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Commentary

Targeting mPGES-1 as a New Strategy against Neuroblastoma

Valentina Comunanza [a,b,*]

[a] Department of Oncology, University of Torino, Candiolo, Italy
[b] Candiolo Cancer Institu - FPO, IRCCS, Candiolo, Italy

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Metastatic neuroblastoma is a developmental cancer and among the most common and deadly childhood solid tumors. Although the survival rate for low- and intermediate-risk patients is excellent, patients with high-risk disease are associated with poor prognosis underscoring the need to identify new therapeutic strategies [6]. The involvement of chronic inflammation in the initiation and progression of solid childhood cancers has not yet been well established, while in adult tumors of epithelial origin the contribution of inflammation and proinflammatory signals has been well characterized [7]. Inflammatory mediators can be produced by the stroma, or directly by cancer cells themselves, and among the pro-cancerous cytokines prostaglandin E2 (PGE2) plays a prominent role. PGE2 is a proinflammatory lipid prostanoid that contributes to tumor progression and aggressiveness by driving immune suppression and angiogenesis [7]. Indeed, clinical and epidemiologic evidence report that daily use of nonsteroidal anti-inflammatory drugs (NSAIDs) have a protective effect against cancer, reducing the incidence, metastasis and mortality of various solid tumors [3]. However, the inhibition of cyclooxygenase enzymes (COX-1/COX-2) not merely hinders the production of PGE2 by tumor and stromal cells, but also alters the production of other distinct prostanoids and thromboxane. Given the known effects of prostaglandins on cardiovascular function, there has been concern of the potential for cardiotoxity with any inhibitor of prostaglandin biosynthesis used as anticancer agents [4] hypothesizes a novel avenue to inhibit the biosynthesis of PGE2 and overcome adverse effects on the gastrointestinal tract and cardiovascular system associated with the use of NSAIDS. Selective inhibition of the terminal synthase prostaglandin E synthase-1 (mPGES-1) should have very low, if any, toxic side effects typically associated with COX-2 inhibitors [1] and this has provided the rationale for this recent in vivo study "Inhibition of microsomal prostaglandin E synthase-1 in cancer-associated fibroblasts suppresses neuroblastoma tumor growth" [4]. They focused on the impact of specific pharmacological inhibition of mPGES-1 in preclinical models of neuroblastoma using a non-toxic single drug treatment, Compound III. They demonstrated that targeting selectively infiltrating cancer-associated fibroblasts (CAFs), the main source of mPGES-1, dampens the associated PGE2 production and reduces tumor progression both in a prophylactic setting of treatment and in the treatment of established tumors. These findings have obvious therapeutic implications for cancer treatment. Of interest, decreased PGE2 concentration has a direct effect not only on tumor cell proliferation and cell death but induces deep alterations in the tumor microenvironment. Beyond impairing angiogenesis, mPGES-1 inhibition reduces CAF infiltration and migration through a mechanism that interferes with downstream autocrine signaling via a G-protein coupled EP4 receptor upon pro-inflammatory stimulus by cytokine IL-1b signaling.

Moreover several lines of evidence support the involvement of PGE2 in the crosstalk between tumor cells and infiltrating leucocytes. In particular, tumor-derived PGE2 secretion directly induces the production of known cancer-sustaining factors such as IL-6, CXCL1 and G-CSF by myeloid cells that polarize macrophages to an M2 activation state, promoting immune evasion and potentially enable tumor cells to evade host immune response [8]. In accordance to this [4] show that mPGES-1 inhibition also exerts an important immunomodulatory role, reverting the M1/M2 macrophage polarization phenotype and shifting the tumor microenvironment to one with anti-tumor activity.

Interestingly, mPGES-1 inhibition is able to simultaneously modulate three different, but strictly connected, tumor microenvironment compartments. In accordance with this, it has been recently demonstrated that targeting tumor vasculature, with anti-VEGF therapy in association with an BRAF inhibitor, deeply influences another two biological processes: the recruitment of M1-polarized macrophages and the infiltrations of CAFs [2].

The results of this work indicate that therapeutic strategies targeting mPGES-1 could be very attractive, in particular, for a subset of neuroblastoma tumors. The therapy-resistant subset of patients with chromosome 11q-deletion are inflammatory-driven and characterized by the

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* Corresponding author.
E-mail address: valentina.comunanza@ircc.it.

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activation of COX/mPGES-1/PGE2 pathway and higher level of PGE2 expression, that correlate with metastatic stage and poor clinical outcome [5]. At the same time, the application of this strategy could be used to treat a wide variety of tumors since elevated levels of mPGES-1, and its enzymatic product PGE2, have been found in several cancers including colorectal cancers (CRC), non-small cell lung cancer (NSLC) and prostate cancer.

The inhibition of mPGES-1 could be used in combination with existing therapies such as standard chemotherapies, targeted therapies, or immunotherapies to open up new treatment strategies.

Although further studies are warranted to evaluate the desired synergistic effect of such combined treatments, the findings from the Kogner laboratory provide a significant advance in the field of oncology by bringing forth a potentially promising therapeutic approach against neuroblastoma.

Disclosure

The author declares no conflicts of interest.

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