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Editorial Open Access

PTGS2 Effectively Suppress Dendritic Cell Immunity

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Abstract

Prostaglandin-endoperoxide synthase (PTGS), also known as cyclooxygenase (COX), is a key enzyme in prostaglandin biosynthesis,regulates dioxygenase and peroxidase activity. The major metabolites of PTGS2 are PGE2, PGF2, PGD2, PGI2, and TXA2. All of these are steroid and act as immunosuppressive agentsbut differ in their regulation of expression and tissue distribution. It is a well-known fact that PTGS2 prompt and aggrandize the cancer condition by proliferation, differentiation, and migration of carcinogenic cells in different organs in animals including human, therefore considered as a novel target for the prevention of cancer. Several researchers have discoverednumerous pharmacological inhibitors of PTGS2 to prevent the cancer,however prevention and treatment of cancer by inhibiting PTGS2 from dendritic cell has not been properly studied. Therefore, indirect/direct molecular silencing of PTGS2 by siRNA/shRNA or PTGS2 knockout from DC to prevent cancer means PTGS2 mediated DC vaccine may be an attractive approach to prevent cancer in near future.

Keywords: PTGS2; Dendritic Cell; Immunity; Cancer

Abbreviations

KO: Knockout; KD: Knockdown; DC: Dendritic Cell; MDCC: Myeloid Derived Suppressor Cell; CD: Cluster of Differentiation; MHC: Major Histocompatibility Complex; MMP: Matrix Metalloproteinase

Editorial

Dendritic cells (DC) are a special type of leukocytic immune sentinel able to aware the immune system for the presence of infections and play a central role in the initiation of both innate and adaptive immune responses [1-3].Nowadays, DC isconsidered as potential candidate for vaccine preparation against cancer and autoimmune diseases[4-5].Cox2 dampen the immune function of several immune cells including dendritic cell[6-7].Increased amounts of COX2 are commonly found in both premalignant tissues and malignant tumors such as lung, breast, prostate, ovary, head, neck, skin, and colorectal cancer [8-20].As a potential inducers of oncogenes, growth factors, and tumor promoters, COX2 affects many processes involved in carcinogenesis, therefore become an attractive therapeutic target. It induces xenobiotic metabolism, angiogenesis, apoptosis, inflammation, immunosuppression, and invasiveness [21].While ample clinical and experimental data support the critical role of COX2 inthe prevention of cancer[13-20], the therapeutic strategy to inhibit PTGS2 in DC to prevent cancer remain to be clarified. Therefore, understanding the mechanism how PTGS2 prevent cancer via DC mediated immunity is a matter of utmost importance.

PTGS2/COX2 is highly induced in different types of cancerous cell and promotes cancer in diverse animals [22-25].Previous studies have shown that PTGS2prompt cancer by inducing immunosuppressive environment [26,30].Recently, it has been shown that, PTGS2 decrease the immune function of T-cell by expressing Foxp3 [27]. Interestingly, PTGS2found to be highly induced in dendritic cell. DC are present in the processed antigen [28], stimulate T-cell to maintain constant immune protection against foreign antigen. PTGS2 highly induced in DCto prevent the immunostimulatory capacity [29-30] and the DC highly express PTGS2are unable to stimulate T-cell against cancer. Interestingly, when COX2 expression dampens or reduces by any means (such as, pharmacological inhibition, KD, KO) from DC, it restores the capacity to stimulate T-cell against cancer and several experiments show that when PTGS2 inhibitor used in DC it can prevent cancer compared of wild type DC[29,30].

High expression of PTGS2 suppresses the immune function of DCthrough the production of several immunosuppressive steroids metabolites such as, PTGS2 like PGG2, PGE2, and PGH2 [21]. PGE2 is the main culprit from them who made the immunosuppressive environment by expressing FOXp3 in DC and these types of DC ultimately fails to stimulate T-cell. Again excessive expression of PTGS2 leads to huge secretion of immunosuppressive cytokines IL10 [30] and maintain immune suppressive tumor microenvironment to protectthe tumor cell and reduce the stimulatory capacity of DC and at the same time prevent the pro-inflammatory cytokine secretion, responsible for T-cell stimulation.

Simultaneously, high amount of PTGS2 produce excessive PGE2 that's enhances production of MDCC (Myeloid derived DC) to suppress immune response[31]. Usually, immature DC shows lower level of MHC and co-stimulatory molecules whereas mature DC hasincreasedlevel of MHC and costimulatorymolecules [28]. However, inhibition of PTGS2 from immature DC greatly increases the costimulatory molecules CD86 and CD80 and also MHC I and MHC class II in contrast to wild type DC [29].The similar results in wild type of DC have been reported even after stimulation with lipopolysaccharide (mDC) compare to cox2 inhibitor treated DC.

PTGS2expression dampens the migration and invasion capacity of DC. It is reported that cox-2 expression enhances the activation of

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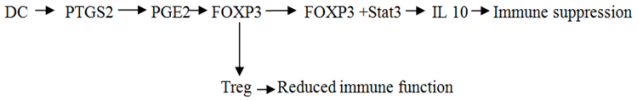

Figure 1: Mechanism how ptgs2 act as a negative regulator of DC mediated immunity[33].

proteolytic enzymes such as matrix metalloproteinase 2 (MMP-2) and MMP-9 and thereby increase lymphovascular invasion of cancer cell [32] and may be it also associated with migratory chemokines CCR7 up regulation in DC. Taken together, these observations suggest that the presence of COX2 appears to play a critical role in tumor cell migration and invasion.When wild type DC culture with T-cell it also reduces the secretion of tumor lysis cytokine INFγ and some studies revealed that PTGS2 silenced DC strongly enhance INFγ[33] to destroy cancer cell. Together these data suggest that PTGS2 act as a negative immune regulator of DC.

Summary

PTGS2 expression exaggerates cancer condition by proliferation, differentiation and migration of cancer cell and creates an effective immunosuppressive condition to immune cells. When PTGS2 induces in DC it gives negative effects on DC proliferation, differentiation and maturation. Silencing of PTGS2 by any means enhances DC immunity and T-cell stimulation capacity by increasing the level of MHCs and co-stimulatory molecules, secretion of immunostimulatory cytokines (IL12, INfγ) and reduction of immunosuppressive cytokine IL10 and FoxP3 expression.

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