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Can licorice lick colon cancer?

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Commentary

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Can licorice lick colon cancer?

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COX-2 promotes colon cancer. While both nonselective NSAIDs and selective COX-2 inhibitors reduce disease burden, their adverse gastrointestinal and cardiovascular side effects limit their therapeutic use. In this issue of the *JCI*, Zhang et al. used gene silencing and a derivative of licorice root to show that inhibition of the enzyme 11β–hydroxysteroid dehydrogenase type II (11βHSD2) reduces tumor COX-2 activity, tumor growth, and metastasis by increasing the tonic glucocorticoid-mediated suppression of the COX-2 signaling pathway without the adverse effects associated with NSAIDs and selective COX-2 inhibitors (see the related article beginning on page 876). Their findings suggest that 11βHSD2 inhibition may be a potential therapeutic option in colon cancer, warranting further investigation.

COX-2 is a crucial enzyme in the synthesis of prostaglandins and prostacyclin, which play a variety of roles in the regulation of cell growth, hemostasis, sensing of pain, and inflammation. In normal colon tissue, there is little or no expression of COX-2; however, COX-2 expression is induced early in colon carcinogenesis, is key to disease progression, and influences the clinical course of disease (Figure 1, A and B, and reviewed in ref. 1). The COX-2 response clearly plays a central role in colon carcinogenesis, because inhibitors of COX-2 enzymatic activity prevent the development of intestinal polyps in mice and humans (reviewed in ref. 1), and deletion of *Cox2* in mice almost completely protects the animals from the development of these polyps (reviewed in ref. 1). However, enthusiasm for the prevention of colon cancer via pharmacological COX-2 inhibition has been tempered by the recognition that such a prevention strategy inherently requires long-term exposure to COX-2 inhibitors. Unfortunately, traditional NSAIDs, which are nonselective COX inhibitors, can cause gastrointestinal hemorrhage, among other complications (2), while selective COX-2 inhibitors confer an increased risk of cardiovascular death (3). Thus, a detailed understanding of how COX-2 expression is induced would be potentially valuable from two perspectives — it would provide insight into both the molecular steps involved in carcinogenesis and potential therapeutic targets.

That COX-2 is overexpressed in colon polyps and cancer has been recognized for more than 15 years (reviewed in ref. 1), but the molecular basis for this overexpression has remained unclear despite extensive investigation of the regulation of the *COX2* gene in many experimental settings. It is likely that what was originally thought to be a cell-autonomous event is instead a response to extracellular signals — a "field effect," with growth factors providing much of the signal that results in induction of *COX2*. From the time of the discovery of *COX2* as an early inducible gene, it was almost immediately recognized that *COX2* induction in vitro could be inhibited by a class of steroid hormones known as glucocorticoids (4, 5). This pharmacologic effect has been attributed to changes in both COX-2 transcription and mRNA stability (6). However, it was not known whether COX-2 was regulated by endogenous glucocorticoids, the most important of which

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Nonstandard abbreviations used: GE, glycyrrhetinic acid; 11βHSD, 11β–hydroxysteroid dehydrogenase; MR, mineralocorticoid receptor.

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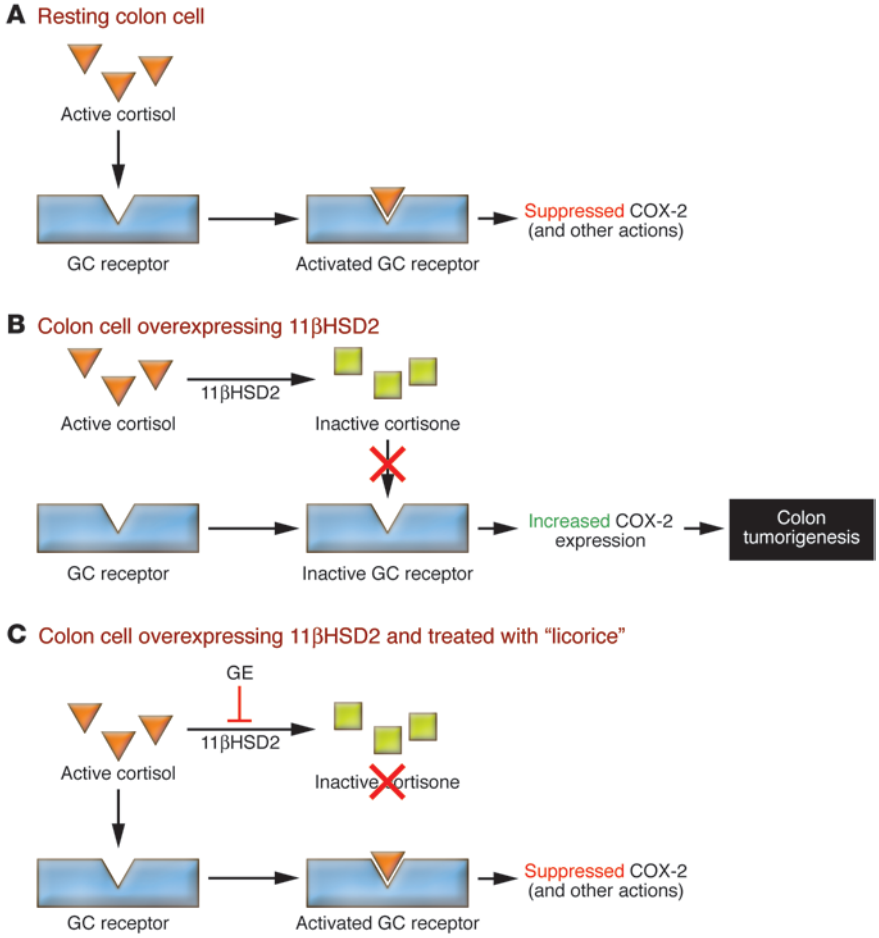

Figure 1
Inhibition of 11βHSD2 blocks COX-2 and suppresses colon carcinogenesis. (**A**) In resting colon cells, COX-2 expression is suppressed by the binding of endogenous cortisol to the glucocorticoid (GC) receptor. (**B**) In the current study, Zhang et al. show that the expression of 11βHSD2 is increased both in human colon adenomas and in intestinal adenomas in *Apc*$^{+/min}$ mice (14). Active cortisol is converted by 11βHSD2 to inactive cortisone that is unable to activate the glucocorticoid receptor. This releases the repression of COX-2, which is then expressed at high levels and generates signals (primarily prostaglandins) that promote colon tumorigenesis. (**C**) The authors also show that these cellular events could be reversed — at least with regard to this signaling pathway — by inhibiting the enzymatic activity of 11βHSD2 via gene silencing or pharmacologically with the licorice root derivative GE. Under these conditions, cortisol is available to suppress COX-2 expression via the glucocorticoid receptor and therefore suppress tumorigenesis.

is cortisol in humans, as it supports a variety of important metabolic, cardiovascular, immunologic, and homeostatic functions.

The actions of cortisol are regulated in target tissues

Endogenous cortisol secretion is regulated by the hypothalamo-pituitary-adrenal axis, which largely dictates the levels of circulating glucocorticoids and tissue exposure. However, within target tissues, the exposure of cortisol to corticosteroid receptors is also regulated through the activity of steroid metabolism pathways, notably via the expression of 11β–hydroxysteroid dehydrogenases (11βHSDs). Two isoforms of 11βHSD exist: the type I oxoreductase, 11βHSD1, which can generate active cortisol from the inactive keto-form, cortisone; and the type II 11βHSD2 isoform, a highly efficient NAD-dependent dehydrogenase responsible for the reverse reaction, converting active cortisol to inactive cortisone (Figure 1B and ref. 7).

Because 11βHSD1 is expressed in glucocorticoid receptor–rich tissues such as liver, adipose tissue, and muscle, there is fervent interest in its therapeutic inhibition in patients with metabolic syndrome. The rationale for this interest is that inhibition of the local generation of cortisol in liver and omental fat reduces hepatic gluconeogenesis and glucose output and reduces omental adipogenesis and lipolysis, thereby reducing the waist/hip ratio and lowering levels of circulating lipids (8).

In contrast, in adult tissues, 11βHSD2 is expressed in epithelial cells in mineralocorticoid receptor–rich (MR-rich) tissues such as kidney, colon, and salivary gland. Here it acts in an autocrine fashion to protect the MR — which, paradoxically, in vitro has the same inherent affinity for the mineralocorticoid aldosterone as it does for the glucocorticoid cortisol — from illicit occupancy by cortisol (9).

Expression of 11βHSD2 has also been reported in cancers, most notably in endocrine tumors such as pituitary and adrenal adenomas (10, 11), but also in osteosarcoma, renal, breast, and lung cancer cells (12). The underlying explanation for aberrant 11βHSD2 expression is uncertain, but it has been postulated to control glucocorticoid regulation of cellular proliferation (reviewed in ref. 13). Results from in vitro studies using malignant transformed cell lines demonstrate the antiproliferative actions of glucocorticoids; thus, the local inactivation of cortisol by 11βHSD2 may be an important oncogenic process promoting cellular proliferation. In vitro, 11βHSD1 brings about changes opposite to those mediated by 11βHSD2 — the local generation of cortisol suppresses cellular proliferation (13). Arguably, for this reason, there are very few malignant transformed cell lines that express the 11βHSD1 isoform.

Inhibition of 11βHSD2 blocks COX-2 activity and tumor growth

In this issue of the *JCI*, Zhang et al. demonstrate similar findings in the colon (14). They report that 11βHSD2 mRNA and the immunoreactive 11βHSD2 protein itself are overexpressed in both human colon adenomas and in intestinal adenomas in *Apc*$^{+/min}$ mice — which are heterozygous for a

nonsense mutation in the *Apc* gene, homologous to human germline and somatic *APC* mutations, and consequently develop intestinal adenomas — and that this overexpression correlates with increased COX-2 expression and activity (Figure 1B). They demonstrate that gene silencing or pharmacological inhibition of 11βHSD2 with the licorice root extract glycyrrhetinic acid (GE) reduced tumor COX-2 activity, tumor growth, and metastasis via inhibition of the COX-2–mediated signaling pathway (Figure 1C). Encouragingly, the authors did not observe any increase in atherogenesis or decrease in the measure of systemic prostacyclin levels after 11βHSD2 inhibition. Their findings suggest that 11βHSD2 inhibition prevents colon cancer by selectively blocking tumor COX-2 activity and that this can be achieved without triggering adverse side effects in the cardiovascular system that are associated with selective COX-2 inhibitors (3).

Zhang et al. (14) suggest that all or most of the carcinogenic actions of 11βHSD2 occur via the COX-2 pathway, including via cytosolic phospholipase A_2 ($cPLA_2$) and microsomal prostaglandin E synthase (mPGES-1), the initial and terminal enzymes, respectively, in COX-2–mediated prostaglandin synthesis. It is not clear whether increased expression of COX-2, and subsequent signaling through prostaglandin E_2, is sufficient to cause cancer — it may depend on the tissue and other stimuli. For example, the answer to this question with respect to mammary tissue seems to be a qualified yes, since transgenic mice with tissue-specific overexpression of COX-2 develop tumors without an additional known inducer, but only after multiple pregnancies (15). In contrast, forced expression of COX-2 in skin sensitizes mice to cancer but is insufficient to trigger disease alone (16). Similar observations have been made in mice with intestine-specific COX-2 expression (17). Thus, if the majority of the effects of 11βHSD2 are mediated via the COX-2 pathway, we predict that COX-2 overexpression will not initiate cancer, but will promote it.

Is licorice — or its relatives — a candy or a therapeutic?

Should we now regard 11βHSD2 as a therapeutic target in patients with colon cancer? Evidence dating back to ancient Eastern civilizations suggests that there is something to this story. Several naturally occurring compounds are known to inhibit 11βHSD2, including GE and flavanoids such as naringenin, found in grapefruit juice. Many of these are ingredients of Eastern herbal medicines such as *shakuyaku-kanzo-to* and *oren-gedoku-to*, which have been shown in clinical studies to treat a variety of tumors, including hepatomas and colon cancers (18). Some in vitro studies have also demonstrated an effect via COX-2 activity (19).

However, there are two broad issues to consider. The first is whether one would expect inhibition of 11βHSD2 to be as good as, or superior to, inhibition of COX-2; the second is whether long-term exposure to such a class of drugs would be safe. With respect to the first issue, there is reason for optimism because there is a good theoretical basis for blocking expression of COX-2 as a therapeutic strategy. Lack of COX-2–mediated prostaglandin E_2 production in tumors would block adenoma formation, tumor growth, and angiogenesis, returning the status of the tissue to that of normal colon tissue. In addition, there is another theoretical benefit: NSAIDs and COX-2 inhibitors can themselves *induce* the expression of COX-2 under some circumstances (20, 21), which could lead to a paradoxical increase in prostaglandin synthesis if COX-2 were induced and then the enzymatic inhibition was relieved. Such relief of inhibition could occur if a patient was not perfectly compliant with the dosage schedule of the inhibitor, which is common during long-term therapy. With respect to the issue of long-term safety, more evidence is needed of the effects of 11βHSD2 inhibition, and the outcomes to date of the use of selective COX-2 inhibitors are sobering (3). Zhang et al. recognize this concern and provide encouraging data that 11βHSD2 inhibition did not show systemic suppression of prostacyclin levels and that there was no worsening of disease in a mouse model of atherosclerosis (14).

The 11βHSD2 inhibitor used in the current report (14) was glycyrrhizic acid, which the authors showed was converted to the active metabolite GE. The GE content of licorice differs across the globe — it is high in Asia and some European countries, such as Holland, but undetectable in confectionary licorice sold in the United States, where tobacco sticks and gums contain the highest quantities of GE.

At this time, tissue-specific 11βHSD2 inhibition is not available, and while GE might have beneficial effects on colon carcinoma, it will also inhibit renal 11βHSD2 expression and activity (22). Despite the reassurances of Zhang et al. as to the lack of cardiovascular side effects of 11βHSD2 inhibition compared with COX-2 inhibition (14), this is unlikely to be the case. Because the MR cannot differentiate between the mineralocorticoid, salt-retaining properties of cortisol or aldosterone, and plasma cortisol concentrations are 1,000-fold greater than aldosterone concentrations, even the most trivial inhibition or lack of renal 11βHSD2 will result in salt-dependent mineralocorticoid hypertension, the speed of onset and severity of which would be directly related to the degree of 11βHSD2 inhibition (23). However, if the present findings are confirmed, locally acting enteric 11βHSD2 inhibitors that are not systemically absorbed may be a way forward in colon cancer therapeutics.

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The voltage-gated K^+ channel subunit Kv1.1 links kidney and brain

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Analysis of Mendelian Mg^{2+} wasting disorders helps us to unravel the mechanisms of Mg^{2+} homeostasis. In this issue of the *JCI*, Glaudemans and colleagues show that mutations in voltage-gated K^+ channel subtype 1.1 (Kv1.1) cause autosomal dominant hypomagnesemia in humans (see the related article beginning on page 936). Interestingly, other mutations in the same protein cause the neurological disease episodic ataxia type 1. The authors show, using cells with heterologous expression of the wild-type and mutant channels, that the mutant channel is dysfunctional and speculate that Mg^{2+} wasting results from changes in apical membrane voltage along the nephron. Mechanisms by which the apical voltage is generated and how Kv1.1 fits within this context are discussed herein.

Rare Mendelian diseases are windows into both physiology and pathogenesis. Examples include the rare Mg^{2+} wasting disorders that form the basis for most of our current understanding of renal Mg^{2+} transport. Several proteins that mediate Mg^{2+} transport, both around and through cells, have now been identified and cloned, using positional cloning approaches. Secondary dysfunction of these proteins may also contribute to hypomagnesemia in the critically ill, where the incidence has been estimated as 20%–60% and has been associated with excess mortality (1). Hypomagnesemia is often drug related, with diuretics, calcineurin inhibitors, and antineoplastic agents (e.g., cisplatin and cetuximab) common offenders (2). The study of Mendelian disorders of Mg^{2+} homeostasis has also led to the identification of novel and sometimes unexpected regulatory pathways that impact transport pathways secondarily.

Eighty percent of plasma Mg^{2+} is ultrafilterable by glomeruli. Whereas the majority of every other ion studied to date is reabsorbed along the proximal tubule, proximal Mg^{2+} reabsorption constitutes only 10%–15% of the filtered load. In contrast, the thick ascending limb (TAL) reabsorbs approximately 70% of filtered Mg^{2+} and clearly plays a central role in regulating Mg^{2+} excretion. What surprised many investigators, however, was that most disorders of Mg^{2+} balance result from dysfunction along the distal convoluted tubule (DCT), a short nephron segment that, just a few years ago, was believed to play only a minor role in Mg^{2+} homeostasis (3). The DCT is now recognized as important not only for Mg^{2+} balance, but also for the control of Na^+, K^+, and Ca^{2+} levels (4). In this issue of the *JCI*, Glaudemans and colleagues report that missense mutations in K^+ voltage-gated channel, Shaker-related subfamily, member 1 (*KCNA1*), which encodes voltage-gated K^+ channel subtype 1.1 (Kv1.1) expressed by DCT cells, causes autosomal dominant hypomagnesemia in humans (5). Surprisingly, other mutations in the same gene cause episodic ataxia type 1 (EA1) (6), a neurological syndrome in which hypomagnesemia has not been reported. In the present study, the investigators showed that Kv1.1 localizes to the apical membrane of DCT cells, where the transient receptor potential cation channel, subfamily M, member 6 (TRPM6) controls Mg^{2+} entry, driven by its electrochemical potential. Expression studies showed that the mutated Kv1.1 protein, while having no direct effect on TRPM6, exhibited reduced

Conflict of interest: The author has declared that no conflict of interest exists.

Nonstandard abbreviations used: CNT, connecting tubule; DCT; distal convoluted tubule; ENaC, epithelial Na^+ channel; KCNA1, K^+ voltage-gated channel, Shaker-related subfamily, member 1; Kv1.1, voltage-gated K^+ channel subtype 1.1; ROMK, renal outer medullary K^+ channel; TAL, thick ascending limb; TRPM6, transient receptor potential cation channel, subfamily M, member 6.

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