Prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2), a complex target for colorectal cancer prevention and therapy

ROBERTO BENELLI, ROBERTA VENÈ, and NICOLETTA FERRARI

GENOA, ITALY

A plentiful literature has linked colorectal cancer (CRC) to inflammation and prostaglandin-endoperoxide synthase (PTGS)2 expression. Accordingly, several nonsteroidal antiinflammatory drugs (NSAIDs) have been tested often successfully in CRC chemoprevention despite their different ability to specifically target PTGS2 and the low or null expression of PTGS2 in early colon adenomas. Some observational studies showed an increased survival for patients with CRC assuming NSAIDs after diagnosis, but no clinical trial has yet demonstrated the efficacy of NSAIDs against established CRC, where PTGS2 is expressed at high levels. The major limits for the application of NSAIDs, or specific PTGS2 inhibitors, as adjuvant drugs in CRC are (1) a frequent confusion about the physiological role of PTGS1 and PTGS2, reflecting in CRC pathology and therapy; (2) the presence of unavoidable side effects linked to the intrinsic function of these enzymes; (3) the need of established criteria and markers for patient selection; and (4) the evaluation of the immunomodulatory potential of PTGS2 inhibitors as possible adjuvants for immunotherapy. This review has been written to rediscover the multifaceted potential of PTGS2 targeting, hoping it could act as a starting point for a new and more aware application of NSAIDs against CRC. (Translational Research 2018;■■:■■–■■)

Abbreviations: PTGS = prostaglandin-endoperoxide synthase; COX-2 = cyclooxygenase-2; CRC = colorectal cancer; NSAIDs = nonsteroidal antiinflammatory drugs; ILF = isolated lymphoid follicles; ACF = aberrant crypt foci; DMH = dimethylhydrazine; PGE2 = prostaglandin E2; FAP = familial adenomatous polyposis; CD = Crohn's disease; GI = gastrointestinal; TXA2 = thromboxane A2; RR = relative risk; Treg = T regulatory cells

ISOLATED LYMPHOID FOLLICLES AND ABERRANT CRYPT FOCI: THE EARLIEST TARGETS OF CHEMOPREVENTION

Human colon contains a huge and complex biocenosis of residing bacteria that are separated from the body by a single, thin epithelial layer. Although most of these organisms play a positive role in colon homeostasis, they necessarily need to be confined to avoid local invasion and systemic dissemination. Moreover, the imbalance of this biome can favor the expansion of pathologic bacterial strains ad promote inflammatory, chronic diseases. Although the gut-associated lymphoid tissue of the small intestine has both specialized lymphoid structures, the Peyer's patches, and isolated lymphoid follicles (ILF), the colon contains only ILF. The number and diameter of ILF is related to the inflammatory condition of the gut.[1] Noteworthy, ILF are physiologically less numerous in the cecum as compared with the rectum, showing a direct correlation to the number of resident bacteria in these districts (about 10^8 and 10^{12}/mL respectively).[2,3] Accordingly, in mouse models, ILF number is reduced after antibiotic therapy.[4,5] This parallelism can be explained by the main function of ILF that is IgA production.[5,6]

From the OU Immunology, OU Molecular Oncology & Angiogenesis, Ospedale Policlinico San Martino (Istituto di ricovero e cura a carattere scientifico per l'oncologia), Genoa, Italy; OU Molecular Oncology & Angiogenesis, Ospedale Policlinico San Martino (Istituto di ricovero e cura a carattere scientifico per l'oncologia), Genoa, Italy.

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Reprint requests: Roberto Benelli, UO Immunology, Ospedale Policlinico San Martino, Largo Rosanna Benzi 10, 16132 Genoa, Italy; e-mail: roberto.benelli@hsanmartino.it.

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It has been proposed that ILF could be the switch points between inflammation and colorectal cancer (CRC)[1]; indeed, animal models of colon carcinogenesis have supported this observation. Rats treated with dimethylhydrazine (DMH) showed a significant association between sessile adenocarcinomas and lymphoid aggregates; this association was not observed for polypoid tumors.[7] Using the same rat model, Hardman and Cameron reported the selective immunohistochemical localization of transforming growth factor α in the proliferative zone of colonic crypts located over lymphoid aggregates,[8] and microscopic endophytic adenocarcinomas were found exclusively associated to lymphoid aggregates in treated rats. Carter et al. evaluated the distribution of aberrant crypt foci (ACF) and tumors in the gut of DMH-treated mice, finding a strong association between colon lymphoid tissue and colon tumors but not ACF, hypothesizing a possible promoting role of lymphoid tissue over tumors but not in the onset of ACF.[9] Only part of these observations have been confirmed in humans. In fact, Shpitz et al. found an increased (2.5×–8×) presence of ILF at the base of ACF.[10] We could argue that ACF onset in the mouse was linked to the rapid and aggressive activity of the carcinogen not relying on ILF support, that could instead be mandatory for sporadic human ACF. In non-polyposis coli patients, Oohara et al. observed the 55.6% of microscopic adenomas originating from the basal cell upon ILF,[11] supporting the observations in rat model. Fu and coworkers analyzed the incidence and localization of ILF in the early colorectal neoplasms of a large cohort of patients.[12] ILF were found in 280 of 1031 neoplasms, preferentially in flat or depressed lesions, confirming rat models. Interestingly, intramucosal ILF were observed in protruding, polypoid tumors, whereas submucosal ILF prevailed in depressed and flat neoplasms. In these established tumors, the presence of ILF could have different functions, and the authors hypothesized an immune reaction against neoplasms, although no attempt was made to detect apoptotic cells in ILF-containing tumors and the histology shown in the paper did not display signs of a macroscopic immune attack. According to these observations, ILF appear to be highly associated to ACF and microadenomas, suggesting a supportive role in the onset of pre and very early tumor stages. Among established neoplasms, only flat or depressed tumors appear to be significantly associated to ILF, although with less frequency, suggesting a progressive emancipation of tumor cells from the paracrine support of ILF. On the other hand, ILF do not usually associate to polyps, excluding their participation to exophytic colorectal tumor progression. In advanced CRC, the role of ILF is apparently subverted and the presence of tumor-associated ILF correlates with increased patients' survival linked to immune activation.[13] We do not know if nonsteroidal antiinflammatory drugs (NSAIDs) could affect ILF number or activation, and prostaglandin-endoperoxide synthase (PTGS)2 positivity has never been reported for ILF, although Barnes et al. observed in DMH-treated rats an increased proliferation and apoptosis of colon crypts selectively located over lymphoid nodules.[14] In this model, aspirin increased crypt apoptosis, showing that the crosstalk between lymphoid nodules and the crypt could be affected by this drug. Because of the tight association between ILF and ACF, some additional information can be obtained also from specific ACF-based studies.

ACF are considered the earliest pre-neoplastic lesions of the gut. ACF histology shows elevated crypts exceeding the normal mucosa, a thickened epithelium and dilated luminal openings. ACF were initially described in animal models of chemical carcinogenesis and eventually discovered in humans.[15] ACF are particularly frequent in patients at high risk of CRC, but rarely progress toward neoplastic transformation. Sporadic ACF show frequent K-Ras mutations. K-Ras mutations are usually concordant in the ACF and CRC of the same patient,[16] suggesting a possible clonal onset, or subjective genetic predisposition. In rat models, both PTGS1 and PTGS2 inhibitors are efficacious in reducing ACF number.[17] In humans, ACF show an increased expression of PTGS2 mRNA as compared with surrounding normal crypts, but this increase is not observed at protein level.[18] Accordingly, celecoxib, a specific PTGS2 inhibitor, failed to modulate ACF number in treated patients, whereas it was able to reduce adenoma occurrence.[19] On the contrary, the unspecific PTGS1/PTGS2 inhibitor sulindac reduced ACF number.[20] Aspirin, preferentially targeting PTGS1, effectively reduced ACF number, especially in the distal colon.[21]

According to these data, ILF associate to ACF and sustain their genesis. Thus, in this very early pretumor stage, the immune system apparently plays a promoting role on aberrant crypts. In these lesions, PTGS2 is not apparently expressed at protein level and consequently does not play a role as target of chemoprevention. On the contrary, PTGS1 targeting has shown a specific and strong effect in reducing ACF number, thus reducing the overall number of aberrant crypts that could progress toward carcinogenesis.

COLORECTAL POLYPS AND ADENOMA: CONTRADICTORY TARGETS FOR PTGS2 INHIBITORS

The study of ACF has demonstrated that the first mutational hit in the colon-rectum affects KRAS or BRAF, whereas the passage from ACF to sporadic adenoma is triggered by the appearance of APC inactivating mutations.[22,23] The consequent activation of the β-catenin