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Review

Regulation of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) by non-steroidal anti-inflammatory drugs (NSAIDs)

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ABSTRACT

NSAIDs are known to be inhibitors of cyclooxygenase-2 (COX-2) accounting for their anti-inflammatory and anti-tumor activities. However, the anti-tumor activity cannot be totally attributed to their COX-2 inhibitory activity as these drugs can also inhibit the growth and tumor formation of COX-2-null cell lines. Several potential targets aside from COX-2 for NSAIDs have been proposed. 15-Hydroxyprostaglandin dehydrogenase (15-PGDH), a key prostaglandin catabolic enzyme, was recently shown to be a tumor suppressor. Effects of NSAIDs on 15-PGDH expression were therefore studied. Flurbiprofen, indomethacin and other NSAIDs stimulated 15-PGDH activity in colon cancer HT29 cells as well as in lung cancer A549 cells and glioblastoma T98G cells. (R)-flurbiprofen and sulindac sulfone, COX-2 inactive analogs, also stimulated 15-PGDH activity indicating induction of 15-PGDH is independent of COX-2 inhibition. Stimulation of 15-PGDH expression and activity by NSAIDs was examined in detail in colon cancer HT29 cells using flurbiprofen as a stimulant. Flurbiprofen stimulated 15-PGDH expression and activity by increasing transcription and translation and by decreasing the turnover of 15-PGDH. Mechanism of stimulation of 15-PGDH expression is not clear. Protease(s) involved in the turnover of 15-PGDH remains to be identified. However, flurbiprofen down-regulated matrix metalloproteinase-9 (MMP-9) which was shown to degrade 15-PGDH, but up-regulated tissue inhibitor of metalloproteinase-1 (TIMP-1), an inhibitor of MMP-9 contributing further to a slower turnover of 15-PGDH. Taken together, NSAIDs may up-regulate 15-PGDH by increasing the protein expression as well as decreasing the turnover of 15-PGDH in cancer cells.

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Contents

1. Introduction

Prostaglandins are a family of eicosanoids biosynthesized from arachidonic acid through cyclooxygenase (COX) pathway. Two isoforms of COX have been recognized. COX-1 is constitutive and is thought to play physiological roles in various tissues, whereas COX-2 is inducible by pro-inflammatory cytokines, growth factors and tumor promoters and is believed to play pathological roles in inflammation and cancer [1]. In fact, COX-2 has been shown to be over-expressed in most tumor tissues and is regarded as an oncogene [2]. COX-2-derived products, such as prostaglandin E_2 (PGE_2) and thromboxane A_2 (TXA_2), induce cell proliferation, invasion and angiogenesis and inhibit cell apoptosis relevant to tumor cell growth and metastasis [2]. However, these prostaglandins are rapidly oxidized and inactivated by NAD^+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH). The catabolic enzyme has been shown to be down-regulated in most tumor tissues and is considered as a tumor suppressor [3–5]. The reciprocal

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regulation of COX-2 and 15-PGDH ensures low and high levels of prostaglandins in normal and tumor tissues respectively.

Classical non-steroidal anti-inflammatory drugs (NSAIDs) are known to be inhibitors of both COX isoforms accounting for their anti-inflammatory activity and unwanted gastrointestinal toxicity. Development of COX-2 selective inhibitors has circumvented unwanted toxicity while retaining potent anti-inflammatory activity [6]. However, these selective inhibitors appear to increase cardiovascular risk resulting in the cessation of use of some of these drugs. Apart from the anti-inflammatory activity of NSAIDs, these drugs have also been found to exhibit anti-tumor activity albeit at higher concentrations [7]. However, the anti-tumor activity of NSAIDs cannot be totally accounted for by their inhibition of COX-2 activity since they can also inhibit growth and tumor formation of COX-2-null cell lines [8]. Furthermore, COX-2 inactive enantiomers and analogs of these drugs also possess anti-tumor activity suggesting that alternative mechanisms are involved in the anti-tumor activity of these drugs [9,10]. Possible mechanisms for the anti-tumor activity of NSAIDs have been proposed. These include, but not limited to, induction of apoptosis [11], inhibition of cell cycle progression [12], down-regulation of anti-apoptotic Bcl-2 [13], up-regulation of pro-apoptotic proteins BAX, Bcl-xl and Par-4 (protease-activated receptor-4) [14,15], inhibition of NF-κB and AP-1 [16], inhibition of PDK/Akt (phosphoinositide dependent kinase/Akt) signaling [17], inhibition of cyclic GMP phosphodiesterase [18], suppression of 14-3-3ε [19], and up-regulation of tumor suppressive proteins NAG-1 (NSAID-activated gene-1) [20], 15-LOX-1 (15-lipoxygenase-1) [21], $p75^{NTR}$ (p75 neurotrophin receptor) [22] and PTEN (phosphatase and tensin homolog) [23]. In this review, we presented that 15-PGDH, a newly identified tumor suppressive protein, was also up-regulated by NSAIDs. Up-regulation of 15-PGDH appeared to involve an increase in transcription and a decrease in turnover of 15-PGDH by flurbiprofen in human colon cancer HT29 cells [24]. Previously, indomethacin was shown to induce 15-PGDH expression in HL-60 cells [25] and human tumerol C cells [26]. Diclofenac was found to induce 15-PGDH expression which mediated the suppression of human glioma growth [27]. Up-regulation of 15-PGDH by NSAIDs and mechanisms of regulation will be summarized and discussed in this review.

2. NSAIDs stimulate 15-PGDH expression and activity in cancer cells

The stimulatory effects of NSAIDs on the 15-PGDH expression and activity were examined in three different cancer cell lines (HT29, A549 and T98G). The drugs include COX-1 inhibitor (SC-560), dual inhibitors of COX-1 and COX-2 (flurbiprofen, indomethacin, diclofenac, sulindac, mefenamic acid, niflumic acid, and piroxicam) and COX-2 inhibitors (celebrex, SC-236 and nimesulide). Among these compounds, flurbiprofen, indomethacin, sulindac and sulindac sulfone were able to stimulate over 2- to 3-fold of the 15-PGDH activity in HT29 and A549 cells. Others were less effective (0–50% increase). It is interesting to note that different cell lines responded differently to some of these compounds. For example, flurbiprofen and indomethacin appeared to stimulate significantly 15-PGDH activity in three different cell lines [24]. However, both of them showed more significant stimulation in HT29 cells as compared to A549 and T98G cells. Flurbiprofen showed best stimulation in these three cell lines and was selected to investigate further on the mechanisms of stimulation in HT29 cells. Stimulation of 15-PGDH activity by flurbiprofen was found to be attributed to, at least in part, to an increase in transcription and translation since levels of mRNA and protein expression were elevated as determined by RT-PCR and Western blot analyses, respectively. Increase in 15-PGDH expression and activity by flurbiprofen was both time and concentration dependent. Induction appeared to level off after 24 h of stimulation. The concentration needed for maximal induction was found to be around 50 μM. Similar increases in transcription and protein expression of 15-PGDH induced by indomethacin in HL-60 and human tumoral C cells [25,26] and by diclofenac in glioma cells [27] were also observed. The optimal concentration for stimulation of human tumoral C cells was 200 μM indomethacin, and that for stimulation of glioma cells was 100 μM diclofenac. Maximal induction of 15-PGDH was observed after 48 h of stimulation in both human tumoral C cells and glioma cells. It appears that higher concentration of indomethacin and diclofenac and longer incubation time are needed in these cell lines for optimal expression of 15-PGDH.

3. Stimulation of 15-PGDH expression by NSAIDs is independent of COX-2 inhibition

Simulation of 15-PGDH expression and activity by NSAIDs appeared to be unrelated to their COX inhibitory activity. Sulindac sulfone which is a COX-2 inactive metabolite of sulindac and induces apoptosis of prostate cancer cells showed significant induction of 15-PGDH expression in these three cell lines [24]. Similarly, flurbiprofen has two optical isomers. R-flurbiprofen is not COX-2 inhibitory, whereas S-flurbiprofen is COX-2 inhibitory. Both isomers showed similar degree of induction of 15-PGDH expression in HT29 cells indicating their activity was not related to COX-2 inhibition [unpublished results]. This is consistent with previous findings that both isomers exhibited similar anti-proliferative activity in rat colonocytes [28] and inhibited lipopolysaccharide-induced activation of NF-κB and AP-1 in rat macrophages [16]. In fact, racemic flurbiprofen exhibited potent inhibition of human brain tumor growth [29]. Therefore, induction of 15-PGDH expression and inhibition of proliferative activity by NSAIDs is independent of their COX-2 inhibitory activity.

4. Stimulation of 15-PGDH expression by NSAIDs and MEK inhibitors is via different mechanisms

Earlier it was reported that transcriptional repressor SNAIL suppressed 15-PGDH expression by binding to E-boxes of 15-PGDH promoter [30]. The expression of transcriptional repressors is known to be ERK (extracellular-signal-regulated kinase) dependent [31]. Inhibition of ERK should result in a decrease in SNAIL expression and an increase in 15-PGDH expression. Yang et al. [32] supported this notion by showing that MEK inhibitors enhanced 15-PGDH expression in lung cancer cells by down-regulation of transcriptional repressors such as SLUG and ZEB1. We found that flurbiprofen inhibited ERK phosphorylation much like MEK (MAP kinase kinase) inhibitors, PD98059 and U-0126. These inhibitors induced as much as 5- to 6-fold of 15-PGDH protein expression and activity in a dose dependent manner in HT29 cells [24]. Surprisingly, these inhibitors did not increase the transcription of 15-PGDH gene as levels of mRNA remained unchanged with increasing concentrations of MEK inhibitors. This is in contrast to NSAIDs which induced increase in transcription in a concentration dependent manner. Furthermore, flurbiprofen was found to up-regulate SNAIL and ZEB1 in HT29 cells [unpublished results] as opposed to MEK inhibitors which were shown to down-regulate these two repressors in lung cancer cells [32]. Other NSAIDs such as diclofenac and meloxicam, however, were not found to alter SNAIL expression in glioma cells [27]. These findings indicate that NSAIDs and MEK inhibitors may suppress different repressors in different cell lines or use different mechanisms to up-regulate 15-PGDH expression and activity.

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