Colorectal Neoplasia Goes with the Flow: Prostaglandin Transport and Termination

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The past 10 to 15 years have witnessed major advances in our understanding of polyunsaturated fatty acid metabolism involving synthesis, activity, and degradation of prostaglandin (PG), especially prostaglandin E2 (PGE2), in neoplasia, in particular colorectal neoplasia. Little is known, however, about the role of PG transport in these processes. The flow of PGs in and out of colorectal cells involves highly coordinated activities of PG transporters that become highly dysregulated in colorectal neoplasia. Recent work by various investigators supports key components of this flow for novel molecular-targeted approaches to prevent or treat colorectal neoplasia.

The DuBois lab first reported that cyclooxygenase (COX)-2 is overexpressed in colorectal adenomas and cancer (1), which led to seminal trials of COX-2 inhibitors in familial adenomatous polyposis (2) and sporadic colorectal adenomas (3). This research group and others showed that COX-2-derived PGE2 promotes tumorigenesis by affecting angiogenesis, cell adhesion, invasion, proliferation, and apoptosis (4–9). These effects of COX-2/PGE2 are implemented by PGE2 binding to and activating certain EP receptors and thus activating important pathways including epidermal growth factor receptor, peroxisome proliferator–activated receptor-δ, Ras, phosphatidylinositol 3-kinase, and β-catenin signaling. More recent work from this and other groups has shown that 15-hydroxyprostaglandin dehydrogenase (15-PGDH), which degrades intracellular PGE2, was suppressed in colorectal neoplasia from pre-adenoma to invasive stages; suppressed growth of human colorectal cancer cells in immunodeficient mice and inhibited the development of murine intestinal neoplasia when its expression was restored by transfection; and was up-regulated by certain agents including epidermal growth factor receptor and histone deacetylase inhibitors (10–15).

Strong evidence suggests that two cellular transporters of PGE2, the transmembrane influx prostaglandin transporter (PGT) (carrying into the cytoplasm) and efflux multidrug resistance–associated protein (MRP)-4 (carrying out to the extracellular milieu), are deeply implicated in colorectal neoplasia. Although it is the first identified (in 1995) and best studied transporter (16, 17), PGT has not previously been implicated in cancer. Effective termination of PGE2 may require both PGT, which has a high affinity and specificity for PGE2, and 15-PGDH (18). As for MRP4, in noncancer model systems, MRP4 knockout or knockdown led to a pronounced reduction in extracellular PGE2, and MRP4 was inhibited by certain non-steroidal anti-inflammatory drugs (19, 20); also, MRP4 is overexpressed in colorectal and other cancers (21).

In their exciting new report “Regulation of the Prostaglandin Transporters in Colorectal Neoplasia” in this issue (22), Holla and his colleagues in the DuBois lab build on the foregoing and other related discoveries to address our limited understanding of PGE2 transport and inactivation in neoplasia. They found that PGT was down-regulated in colorectal cancer in the vast majority of their human specimens and cell lines. Although focused on colorectal neoplasia, this study indicated that PGT expression is also dysregulated in stomach, ovary, kidney, and lung cancers. PGT down-regulation occurred early or at the level of adenomas in MIN mice. Forced PGT overexpression in vitro in HCA-7 cells reduced extracellular PGE2 levels and increased intracellular levels of 15-keto PGE2, the catabolic product of PGE2; both events occurred in a dose-dependent fashion, which is consistent with PGT transporting PGE2 into cells and with the known expression of 15-PGDH in HCA-7 cells, which therefore was still available for degrading PGE2 into the Keto product (11). These investigators also showed evidence of epigenetic regulation of PGT by a histone deacetylase inhibitor and a demethylating agent. These PGT results are the first reported for any cancer setting.

These new results of Holla et al. amplify on the known patterns of PG signaling events in colorectal neoplasia. We now can say that colorectal neoplasia throttles down PGT expression in addition to revving up the expressions of COX-2, microsomal PGE synthase 1, and MRP4 and throttling down 15-PGDH (Fig. 1). Data now suggest that cellular efflux of PGE2 in normal cells can occur via two mechanisms, diffusion and MRP transport, whereas PGE2 influx occurs primarily via the PGT. MRP4 seems to increase its efflux role in neoplasia, although diffusion likely continues. This flexibility in efflux suggests that limiting PGE2 influx through reduced PGT may play an important role in up-regulating the effects of the COX-2 pathway in colorectal neoplasia and in producing increased levels of extracellular PGE2 to bind and activate EP receptors. The suggestive timing of these events involves stepwise progressions from early (adenomas) through late stages of colorectal neoplasia.

The novel findings of Holla et al. support the conclusion that PGT may collaborate functionally with 15-PGDH to inactivate PGE2. Figure 1 provides a model summarizing the elements involved in the PG transport–related flow of PGE2 into and out of normal and neoplastic colorectal cells, and highlights opportunities for using preventive or therapeutic agents to target this flow in neoplasia. The PGE2 influx–dominated flow of normal colorectal cells is associated with a relatively low level of PGE2 (compared with the level in neoplastic cells) originating in the cytoplasm and either undergoing...
degradation and inactivation by highly expressed 15-PGDH or escaping from the cell via diffusion and MRP4 (MRP1 and MRP2 also have been implicated in PGE2 efflux in non-cancer experimental systems (23); Fig. 1A). The resultant extracellular PGE2 then flows by means of highly expressed PGT back into the cytoplasm, where it can be inactivated by 15-PGDH. This cycle keeps the level of PGE2 below that generally associated with dysregulated neoplastic cells. The PGE2 efflux–dominated flow of neoplastic colorectal cells is associated with a relatively high level of PGE2 (produced by up-regulated COX-2 and microsomal PGE synthase 1) in the cytoplasm that flows out of the cell via diffusion and

Fig. 1. The flow of colorectal neoplasia passes through the PGE2 transporters. A, the PGE2 influx–dominated flow of normal colorectal cells; the dotted blue circular line represents the general pattern of this flow. B, the PGE2 efflux–dominated flow of neoplastic colorectal cells; the dotted red circular line represents the general pattern of this flow. C, a conceptual approach for preventing or treating colorectal cancer via molecular targeting of the processes shown in A and B. The colorectal neoplasia risk factors shown in C (top left) are key early events associated with up-regulated COX-2 and neoplasia in the colorectal region. The agent classes shown in C (bottom right) are supported by PGT and/or 15-PGDH up-regulation data. All of the processes suggested in A to C are well described toward the end of the text. AA, arachidonic acid; DNMT, DNA methyltransferase; mPGES1, microsomal PGE synthase 1; PPAR-γ, peroxisome proliferator–activated receptor γ. 

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It is clinically important to identify promising non–COX-2 targets within the polyunsaturated fatty acid metabolic signaling pathway (27, 28) because COX-2–selective nonsteroidal anti-inflammatory drugs increased adverse cardiovascular events in long-term prevention trials also showing significant suppression of colorectal neoplasia (3, 29). As indicated in Fig. 1, promising such targets include microsomal PGE synthase 1, EP-2 and EP-4, 15-PGDH, MRP4, and PGT (8–14, 22, 28). Future studies should examine whether the beneficial effects of epigenetic regulation in colorectal neoplasia (27, 30, 31) involve the PG transport–related mechanisms hypothesized above in this article. Mechanistic studies of PGT down-regulation in neoplasia may identify additional new and promising prevention and therapy targets. We look forward to future studies that will assess the functional role of PGT in neoplasia, testing whether restoration of PGT expression suppresses tumorigenesis and elucidating the interactions between PGT and 15-PGDH in antagonizing the activity of the COX-2 oncogenic pathway.

Disclosure of Potential Conflict of Interest
No potential conflicts of interest were disclosed.

References
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