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Commentary

Circulating prostaglandins as biomarkers for colorectal cancer?

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Despite increases in our understanding of intestinal tumour biology, colorectal cancer remains a leading cause of cancer-related death worldwide. Most colorectal cancers develop from benign adenomas, presenting an opportunity for early detection and intervention prior to the onset of malignancy. For patients with early-stage tumours, five-year survival rates are high. However, as early-stage tumours are typically asymptomatic, strategies to identify at risk individuals are critical to enable early detection. Therefore, a key challenge is improving (the currently suboptimal) patient uptake to screening programmes, as well as the development of good prognostic and predictive biomarkers for cancer risk and response to treatment. In this context and because of the well-established role of prostaglandins in colorectal tumorigenesis there are an increasing number of studies evaluating the utility of circulating prostaglandins in association with cancer risk and disease progression. In this issue of *EBioMedicine*, Li et al. (2015) provide evidence suggesting that the measurement of circulating prostaglandins in the blood may have potential utility in identifying patients at risk of developing, or with, colorectal cancer. This is an attractive premise, as a convenient blood-based test may increase uptake amongst eligible individuals that do not presently participate in current screening procedures (such as the faecal occult blood test).

Prostaglandins are well-known to cancer biologists and have attracted a lot of attention as important targets for chemoprevention (Chan et al., 2005). They are generated by cyclooxygenase (COX) enzymes (COX-1 and COX-2), which are targets of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin. COX-2 is known to be upregulated in a size-dependent manner in about half of colorectal adenomas and in the majority of colorectal cancers, leading to increased PGE_2 levels (Eberhart et al., 1994; Elder et al., 2002). PGE_2 has a major influence on colorectal tumour biology (Greenhough et al., 2009), and the chemopreventive action of NSAIDs is thought to be mediated, at least in part, by blocking PGE_2 production. A number of studies have highlighted that PGE-M, a urinary PGE_2 metabolite that reflects systemic PGE_2 levels, could serve as a prognostic biomarker in colorectal, gastric, and more recently breast cancers (Dong et al., 2009; Johnson et al., 2006; Wang and DuBois, 2013).

At present, it is not clear whether prostaglandins other than PGE-M could also serve as prognostic or predictive biomarkers for colorectal cancer. To examine this, Li et al. took blood samples from healthy individuals, as well as from patients with familial adenomatous polyposis (FAP, an inherited predisposition to colorectal tumour formation due to germline heterozygosity in the *APC* gene) and sporadic colorectal cancer. The authors then examined the levels of circulating PGE_2, PGD_2, $PGF_2\alpha$, PGI_2 and thromboxane A_2 [TXA_2] — in most cases by measuring their stable metabolites as surrogates. Perhaps surprisingly, the authors only observed a modest increase in circulating PGE_2 (and PGD_2) levels in FAP patients, but the levels of TXA_2 (inferred by measurement of its more stable derivative TXB_2) were dramatically elevated in both FAP and sporadic colorectal cancer patients relative to healthy individuals. These observations were confirmed by measuring TXA_2 levels in the urine of colorectal cancer patients (by measuring 11-dehydro-TXB_2) and are consistent with a previous report of increased urinary TXA_2 in FAP patients (Dovizio et al., 2012). The authors went on to show that the majority of patients with colorectal cancer in their study could be identified by measuring circulating TXA_2 levels, and suggest that TXA_2 levels may therefore have prognostic value in colorectal cancer patients.

What could account for the high levels of circulating TXA_2 in patients with colorectal cancer? Could there be a role for TXA_2 signalling in tumour development? In an effort to understand this, Li et al. performed immunohistochemistry on patient colorectal tumour biopsies to examine the expression of TXA_2 synthase (TBXAS1), an important enzyme for TXA_2 production (Li et al., 2015). Expression of TBXAS1 was upregulated in tumour tissue, as was the TXA_2 receptor (TBXA2R), raising the possibility that they have a functional role in tumour development. In a series of in vitro experiments using colorectal cancer cells, the authors found that RNAi-mediated depletion of either TBXAS1 or TBXA2R resulted in decreased anchorage-independent growth — suggestive of reduced malignant potential. These findings are consistent with a previous study in which enforced expression of TBXAS1 accelerated tumour growth and angiogenesis in vivo (Pradono et al., 2002). Finally, the authors asked whether aspirin might target TXA_2 signalling as part of its chemopreventive action. Tumour biopsies from FAP patients grouped into aspirin users and non-users revealed an association between reduced TBXAS1 and TBXA2R expression and aspirin use. In support of these data, aspirin treatment of colorectal cancer cell lines in vitro decreased the protein expression of TBXAS1 and TBXA2R.

The findings of Li et al. highlight the possibility that the measurement of circulating prostaglandins might be useful in cancer screening and prevention, but naturally there are caveats (Li et al., 2015). The study used small patient numbers, so further validation will be necessary to determine the usefulness of circulating TXA_2 as a prognostic or predictive biomarker, and the study does not address the role of confounding factors such as inflammation and infection. Furthermore, it is

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unclear what contribution tumour-derived vs platelet-derived TXA_2 made to the level detected in the circulation. Does exogenous TXA_2 (or a stable analogue) promote colorectal tumour cell growth in vitro and would this rescue the inhibitory effects of TBXAS1-depletion the authors observe on anchorage-independent growth? If so, what signal transduction pathways are activated by TXA_2 in colorectal tumour cells? It will also be interesting to determine whether circulating TXA_2 levels can be used to report the efficacy of NSAIDs in cancer prevention and/or an adjuvant setting.

In summary, there is much to do before TXA_2 metabolites are used as biomarkers for cancer screening, but with careful validation in larger patient populations the case for using circulating prostaglandins as biomarkers for early detection, disease progression and response to treatment is gaining momentum.

Conflicts of interest

The authors declared no conflicts of interest.

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