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Inflammatory mediator prostaglandin E_2 in colorectal cancer

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Abstract

It is widely accepted that dietary fats and chronic inflammation are risk factors for developing colorectal cancer. Arachidonic acid is a major component of animal fats and the bioactive lipids produced from this substrate play critical roles in a variety of biologic processes, including cancer. Cyclooxygenase-derived prostaglandin E_2 (PGE_2) is a known pro-inflammatory lipid mediator and promotes tumor progression. Metabolism of arachidonic acid by the cyclooxygenase pathway provides one mechanism for the contribution of dietary fats and chronic inflammation to carcinogenesis. In this review, we highlight recent advances in our understanding of how pro-inflammatory mediator PGE_2 promotes colorectal cancer immune evasion. These findings may provide a rationale for the development of new therapeutic approaches to subvert tumor-induced immunosuppression.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignant neoplasm and the second leading cause of cancer deaths in the USA. Currently, the most effective treatment for CRC, including various approaches using surgical resection, radiation, and/or chemotherapy, works best when the disease is detected at a very early stage. Although colonoscopy screening is an effective way to detect and prevent CRC by removing precancerous adenomas, even today over fifty percent of patients still present to their physician with advanced cancer when standard treatments are not as effective resulting in low 5-year survival rates. Thus, we have always known that a more effective approach to control cancer is to develop improved prevention and early detection measures. Chemoprevention and cancer vaccines have been considered plausible approaches for cancer prevention. A significant effort has been made in the development of novel drugs for both cancer prevention and treatment over the past two decades. One group of compounds found to have beneficial effects on reducing the risk of developing some solid tumors including the four most prevalent cancers worldwide (colorectal, breast, lung, and prostate cancer) is nonsteroidal anti-inflammatory drugs (NSAIDs), which primarily target the cyclooxygenase

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Conflict of Interests

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enzymes (COX-1 and COX-2). Epidemiologic and clinical studies have demonstrated that long-term use of NSAIDs reduces the relative risk of CRC by 40-50% (Smalley and DuBois, 1997). Unlike COX-2 selective inhibitors (COXIBs) and other nonselective NSAIDs, long-term daily aspirin use is beneficial for prevention of both CRC and cardiovascular diseases. Treatment of FAP patients with celecoxib significantly reduced the polyp burden (Steinbach et al., 2000), while daily use of aspirin significantly suppressed polyp growth in FAP patients (Burn et al., 2011a) and substantially reduced cancer incidence in patients with Lynch syndrome (Burn et al., 2011b). In sporadic CRC, four randomized controlled trials demonstrated that aspirin use reduced risk of adenoma recurrence in patients with a history of colorectal adenomas (Baron et al., 2003; Benamouzig et al., 2003; Logan et al., 2008; Sandler et al., 2003). More intriguingly, recent observational and clinical studies revealed that daily use of aspirin was associated with a reduced risk of metastatic spread (Algra and Rothwell, 2012) and inhibited the spread of primary tumor cells to other organs after the diagnosis of localized disease, in particular CRC (Rothwell et al., 2012), suggesting the potential therapeutic efficacy of NSAIDs in advanced CRC. Furthermore, epidemiologic studies showed that regular use of aspirin specifically reduced risk of the subgroup of patients whose colon tumors expressed COX-2 at higher levels (Chan et al., 2007) and its use after the diagnosis of CRC at stage I, II and III prolonged overall survival, especially among individuals whose tumors overexpress COX-2 (Chan et al., 2009). These results suggest that the preventive and inhibitory effects of aspirin on CRC might depend on the presence of COX-2. COX-2 expression is elevated in approximately 50% of colorectal adenomas and 85% of adenocarcinomas (Eberhart et al., 1994; Gupta and Dubois, 2001; Marnett and DuBois, 2002) and is associated with a worse survival among CRC patients (Ogino et al., 2008).

Cyclooxygenase enzymes catalyze the conversion of arachidonic acid into prostanoids, including prostaglandins (PGs) and thromboxane A_2 (TxA_2). These bioactive lipids exert their biological effects in autocrine and/or paracrine manner by binding to their cognate cell surface receptors that belong to the G protein-coupled receptors (Fig. 1). It has been hypothesized that some of the adverse cardiovascular effects related to NSAID use are associated with a global reduction in prostanoid production (Fitzgerald, 2004). One possible way to avoid these undesired effects is to only target COX-derived prostanoids that mediate the tumor-promoting effects. Among prostanoids, pro-inflammatory PGE_2 plays a predominant role in promoting tumor growth in colorectal cancer. PGE_2 is the most abundant PG found in various types of human malignancies including colon, lung, breast, head and neck cancer and is often associated with a poor prognosis (Hambek et al., 2007; McLemore et al., 1988; Rigas et al., 1993; Wang and Dubois, 2004). A urinary PGE_2 metabolite (PGE-M) has been used as a promising biomarker for CRC (Cai et al., 2006; Johnson et al., 2006) and other cancer patients (Dong et al., 2009; Kekatpure et al., 2009; Kim et al., 2013; Morris et al., 2013). The steady-state accumulation of PGE_2 in tumor tissues depends on the relative rates of COX-2/PGE synthase-dependent biosynthesis and 15-hydroxyprostaglandin dehydrogenase (15-PGDH)-dependent degradation (Fig. 1). 15-PGDH is highly expressed in normal tissues but is ubiquitously lost in many human cancers including colorectal cancer (Backlund et al., 2005; Yan et al., 2004), lung (Ding et al., 2005) and transitional bladder cancer (Gee et al., 2003). Loss of 15-PGDH in these tumor tissues

results in increased endogenous PGE_2 levels. More importantly, epidemiologic studies revealed that levels of urinary PGE-M in healthy humans (Murphey et al., 2004) and breast cancer patients (Kim et al., 2013; Morris et al., 2013) are suppressed significantly not only by treatment with nonselective NSAIDs, including aspirin, but also by COXIBs, suggesting that the majority of PGE_2 formed *in vivo* may be derived from COX-2.

Direct evidence that PGE_2 promotes tumor growth came from our previous work and other studies showing that PGE_2 treatment dramatically increased both small and large intestinal adenoma burden in $Apc^{Min/+}$ mice and significantly enhanced AOM-induced colon tumor incidence and multiplicity (Kawamori et al., 2003; Wang et al., 2004). Furthermore, elevated endogenous PGE_2 by genetic deletion of *15-Pgdh* promotes colon tumor growth in $Apc^{Min/+}$ and AOM mouse models (Myung et al., 2006). In contrast, inhibition of endogenous PGE_2 by genetic deletion of PGE_2 synthase (*mPges-1*) suppresses intestinal tumor formation and growth in $Apc^{Min/+}$ and AOM models (Nakanishi et al., 2008). The central role of PGE_2 in colorectal tumorigenesis has been further confirmed by evaluating mice with a homozygous deletion of individual PGE_2 receptors (Mutoh et al., 2002; Sonoshita et al., 2001; Watanabe et al., 1999). PGE_2 has been shown to promote tumor formation, growth, and metastasis through 1) directly inducing tumor epithelial cell proliferation, survival, and migration/invasion as well as epigenetic changes and 2) switching the tumor microenvironment from “normal” to one supporting tumor growth and metastatic spread by inhibiting immunosurveillance and inducing angiogenesis (Wang and DuBois, 2010; Xia et al., 2012). Given that PGE_2 appears to play a dominant role in carcinogenesis, more selective pharmacological inhibition of PGE_2 production and signaling may be efficacious and may avoid some of the cardiovascular side effects associated with NSAIDs and COXIBs.

The roles of PGE_2 in colon tumor epithelial cells and tumor-associated angiogenesis have been summarized in recent reviews (Wang and Dubois, 2006; Wang and DuBois, 2010). In this review, we highlight recent breakthroughs in our understanding of the role of PGE_2 in tumor-induced immunosuppression.

PGE_2 AND IMMUNE CELLS

CRC formation and progression depends on the escape from the host immuno-surveillance. Cross talk between transformed epithelial cells and their surrounding stromal cells switch a normal tissue microenvironment to tumor microenvironment that supports tumor growth and spread by inducing angiogenesis and/or immune evasion. Similar to other solid tumors, the CRC immune evasion involves a shift from Th1 to Th2 immune responses, a defective antigen-presenting cell (APC) function, impaired cytotoxic activity of $CD8^+$ T cells and nature killer (NK) cell activity, and enhancement of immunosuppressive cells such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Emerging evidence supports the concept that PGE_2 signaling is one of essential pathways that govern tumor-mediated immune dysfunction. Overall, PGE_2 contributes to a shift in the tumor microenvironment from anti-tumor responses to immunosuppressive responses (Fig. 2).

Antigen-presenting cells

Antigen-presenting cells (APCs) include dendritic cells (DCs), monocytes/macrophages and B cells.

Dendritic cells—Dendritic cells (DCs), including myeloid dendritic cells (MDCs) and plasmacytoid dendritic cells (PDCs), are thought to participate in tumor immunity by inducing primary and secondary T cell responses as well as immune tolerance (Banchereau and Steinman, 1998). Reduced DC numbers and activity affects the prognosis of patients with CRC (Della Porta et al., 2005; Huang et al., 2003). Mature DCs interact with antigen-specific T cells that initiate a Th1-type immune response. For example, mature DCs pulsed with tumor cell lysate can induce tumor-specific cytotoxic T cell (CTL) activity that inhibits colon tumor growth both *in vitro* and in mice implanted subcutaneously with CT26 colon tumor cells (Wu et al., 2010). Immature dendritic cells (iDCs) exhibit reduced phagocytic ability and reduced antigen presentation to T cells (Pockaj et al., 2004) and promote tumor angiogenesis by secreting proangiogenic cytokines (Curiel et al., 2004). In breast cancer patients, PGE_2 levels are positively correlated with inhibition of DC maturation (Pockaj et al., 2004).

PGE_2 modulates the activities of DCs by altering their differentiation, maturation, and their ability to secrete cytokines (Fig. 3). PGE_2 has been shown to induce intestinal immune tolerance via DCs *in vivo* (Chinen et al., 2011). In tumor implantation models of colon and lung cancers, PGE_2 promoted tumor growth by suppressing differentiation of DCs from bone marrow progenitors (Yang et al., 2003). A recent study revealed that PGE_2 inhibited DC differentiation via downregulation of retinal dehydrogenases (RALDH) *in vitro* and *in vivo* (Stock et al., 2011). RALDH is the enzyme responsible for synthesis of retinotic acid (RA) that is required to modulate intestinal DC function. Another study reported that PGE_2 inhibited LPS-induced DC maturation via blocking LPS-induced indoleamine 2,3-dioxygenase (IDO), IL-12 p70, and TNFα expression as well as the mature markers such as CD80, CD86 and MHC class I in murine bone marrow-derived DCs (BM-DCs) (Jung et al., 2010). Multiple i*n vitro* studies elucidated the mechanisms underlying PGE_2 inhibition of DC function. PGE_2 switches the function of DCs from induction of immunity to T-cell tolerance via upregulation of CD25 and IDO (von Bergwelt-Baildon et al., 2006). PGE_2 inhibits the antigen presentation ability of bone marrow-derived DC (BM-DC) by up-regulation of IL-10 (Harizi et al., 2002). Furthermore, PGE_2 shifts the IL-12/IL-23 balance in DCs via EP2 and EP4 receptors in favor of IL-23, which in turn increases the number of Th17 cells *in vitro* (Sheibanie et al., 2007). IL-12 promotes Th1 responses and suppresses Th17 development and function whereas IL-23 is essential for Th17 expansion and survival. Similarly, PGE_2 inhibits secretion of IFNα by Toll-like receptor (TLR)-activated PDCs via EP2/4, which results in reduction of Th1 cytokine secretion and induction of Th2 cytokine secretion by T cells (Fabricius et al., 2010). PGE_2 also inhibits the ability of DCs to produce CCL19 that attracts CCR7-expressing naïve $CD4^+$ T cells (Muthuswamy et al., 2010). More interestingly, PGE_2 has been recently showed to redirect the differentiation of human DCs into monocytic MDSCs (Obermajer et al., 2011a). This body of work strongly supports the notion that PGE_2 represents a crucial signaling pathway regulating DC differentiation, maturation, and function.

Macrophages—Macrophages are highly plastic and can be activated to either M1 (Th1 response) or M2 (Th2 response) polarization states depending on the microenvironment stimuli. The M1 designation is given for classically activated macrophages characterized by elevated expression of IL-12, TNFα, IL-23, and MHCII. Also, M1 macrophages typically generate reactive nitrogen (NO) and oxygen intermediates (ROI) to counteract pathogens and tumor cells. In contrast, the M2 designation is for alternatively activated macrophages expressing high levels of IL-10, IL-4, and IL-13. In most cancers, tumor associated macrophages (TAMs) resemble an M2-like phenotype (Mantovani et al., 2002) and are a major component of the leukocytic tumor infiltrate. TAMs are recognized as a poor prognostic sign in various tumors, including CRC (Bacman et al., 2007; Qian and Pollard, 2010). It has be well established that TAMs promote cancer progression and metastasis through supporting tumor-associated angiogenesis, enhancing tumor cell migration, invasion, and intravasation, and suppressing immuno-surveillance (Qian and Pollard, 2010).

Limited data are available on the regulation of macrophage function by PGE_2. In a colon tumor implantation model, overexpression of 15-PGDH in tumor tissue is sufficient to redirect the differentiation of intratumoral CD11b cells from immunosuppressive M2-oriented TAMs to M1-oriented macrophages (Eruslanov et al., 2009), suggesting that PGE_2 can alter the differentiation of monocytes favoring the development of M2-type TAMs at the tumor sites. In a spontaneous murine model of gastric cancer, PGE_2 and bacterial infection promote tumor growth by cooperatively recruiting macrophages into tumors via up-regulation of CCL2 expression (Oshima et al., 2010). An *in vitro* study showed that treatment of LPS-activated macrophages with PGE_2 diminished LPS-induced TNFα expression, suggesting that PGE_2 can downregulate cell-mediated immune responses (Th1 response) (Kunkel et al., 1988). These studies suggest that PGE_2 may be able to recruit monocytes/macrophages to tumor sites and shift them into M2-type macrophages (Fig. 3). Moreover, PGE_2 is able to inhibit alveolar macrophage phagocytosis via multiple signaling pathways such as EP2-cAMP (Aronoff et al., 2004), PTEN (Canetti et al., 2007), and IL-1R-associated Kinase-M (Hubbard et al., 2010). However, there is no direct evidence demonstrating that PGE_2 regulates macrophage function during tumor initiation and progression.

B cells—B cells not only function to produce antibodies against antigens but also as important APCs for CD4 and CD8 T cells. At present, little is known about the role of B cells in human CRC and other solid tumors. In tumor implantation mouse models of CRC, B cell-deficient mice exhibit spontaneous regression of tumor growth as compared to WT mice (Shah et al., 2005), suggesting that B cells promote tumor growth.

PGE_2 is able to inhibit B cell development *in vivo* (Shimozato and Kincade, 1999). *In vitro* studies further reveal that PGE_2 promotes B cell receptor (BCR)-induced apoptosis in immature B cells and inhibits BCR-stimulated proliferation of mature B cells via EP4 (Brown et al., 1992; Murn et al., 2008; Prijatelj et al., 2011) and B cell activation (Roper and Phipps, 1992). In addition, PGE_2 promotes the production of switched isotypes in B cells. For example, PGE_2 significantly induces IgG1 production in resting B cells and uncommitted B cells expressing high levels of surface IgM (Roper et al., 2002). PGE_2 also induces activated B cell Ig isotype switching to IgE (Roper et al., 1995). The PGE_2

induction of IgG1 and IgE supports the notion that PGE_2 acts predominantly to induce Th2 responses (Fig. 3). In the context of the colonic tumor microenvironment, however, the precise role of PGE_2 in B cells has not been investigated.

Natural killer cells

Although NK cells are functionally similar to cytotoxic T cells, NK cells are able to kill transformed or virus-infected cells but spare normal cells without prior sensitization. Suppressed NK cell activity has been found in human CRC and is an important prognostic factor for the development of distant metastases (Espi et al., 1996; Kondo et al., 2003).

Multiple lines of studies have investigated the effects of PGE_2 on NK cells (Fig. 4). I*n vivo* studies showed that treatment of rats with PGE_2 inhibited NK cell activity and enhanced lung metastases (Yakar et al., 2003) and reversed the effects of a NSAID on enhancing NK cell activity (Voth et al., 1986). A recent report revealed that EP4 receptor mediated the effects of PGE_2 on suppression of NK cell function and promoted breast cancer metastasis in a syngeneic murine model of metastatic breast cancer (Ma et al., 2013). Several *in vitro* studies have demonstrated that PGE_2 suppresses NK cell function (Bankhurst, 1982; Goto et al., 1983). PGE_2 not only directly inhibits NK cells to produce INFγ, which is essential for NK cell functions, but also attenuates IL-12-induced or IL-18-induced INFγ expression in NK cells via EP2 receptor (Mailliard et al., 2005; Walker and Rotondo, 2004). Moreover, PGE_2 inhibits IL-15-activated human NK cell function through downregulation of common gamma-chain (Joshi et al., 2001) and hepatic NK cell activities (Liu et al., 2000). PGE_2 reduces the cytotoxic activities of NK cells by inhibiting NK receptors (NKR) including NKG2D, CD16 and natural cytotoxicity receptors (NCR: NKp30, NKp44, NKp46) (Martinet et al., 2010).

Myeloid-derived suppressor cells

MDSCs are a heterogenous population of immature myeloid cell that suppress T and NK cell functions. The levels of MDSC in the blood are positive correlated with clinical cancer stage and metastatic tumor burden in mice and patients including colon cancers (Diaz-Montero et al., 2009; Mandruzzato et al., 2009). It is widely accepted that myeloid-derived suppressor cells (MDSCs) contribute to cancer immune evasion via suppressing functions of T and natural killer (NK) cells (Gabrilovich and Nagaraj, 2009). Emerging evidence demonstrates that MDSCs are also able to promote the development of Foxp3 positive Treg cells (Huang et al., 2006).

It has been reported that PGE_2 promoted tumor progression via inducing the differentiation of MDSCs from bone marrow myeloid progenitor cells, whereas inhibition of PGE_2 signaling by deletion of EP2 or its antagonists blocked this differentiation in mice with implanted 4T1 mammary carcinoma (Sinha et al., 2007) (Fig. 4). Similarly, treatment of tumor-bearing mice with a COX-2 selective inhibitor prevented the local and systemic expansion of MDSCs *in vivo* (Veltman et al., 2010). *In vitro* studies showed that PGE_2 induced arginase I expression via EP4 in MDSCs (Rodriguez et al., 2005). Arginase I is involved in MDSC-mediated immune suppression by blocking effector T cell function. PGE_2 also mediates the Fas ligation-induced MDSC recruitment in 3LL Lewis lung

carcinoma (Zhang et al., 2009) and is required for CXCL4-induced MDSC chemotaxis via induction of CXCR4 expression on MDSCs (Obermajer et al., 2011b). However, the mechanism(s) by which PGE_2 regulates MDSC differentiation, expansion, and suppressive functions in cancers remains unclear.

T cells

T helper cells—The progression of human CRC is associated with imbalance in Th1/Th2 responses with reduced production of cytokines from Th1 cells and normal or even elevated levels of cytokines from Th2 cells (O'Hara et al., 1998; Pellegrini et al., 1996; Shibata et al., 2002). PGE_2 contributes to this imbalance by switching anti-tumor Th1 responses to immunosuppressive Th2 responses via downregulation of Th1 cytokines (TNFα, IFNγ, and IL-2) and upregulation of Th2 cytokines (IL-4, IL-10, and IL-6) in T helper cells (Hilkens et al., 1995; Snijdewint et al., 1993). In addition, PGE_2 exacerbates inflammation and disease severity through elevating infiltration of IL-17-producing T helper (Th17) cells to the colonic tissue in a murine model of IBD (Sheibanie et al., 2007). In mammary gland-bearing mice, PGE_2 secreted from tumor induces IL-23, which results in Th17 cell expansion in the tumor microenvironment (Qian et al., 2013). In addition, PGE_2 can facilitate IL-23-induced Th17 expansion from peripheral blood mononuclear cells and naive T cells *in vitro* (Boniface et al., 2009; Chizzolini et al., 2008). PGE_2 also directly promotes differentiation of memory $CD4^+$ T cells to Th17 cells by induction of IL-17 expression and reduction of INFγ expression (Napolitani et al., 2009). PGE_2 induces Th1 cell differentiation and Th17 cell expansion *in vitro* and treatment with an EP4 antagonist reduces accumulation of both Th1 and Th17 cells in regional lymph nodes and suppresses the disease progression in an animal model of chronic inflammation (Yao et al., 2009). However, relative little is known about the impact of PGE_2 on the imbalance of Th1/Th2 response and Th17 cells in tumor microenvironment.

$CD8^+$ T cells—The massive infiltration of $CD8^+$ T cells at the site of tumors is significantly associated with a better survival of CRC patients (Naito et al., 1998). Although much less is known about directly suppressive effects of PGE_2 on $CD8^+$ T cells, a few reports indicated that PGE_2 can directly inhibit $CD8^+$ T cell proliferation (Hendricks et al., 2000) and the cytotoxic activity of $CD8^+$ T cells via upregulation of CD94 and the NKG2A complex *in vitro* (Zeddou et al., 2005). PGE_2 also attenuates TCR-induced IFNγ release from $CD8^+$ T cells (Ganapathy et al., 2000). Reduction of IFNγ production favors type-2 responses in general. In addition to the direct effects of PGE_2 on $CD8^+$ T cells, PGE_2 produced by cancer cells and their surrounding stromal cells can also indirectly abolish the anti-tumor effects of cytotoxic T cells *in vivo* and *in vitro* through downregulation of both direct antigen presentation by tumor cells and cross-presentation by APCs such as DCs (Ahmadi et al., 2008).

Regulatory T cells—Regulatory T cells (Tregs) are essential for suppressing immune responses and maintaining self-tolerance by regulating the activity of other immune cells. The frequency and suppressor function of Tregs are elevated in the peripheral blood and at the tumor sites of cancer patients including CRC (Strauss et al., 2007; Wolf et al., 2003). There is a positive correlation between PGE_2 levels and the numbers of $Foxp3^+$ Tregs in

peripheral blood, tumor tissues and draining lymph nodes of CRC patients (Yaqub et al., 2008).

In the polyps of *Apc*Δ^{468} mice, Tregs shift from a protective anti-inflammatory ($CD4^+CD45RB^{low}CD25^{high}$) to a cancer-promoting pro-inflammatory phenotype ($CD4^+CD25^+Foxp3^+$) (Gounaris et al., 2009). In a mouse model, deletion of *mPges-1* gene suppresses AOM-induced colon carcinogenesis accompanied with reduced frequency of $CD4^+Foxp3^+$ Tregs in the draining mesenteric lymph nodes and serum PGE_2 levels (Nakanishi et al., 2011), indicating that PGE_2 may enhance tumor growth via expansion of Tregs. Moreover, PGE_2 can directly enhance the differentiation of naïve $CD4^+$ T cells into FOXP3-positive Tregs *in vitro* and induce FOXP3 expression and Treg activities in lung cancer *in vivo* (Baratelli et al., 2005; Sharma et al., 2005). PGE_2 has also been reported to indirectly attract $FOXP3^+$ Tregs via induction of CCL22 in mature DCs (Muthuswamy et al., 2008) (Fig. 3). Interestingly, $CD4^+CD25^+Foxp3^+$ Tregs produce PGE_2 and suppress effector T cell responses in a PGE_2-dependent manner (Mahic et al., 2006). In addition, treatment with an EP4 antagonist resulted in a decreased number of Tregs in LNs and the skin after UV irradiation (Soontrapa et al., 2011), suggesting that EP4 mediates the effect of PGE_2 on Treg expansion. An *in vitro* study indicated that PGE_2 secreted from breast cancer cells induced Treg cell migration (Karavitis et al., 2012). Collectively, PGE_2-enhanced Treg expansion, migration, and activities provide another mechanism for contribution of PGE_2 to promotion of an immunosuppressive microenvironment (Fig. 4).

Mast cells

Although mast cells (MCs) are key effector cells in allergic diseases, it has become apparent that they also contribute to other pathologies, including cancers. Recent studies revealed that lower numbers of mast cells (MCs) are associated with hypovascularity and better survival in CRC patients (Gulubova and Vlaykova, 2009). In contrast, higher MC infiltration is associated with poor clinical outcome with increased vascularity, tumor growth and invasion in the many of human cancers including CRC (Groot Kormelink et al., 2009; Kashiwase et al., 2008). In *Apc*Δ^{468} mice, MCs have been demonstrated to be an essential component for polyp growth (Gounaris et al., 2007). These findings suggest that the infiltration of MCs into tumor contributes the tumor growth.

PGE_2 functions as a chemotactic factor for immature and mature bone marrow-derived mast cells (BMMCs) *in vitro* and *in vivo* (Weller et al., 2007). The PI3K-mTOR signaling pathway mediates the effects of PGE_2 on attracting BMMCs (Kuehn et al., 2011). Moreover, PGE_2 has been shown to enhance mast cell induction from murine spleen mononuclear cells and BMMCs as well as human umbilical cord blood mononuclear cells (Gomi et al., 2000; Hu et al., 1995; Saito et al., 1996). In addition, PGE_2 promotes release of pro-inflammatory cytokines and chemokines as well as proangiogenic factors such as IL-6, CCL2, and VEGF-A from BMMCs, human umbilical cord blood mononuclear cell-derived MCs, and spleen-derived MC (Abdel-Majid and Marshall, 2004; Gomi et al., 2000; Nakayama et al., 2006). These results indicate that PGE_2 promotes colon tumor growth via enhancing recruiting MCs, MC maturation, stimulating MCs to produce proinflammatory cytokines and chemokines as well as proangiogenic factors (Fig. 4).

Conclusions

PGE_2 promotes cancer progression via several mechanisms. PGE_2 can directly bind to its cell surface receptors on tumor epithelial cells to regulate cell proliferation, apoptosis, migration and invasion as well as to induce tumor epithelial cells to secrete growth factors, pro-inflammatory mediators, and angiogenic factors that stimulate angiogenesis and local inflammation. In addition to the direct effects of PGE_2 on tumor cells, PGE_2 also serves as an immunomodulator that shifts the tumor microenvironment from anti-tumor to immunosuppressive responses, resulting in escape of tumor cells from effective immunosurveillance.

Most cancer immunotherapies have poor clinical efficiency. The observations that use of selective COX-2 inhibitors enhances the efficacy of certain cancer vaccines (DeLong et al., 2003; Hahn et al., 2006; Zeytin et al., 2004) support a hypothesis that a major barrier to successful immunotherapies against cancer is the immune modulators secreted by cancer cells and their surrounding stromal cells, such as PGE_2. Therefore, understanding the diverse functions of PGE_2 in the tumor microenvironment is crucial for the development of novel combinational therapies aimed at targeting PGE_2 production and signaling along with immune intervention for prevention and amelioration of CRC with decreased cardiovascular side effects associated with selective COX-2 inhibitors and enhanced efficacy of immunotherapies.

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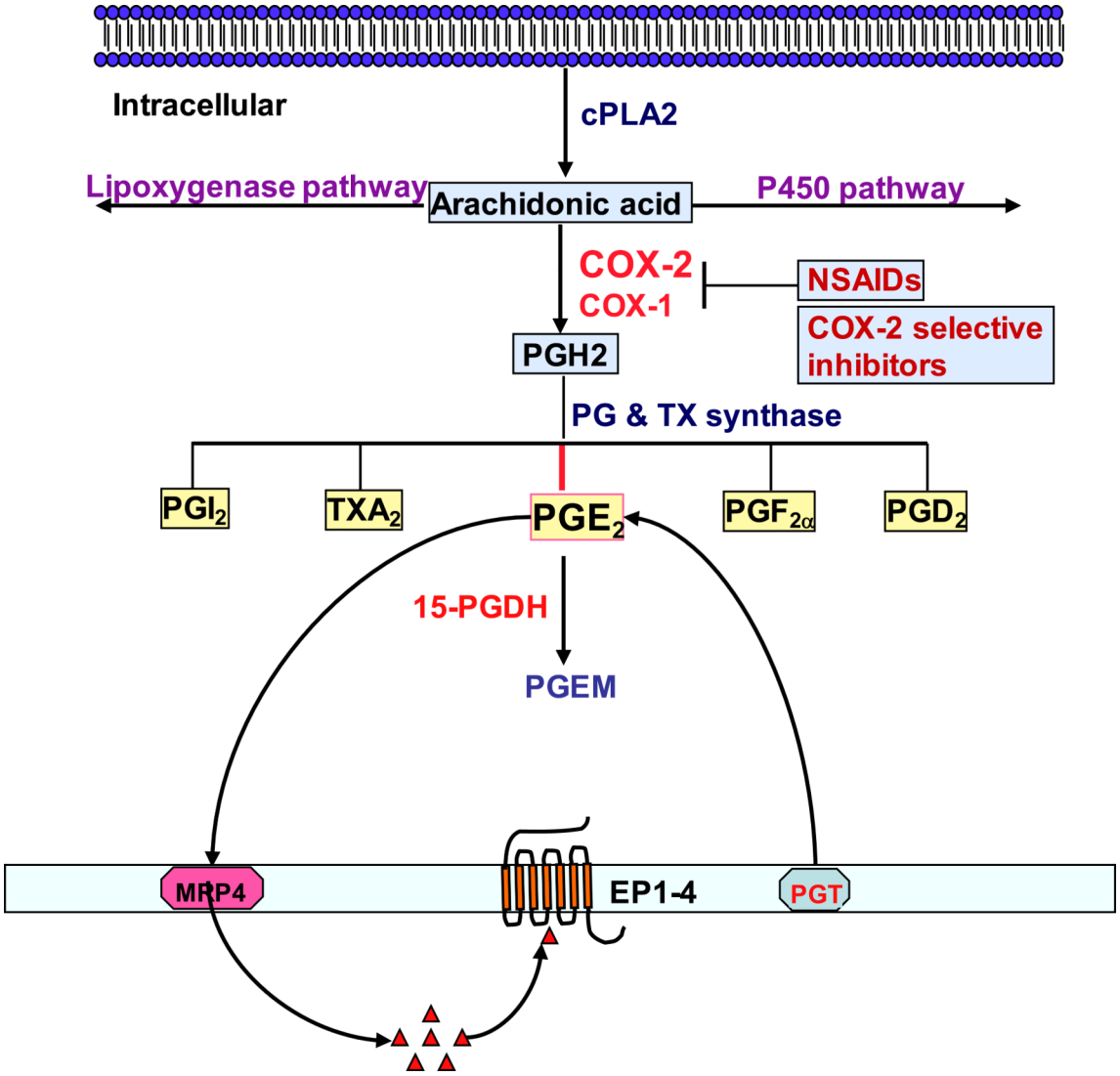

Figure 1. An overview of prostanoid synthesis pathways

Arachidonic acid (AA) is a polyunsaturated fatty acid that constitutes the phospholipid domain of most cell membranes and is liberated from the cellular membranes by cytoplasmic phospholipase A_2 (cPLA2). Free AA can be metabolized to eicosanoids through three major pathways: the cyclooxygenase (COX), the lipoxygenase (LOX), and the cytochrome P-450 monooxygenase pathway. In the COX pathway, the key step is the enzymatic conversion of the AA to intermediate PGG_2, which is then reduced to an intermediate PGH_2 by the peroxidase activity of COX. PGH_2 is sequentially metabolized to prostanoids, including prostaglandins (PGs) and thromboxanes (TXs) via specific PG and TX synthases. The MRP gene family is comprised of efflux transporters for both PGs while PGT is an influx transporter for PGs. 15-PGDH mainly metabolizes the intracellular PGE_2 and $PGF_{2\alpha}$ to a stable 13,14-dihydro-15-keto-PGA_2 (PGEM) and 13,14-dihydro-15-keto-$PGF_{2\alpha}$.

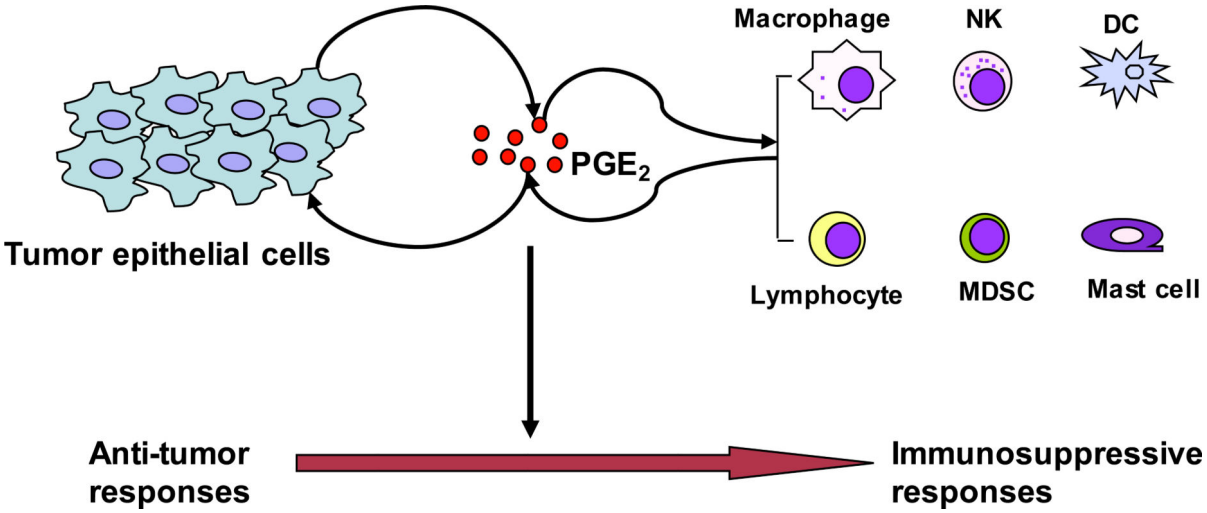

Figure 2. Models of pro-inflammatory PGE_2 in switching tumor microenvironment from anti-tumor to immunosuppressive responses

Following the initiation of epithelial tumors, the reciprocal interactions between transformed epithelial and immune cells play a key role in facilitating cancer progression. Pro-inflammatory PGE_2 produced by tumor epithelial cells and infiltrating immune cells is a key mediator in this cross talk and can accelerate tumor growth and metastasis through evading attack by the immune system.

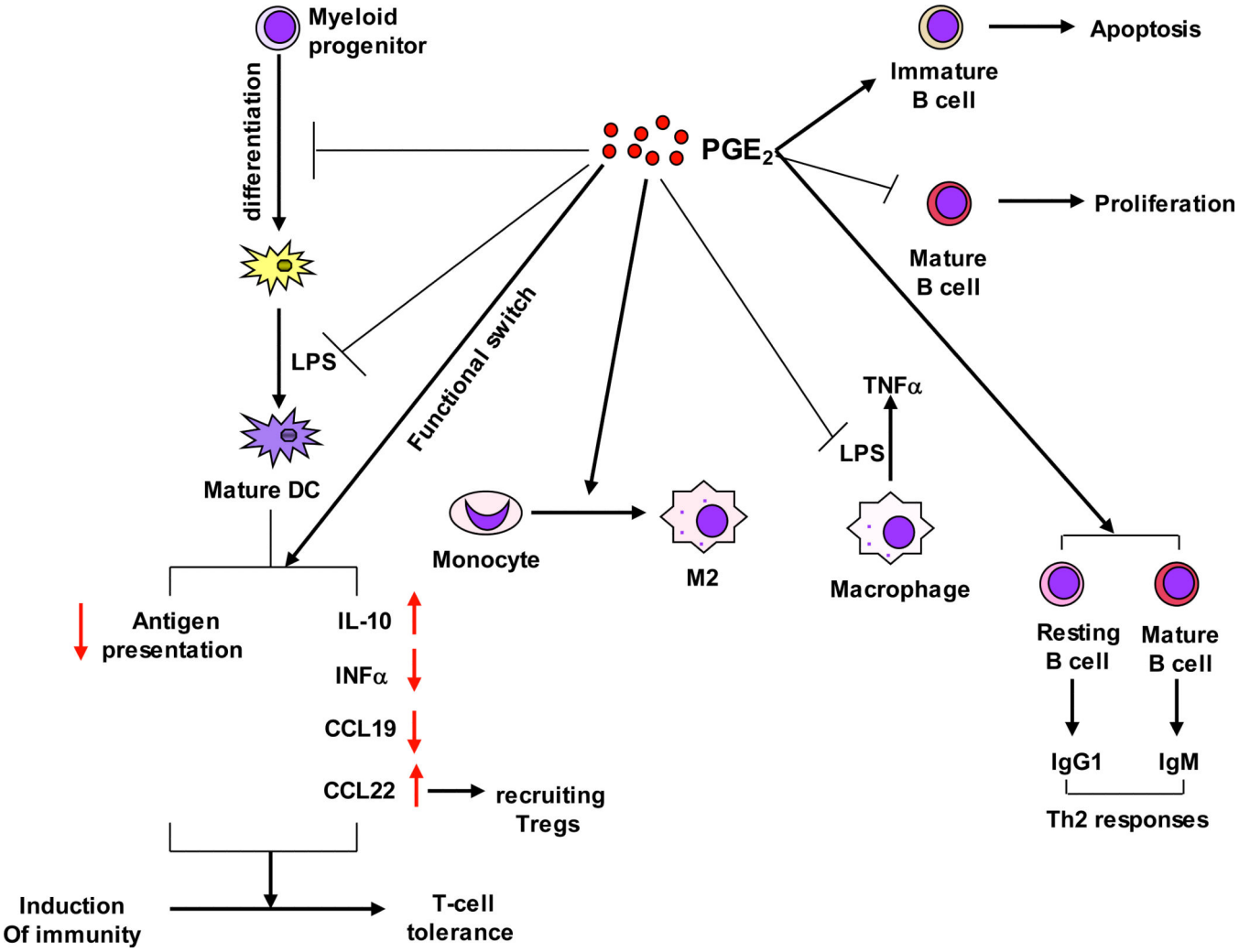

Figure 3. PGE_2 provides coordinated regulation of tumor immunosuppression

Pro-inflammatory PGE_2 produced by tumor epithelial cells and/or their surrounding stromal cells induces immunosuppression through 1) inhibiting DC differentiation, and switching the function of DCs from induction of immunity to T-cell tolerance; 2) inducing monocytes to M2 macrophages and inhibiting LPS-induced TNFα in macrophages; and 3) inhibition of mature B cell proliferation and induction of immature B cell apoptosis as well as stimulation of B cell Th2 responses.

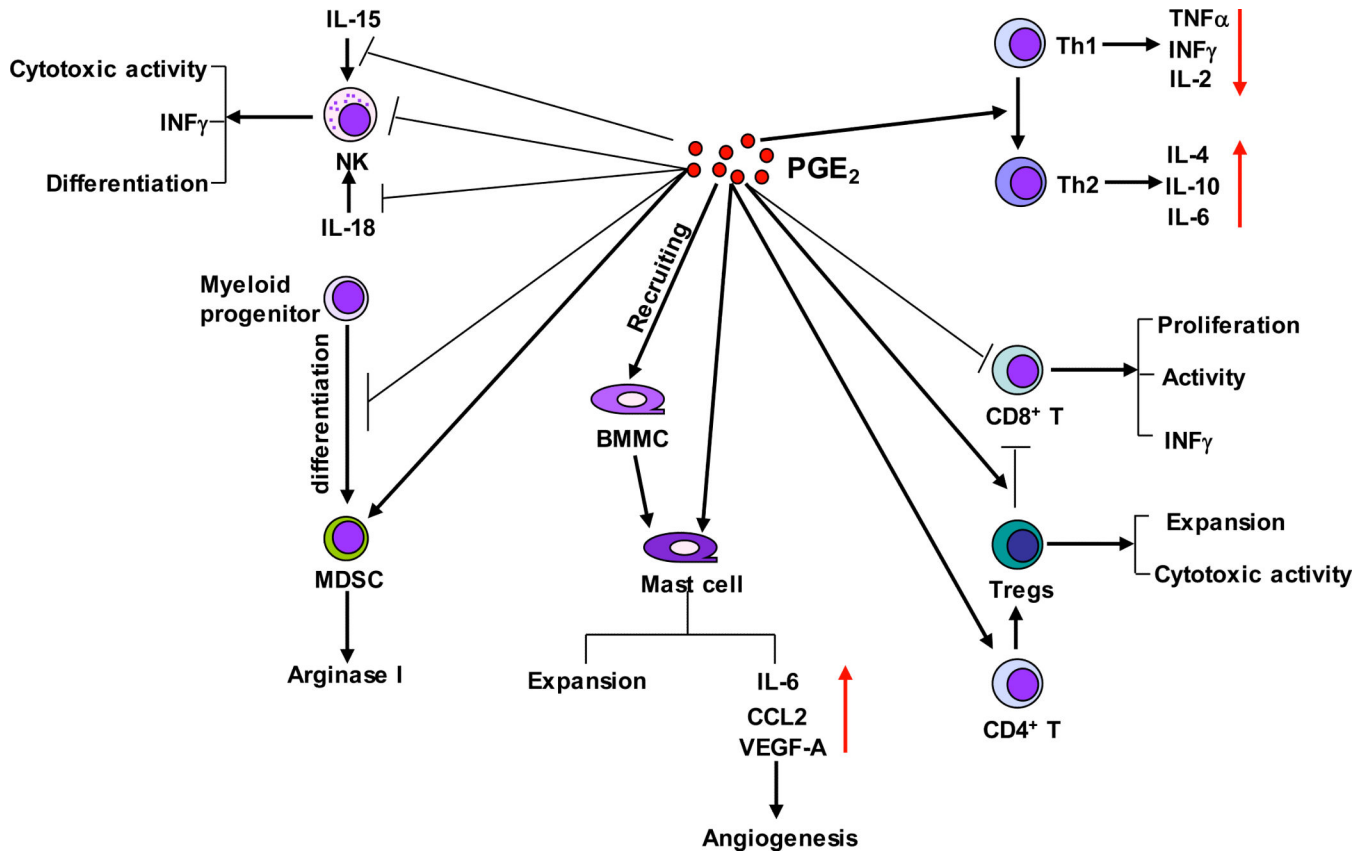

Figure 4. PGE_2 provides coordinated regulation of tumor immunosuppression

Pro-inflammatory PGE_2 produced by tumor epithelial cells and/or their surrounding stromal cells induces immunosuppression through 1) suppressing NK cell function; 2) inducing MDSC differentiation and production of arginase I; 3) recruiting BMMCs and stimulating pro-angiogenic factors; 4) downregulation of antitumor Th1 cytokines and upregulation of immunosuppressive Th2 cytokines; 5) inhibiting $CD8^+$ T cell proliferation and activity, and 6) inhibition of $CD8^+$ T cell anti-tumor functions through Tregs.