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade then amplified the response—PGE_2-related suppression was relieved before immune amplification [29].

What the optimal combination looks like may depend on treatment order. Upstream COX-2 or mPGES-1 inhibition, for instance, could shrink the suppressive field before cell infusion, while EP4 blockade might matter more during NK-cell trafficking and tumor engagement. Engineered PGE_2-resistant NK cells might reduce the need for systemic inhibition, but they may not change PGE_2-driven tumor-cell proliferation or myeloid suppression. This argues for testing combinations mechanistically, rather than lumping all PGE_2 interventions into a single class.

Pathway heterogeneity continues to limit clinical translation. In one cancer, tumor cells may produce PGE_2; in another, stromal or myeloid cells may be the main source. EP2 and EP4 expression also shift with NK-cell differentiation, prior cytokine exposure, and treatment history. And EP2/EP4 blockade can reshape suppressive myeloid and dendritic-cell compartments as well [33, 40, 41]. Systemic prostanoid inhibition can cause dose-limiting effects, while receptor antagonism often hits several compartments at once. Early trials need to include tissue and blood pharmacodynamic analyses, define a biologically active exposure range, and link PGE_2 suppression to NK-cell recovery prospectively.

A practical translational framework might sort patients by three things—pathway activity, NK-cell reserve, and treatment context. Pathway activity could be estimated from PGE_2, PTGS2, PTGES, and receptor measurements. NK-cell reserve would be assessed through infiltration, activating-receptor expression, degranulation, cytokine production, and ex vivo rescue by antagonists. Treatment context includes prior checkpoint blockade, chemotherapy, radiotherapy, and cellular therapy. Such a framework could identify patients whose NK-cell defect is suppressive but still reversible—more informative than choosing patients by tumor type alone.

Combination trial design also needs to account for how PGE_2 signaling behaves pharmacologically. A short-lived drop in circulating PGE_2 may not reflect sustained suppression inside the tumor, where local synthesis and diffusion can quickly restore the mediator. On the other hand, continuous high-dose inhibition might add little immune benefit while raising systemic toxicity. Intermittent dosing, tumor-targeted delivery, or schedules timed with NK-cell infusion may work better. Pharmacodynamic sampling should capture both drug exposure and pathway response —intratumoral PGE_2, downstream cAMP signatures linked to EP2/EP4, and recovery of NK-cell degranulation after ex vivo stimulation.

Clinical endpoints need to capture the biology of an NK-cell intervention. Objective tumor response still matters, but early changes in tumor infiltration, circulating NK-cell phenotype, cell-free tumor DNA, and chemokine profiles may signal pathway engagement before any radiographic shrinkage. For metastatic disease, fewer new lesions or a delay in progression may be more informative than a transient change in the primary tumor. For cellular therapies, one would want to look at persistence, serial killing, and whether infused-cell phenotype relates to tumor localization. These endpoints could help distinguish whether a negative trial was due to poor target engagement, too little NK-cell reserve, or a failure of the proposed mechanism itself.

Safety assessment needs to go beyond the toxicities usually associated with cellular immunotherapy. Prostaglandins are involved in mucosal protection, vascular regulation, platelet function, and tissue repair, so broadly interfering with their production may cause effects not seen in short animal experiments. EP2 and EP4 are also expressed in nonmalignant tissues, and dual

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blockade could change inflammatory responses or wound healing. Engineered NK cells with altered receptor signaling might also show unexpected persistence or tissue distribution. Release criteria for products should therefore cover receptor editing, cytokine dependence, proliferation control, genomic stability, and the ability to shut off activity after targets are cleared.

Interpreting negative or discordant studies brings another challenge. If a COX-2 inhibitor fails to improve NK-cell activity, that does not automatically refute the PGE_2 mechanism—the tumor might use mPGES-1-independent sources, the dose might not have suppressed intratumoral PGE_2, or NK cells could already be irreversibly dysfunctional. Likewise, no increase in NK-cell infiltration after EP4 blockade may mean resident cells were successfully rescued, not that the drug failed. Studies should predefine mechanistic response criteria and report positive and negative pharmacodynamic findings alike. That would reduce the chance of calling a pathway inactive when the intervention never reached the relevant compartment.

The PGE_2 axis could also shape NK-cell product quality before infusion. Culture media, serum composition, feeder cells, and cytokine combinations can introduce prostanoids or turn on COX-2 in accessory cells. If manufacturing protocols don't monitor this environment, they may inadvertently select for cells with altered cAMP handling or lower receptor expression. Standardized expansion conditions, functional assays run with and without PGE_2, and orthogonal measurement of EP2/EP4 signaling might identify products intrinsically better suited to solid tumors. These quality attributes could become as important as expansion yield when comparing next-generation CAR-NK platforms.

One more point: the mechanistic model should stay open to tumor-specific variation. PGE_2 may dominate in tumors with high COX-2 activity, but it could be secondary in tumors driven mainly by TGF-β, adenosine, or hypoxia. The best intervention, then, may not be a universal PGE_2 inhibitor but a combination matched to the dominant suppressive hierarchy. Bringing together spatial transcriptomics, lipidomics, single-cell receptor profiling, and functional NK-cell assays would help show where PGE_2 sits in that hierarchy. A systems-level approach like this could turn a biologically plausible pathway into a selection strategy that can be tested clinically.

5. Conclusion and future perspectives

What emerges from the evidence is an immunosuppressive circuit—PGE_2–EP2/EP4–cAMP/PKA—that links tumor metabolism with NK-cell dysfunction. Activation is dampened, cytokine production drops, activating-receptor expression shifts, immune-synapse organization and degranulation are disrupted, target-cell killing is delayed, and chemotaxis is redirected away from inflammatory tumor regions. These changes accumulate, leaving NK cells both less cytotoxic and less likely to be where they are needed. Immune escape, in this setting, is not a single defect but the combined result of weak effector function and limited spatial access [3, 9, 42].

COX-2/mPGES-1 inhibition, EP2/EP4 blockade, and engineering NK cells to be intrinsically PGE_2-resistant interrupt the circuit at different points. Future work, in our view, should combine spatial PGE_2 measurements with functional profiling of NK cells, validate biomarkers in patient-derived samples, and clarify which combinations produce durable tumor control rather than transient immune activation. A clinically useful PGE_2 strategy is likely to depend on pathway-based patient selection, pharmacodynamic monitoring, and an explicit distinction between direct tumor effects and effects that run through NK cells.

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