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11β-hydroxysteroid dehydrogenase type II: a Potential target for prevention of colonic tumorigenesis

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Abstract

Cancer is the second most common cause of death in the world, and primary prevention remains the best approach to reducing overall morbidity and mortality. There is a molecular link between cyclooxygenase-2 (COX-2)-derived prostaglandin E2 (PGE2) production and colonic tumorigenesis. Selective COX-2 inhibitors as well as non-steroidal anti-inflammatory drugs (NSAIDs) reduce the number and sizes of colonic adenomas; however, increased cardiovascular risks of selective COX-2 inhibitors and increased gastrointestinal side-effects of NSAIDs limit their use. Glucocorticoids induce cancer cell apoptosis and are endogenous, potent COX-2 inhibitors. In tissues, glucocorticoid actions are down-regulated by type 2 11ß-hydroxysteroid dehydrogenase (11ßHSD2), and inhibition of 11ßHSD2 activity will elevate intracellular active glucocorticoids to levels that effectively suppress COX-2 expression. Both COX-2 and 11ßHSD2 increase in *Apc+/min* mouse intestinal adenomas and human colonic adenomas, and either pharmacologic or genetic 11βHSD2 inhibition leads to decreases in COX-2–mediated PGE2 production in tumors and prevents adenoma formation, tumor growth, and metastasis. 11ßHSD2 inhibition may represent a novel approach for CRC chemoprevention by increasing tumor cell intracellular glucocorticoid activity, which in turn inhibits tumor growth by suppressing the COX-2-derived PGE2 pathway, as well as other pathways, without potential side-effects relating to chronic application of COX-2 inhibitors, NSAIDs and glucocorticoids.

Introduction

Cancers are leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths per year after 2012. The number of new cases is expected to rise by about 70% over the next 2 decades [1]. Primary prevention remains the best approach to reducing overall morbidity and mortality.

The etiology of cancer is undoubtedly multifactorial, but there is experimental and clinical evidence linking abnormalities in the cyclooxygenase/prostaglandin system to its pathogenesis. Cyclooxygenase (prostaglandin synthase G2/H2, COX) is the rate-limiting enzyme in the metabolism of arachidonic acid to prostaglandin G2 and subsequently to prostaglandin H2 (PGH2), which serves as the precursor for prostaglandin E synthetase to produce prostaglandins [2]. Two isoforms of cyclooxygenase exist in mammals, COX-1 and COX-2. COX-2 derived PGE2 has been reported to promote tumor growth through stimulation of cell proliferation, cell migration, cell invasion, angiogenesis and immunosuppression [3].

Cyclooxygenase-2 and glucocorticoids in tumorigenesis

COX-2 was initially described as an inflammatory-mediated cyclooxygenase. COX-2 plays an important role in tumor cell growth and in cancer metastasis [4-7]. Hepatic metastases in colorectal cancer (CRC) develop more frequently when tumors express high COX-2 levels. COX-2 expression increases not only in the CRC and lung cancer, but to even higher levels in hepatic metastases [4].

COX-2 expression is sensitive to glucocorticoid inhibition. Glucocorticoids (GCs) are the most potent, endogenous, specific COX-2 inhibitors, acting to suppress COX-2 expression through stimulating glucocorticoid receptors [8-10]. Glucocorticoids are produced in the zona fasciculata (middle cortical layer) of the adrenal gland. Activation of glucocorticoid receptors inhibits COX-2 expression primarily through three mechanisms: **1**. Transcriptional inhibition. Activation of either activator protein-1 (AP-1) or nuclear factor- κB (NF-κB) leads to increased COX-2 transcription. GCs inhibit COX-2 expression by direct interaction with AP-1 and NF-κB. **2**. Post-transcriptional inhibition. Sustained p38 activity is required for the stabilization of COX-2 mRNA. MAPK phosphatase-1 (MKP-1), the founding member of MAPKs family, which plays an important role in cell proliferation, apoptosis and immune defense, is induced by GCs and inactivates pp-38, leading to destabilization of COX-2 mRNA. **3**. Indirect transcriptional inhibition. In addition to the transcriptional inhibition, GCs also induce the expression of several proteins that suppress COX-2 expression such as IκBα, which directly inhibits NF-κB activity [11]. GCs can also inhibit COX-2 expression through induction of lipocortin-1, which suppresses phospholipase A2 and inhibits leukocyte inflammatory events (epithelial adhesion, emigration, chemotaxis, phagocytosis, etc). In addition to inhibiting COX-2 expression, GCs reduce PG production through inhibition of cytosolic PLA 2 (cPLA2) activity, which prevents the release of arachidonic acid from membrane phospholipids, and through inhibition of microsomal prostaglandin E synthetase (mPGES-1) expression, a major terminal synthetase in PGE2 biosynthesis [12]. mPGES-1 and COX-2 expression are significantly increased in human colorectal tumors [12,13]. Local tissue levels of PGE 2 are determined by PGE2 biosynthesis and degradation.

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The NAD+-dependent 15-hydroxyprostaglandin dehydrogenase (15-PGDH) catalyzes the rate-limiting step of PG catabolism, and 15-PGDH expression decreases in CRC [14]. GCs induce 15-PGDH expression in A549 human lung adenocarcinoma cells [15]. Therefore, GCs may reduce tissue levels of PGs through coordinated inhibition of cPLA2 activity, COX-2 and mPGES-1 expression, and induction of 15-PGDH.

GCs have been used to treat diseases caused by an overactive immune system, such as allergies, asthma, and autoimmune diseases as well as a broad spectrum of hematologic malignancies, including leukemia, lymphoma, and myeloma due to their ability to induce apoptosis [16-18]. Recent studies found the inhibitory effect of GCs to COX-2 could suppress solid tumor growth, regress tumor mass, and prevent metastasis by blocking angiogenesis [19,20]. However, the undesirable side effects of immunosuppression limit their application in cancer chemoprevention and chemotherapy.

Circulating glucocorticoid levels are regulated by the hypothalamo-pituitary-adrenal axis [21]. Peptide corticotropin-releasing hormone (CRH) released from the hypothalamus following stressors stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn stimulates the adrenal gland to secrete glucocorticoids. When blood concentrations of glucocorticoids rise above a certain threshold, CRH secretion is inhibited from the hypothalamus, leading to turning off of ACTH secretion and subsequent turning off of glucocorticoid secretion from the adrenal gland. In addition to systemic regulation, glucocorticoid effects are also regulated locally in tissues by a "pre-receptor" regulatory mechanism involving 11ß-hydroxysteroid dehydrogenase type I (11ßHSD1) and 11ßHSD2 [22]. 11ßHSD1 produces active glucocorticoids from inactive metabolites, while 11ßHSD2 converts glucocorticoids to their inactive ketoforms. 11ßHSD1 is expressed in key glucocorticoid target tissues such as liver and adipose tissue, while 11ßHSD2 is expressed predominantly in mineralocorticoid responsive tissues such as the kidney, salivary gland and colon [23-26].

11ßHSD2 acts as a procarcinogenic agent through attenuation of glucocorticoid actions and suppresses tumorigenesis through enhancing glucocorticoid-mediated inhibition of COX-2 pathway

11ßHSD2 has been proposed to be a pro-proliferative agent due to its ability to attenuate the anti-proliferative effects of glucocorticoids. The most conclusive evidence for the role of 11ßHSD2 in tumorigenesis comes from the analysis of 11ßHSD isoenzyme expression in a large cohort of human pituitary tumors [27-29]. 11ßHSD1 expression decreases, while 11ßHSD2 expression dramatically increases in pituitary tumors compared with normal tissues. Inhibition of 11ßHSD2 activity suppresses pituitary cell proliferation and augments glucocorticoid anti-proliferative effects. 11ßHSD2 expression increases in human adrenal cortical carcinoma/adenoma, breast cancers, and neoplastic cell lines [30-35]. In cultured cell lines, overexpression of 11ßHSD2 stimulates cell proliferation, while inhibition of 11ßHSD2 activity suppresses cell proliferation [31-34].

11ßHSD2 activity is higher in the colon than in the small intestine in the rat and it is primarily localized to intestinal epithelia [36]. In intestinal tumors, 11ßHSD2 is expressed in epithelial and stromal cells [37-39]. Interestingly, the incidence of intestinal tumors is higher in the colon than in the small intestine. The mechanism underlying increases in COX-2 expression in CRC is not completely understood. Recent studies have found that 11ßHSD2 mRNA levels are significantly higher in both human colonic small and large adenomas compared to adjacent normal colon tissues [40]. Immunohistochemical staining showed that increased 11ßHSD2 expression is primarily localized to adenoma epithelia and co-localized with increased COX-2 expression in human colonic adenomas. Both 11ßHSD2 and COX-2 expression also increase in adenomas of Apc+/min mice. Mouse adenocarcinoma CT26 cells demonstrate significant tumorigenic activity and express high levels of COX-2, and both their proliferation in vitro and the size and number of CT26 tumors in vivo are sensitive to COX-2 inhibition [40]. CT26 cells also express 11ßHSD2. Corticosterone treatment (the active glucocorticoid in rodents) leads to inhibition of CT26 cell COX-2 expression, which is enhanced by pharmacologic or genetic inhibition of 11ßHSD2 activity but is attenuated by overexpression of 11ßHSD2. Pharmacologic inhibition of 11ßHSD2 activity with glycyrrhizic acid (GA) suppresses adenoma development and growth, associated with inhibition of adenoma COX-2 and mPGES-1 expression in Apc+/min mice. Knockdown of 11ßHSD2 in CT26 cells leads to inhibition of CT26 tumor growth associated with inhibition of CT26 tumor COX-2 and mPGES-1 expression as well as PGE2 production. Pharmacologic inhibition of 11ßHSD2 activity with GA increases active glucocorticoid levels but decreases inactive 11-keto-corticosterone levels in CT26 tumors as well as in tissues with high levels of 11ßHSD2 activity such as kidney and colon. GA treatment leads to decreases in CT26 tumor incidence, inhibition of CT26 tumor growth, decreases in tumor phosphorylated cPLA2 (active form), COX-2 and mPGES-1 expression as well as tumor PGE2 levels; all of these parameter are reversed by treatment with RU486, an inhibitor of glucocorticoid receptors. Human colon carcinoma HCA-7 cells constitutively express both 11ßHSD2 and COX-2, and COX-2 activity is essential for the proliferation of HCA-7 cells [41]. On the other hand, human colon carcinoma HT-29 cells constitutively express similar levels of 11ßHSD2 with minimal COX-2 expression, and COX-2 activity is not essential for HT-29 cell proliferation [42]. Inhibition of 11ßHSD2 activity with glycyrrhizic acid has no effect on HT-29 tumor growth, but significantly inhibits HCA-7 tumor growth, which is associated with decreases in tumor COX-2 and mPGES-1 expression. Therefore, 11ßHSD2 inhibition represents a novel approach for colorectal cancer chemoprevention and therapy by increasing tumor glucocorticoid activity, which in turn selectively blocks local COX-2 activity.

In addition to inhibition of the COX-2 pathway, increased intracellular glucocorticoids due to 11ßHSD2 inhibition may suppress proliferation and induce apoptosis and differentiation through other mechanisms. The retinoblastoma protein (Rb), a tumor suppressor, inhibits cell proliferation through its interaction with the E2F family of transcription factors and the resultant regression of genes that are essential for DNA synthesis [43]. The inactivation of retinoblastoma protein is a prerequisite for cell proliferation. Inactivation of Rb is achieved through cyclin-dependent protein kinase-mediated phosphorylation during cell cycle progression. Glucocorticoids inactivate Rb through p53-mediated induction of p21waf1/cip1, an inhibitor of cyclin-dependent kinase [44-48]. Glucocorticoids may also inhibit tumor growth through suppression of the mTOR signal pathway [49,50]. REDD1 (RTP801, an mTOR complex 1, mTORC1, repressor) is a novel stress-induced gene linked to regression of mTOR signaling and is induced by glucocorticoids [51-53]. Recently, we generated Apc+/min mice with selective deletion of 11ßHSD2 in intestinal epithelial cells, and intestinal tumorigenesis is inhibited in these mice. In adenomas from these mice, p53 and p21 levels increased, with concomitant decrease in phosphorylation of retinoblastoma protein. In addition, adenoma REDD1 increased, while the activity of mTOR signaling pathway was inhibited.

The lipoxygenase (LOX) pathway is another important pathway for metabolism of arachidonic acid. 5-LOX and its metabolite, leukotriene B4, have been reported to stimulate the proliferation of several human colon carcinoma cell lines [54,55]. 5-LOX increases in human colorectal tumors, and inhibition of the 5-LOX pathway suppresses the proliferation of human colon carcinoma cell lines and inhibits CRC development [56-60]. Dexamethasone has been reported to inhibit 5-LOX expression and its metabolite production [61,62].

Conclusion and future perspective

The inhibition of 11βHSD2 activity may provide a new target for chemoprevention and/or adjunctive therapy for cancers (CRC, lung cancer, etc), particularly for patients with increased risk, such as familial adenomatous polyposis (FAP) patients, as a result of increased tumor intracellular active glucocorticoids, because of the following advantages (Figure 1): **1**. Glucocorticoids selectively inhibit COX-2, but not COX-1, mediated prostaglandin production. Therefore, inhibition of 11βHSD2 activity has the beneficial effects of traditional NSAIDs to prevent and regress colorectal cancers without the gastrointestinal side effects associated with COX-1 inhibition; **2**. Physiologic 11βHSD2 is most highly expressed in colon and kidney. Therefore, inhibition of 11βHSD2 activity is not expected to incur the cardiovascular risk posed by COX-2 inhibitors that suppress COX-2–derived PGI2 production in vascular endothelial cells; **3**. Increased levels of intracellular active glucocorticoids are observed only in tissues with elevated 11βHSD2 expression. Inhibition of 11βHSD2 will not produce immunosuppression or other systemic side effects of conventional glucocorticoid therapy; **4**. Increased tumor active glucocorticoids also inhibit tumor development and growth through induction of G1 cell cycle arrest and inhibition of the mTOR pathway; **5.** Tissue prostaglandin levels are determined by both biosynthesis and catabolism. A key enzyme in prostaglandin catabolism, 15-hydroxyprostaglandin has been reported to be decreased in Apc+/min mouse intestinal adenomas and in human colorectal cancer [63], and glucocorticoids have been shown to induce 15-hydroxyprostaglandin in A549 human lung adenocarcinoma cells [64]. Therefore, it is possible that increased intracellular active endogenous glucocorticoids may inhibit tumorigenesis not only by inhibiting prostaglandin synthesis, but also by enhancing prostaglandin degradation; and finally **6**. Glucocorticoid also inhibit the activity of cPLA2, preventing potential shunting of arachidonic acid metabolism to other procarcinogenic metabolizing pathway such as the 5-lipoxygenase lipoxygenase pathway [60-62,65]. In addition, glucocorticoids inhibit both COX-2 and 5-LOX.

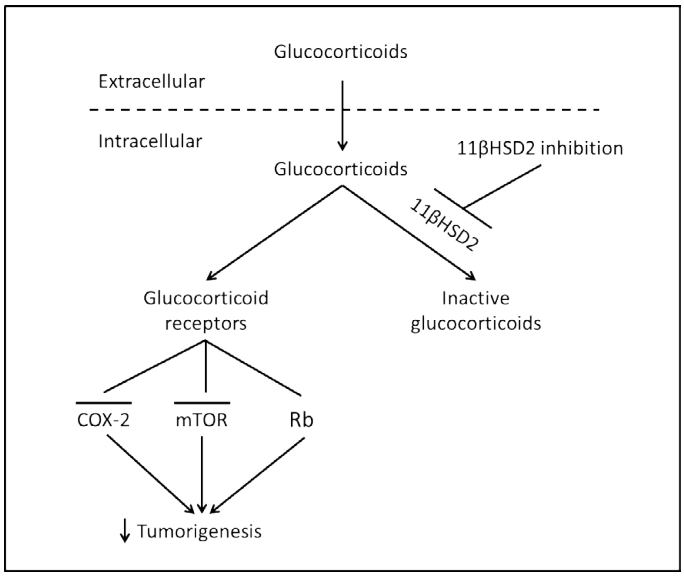

Figure 1. Proposed mechanism underlying epithelial cell 11ßHSD2 activity and tumorigenesis. In tumor epithelial cells, glucocorticoids are converted to inactive 11-keto-forms, reducing glucocorticoid receptor activity, while 11ßHSD2 inhibition leads to increased levels of epithelial intracellular active glucocorticoid. The subsequent inhibition of the COX-2 pathway and induction of G1 cell cycle arrest through activation of retinoblastoma protein (Rb, a tumor suppressor) and inhibition of the mTOR pathway lead to inhibition of colorectal tumorigenesis.

Glycyrrhizic acid and its analogs are excellent prototypes for 11βHSD2 inhibitors. It is a natural compound contained in licorice, a natural botanical antiinflammatory agent and a powerful 11βHSD2 inhibitor. Long-term excessive ingestion of licorice has been reported to induce hypokalemia and elevation of blood pressure in a subset of people [66]. Although these side effects were not seen in animal experiments, studies did observe that the concentrations of glycyrrhizic acid increased levels of active glucocorticoid levels in the kidney [40]. Although 11βHSD2 inhibition may result in salt-dependent hypertension due to activation of mineralocorticoid receptor by glucocorticoids in kidney, development of locally acting enteric 11ßHSD2 inhibitors that are not systemically absorbed would be a potential therapeutic means to prevent tumorigenesis [67].

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