Perspective
Perspective on Jin et al., p. 910

Estrogen Receptors in Colorectal Cancer: Goalkeepers, Strikers, or Bystanders?

Johan Hartman¹ and Jan-Åke Gustafsson²,³

Abstract
This perspective on Jin et al. (beginning on page 910 in this issue of the journal) discusses the importance of estrogen signaling in colorectal carcinogenesis, with a focus on estrogen receptor β (ERβ), which is the predominant ER in the colorectal epithelium. The importance of ERβ in breast cancer is well described in the literature, and recent studies reveal that ERβ functions similarly in colorectal cancer. The implications of this pathway include new possibilities to treat or prevent colorectal cancer with targeted endocrine drugs and the potential of ERβ as a novel diagnostic tool. Cancer Prev Res; 3(8): 897–9. ©2010 AACR.

Introduction
Colorectal cancer (CRC) is widely considered to be a disease of the industrialized world and a consequence of a certain dietary intake. Based on epidemiologic studies, diets with substantial amounts of meat and fat traditionally have been hypothesized to increase CRC incidence, whereas fruit, vegetables, and fibers have been suggested to protect against CRC (1, 2). In recent years, however, investigators have found a poor correlation between diet and CRC incidence. Therefore, dietary intake might influence CRC risk less than previously reported (3). For example, a large meta-analysis by Alexander et al. (4) based on six prospective cohort studies found no correlation between either dietary fats or animal protein and CRC. A meta-analysis by Koushik et al. based on 14 cohort studies found that fruit and vegetable intakes were not associated with CRC risk overall but might be associated with a lower risk of rectal cancer (5).

Other etiologic factors could be more important than diet in initiating CRC. For example, the Women’s Health Initiative trial highlighted the importance of estrogens and hormone replacement therapy (HRT) in CRC (6), and CRC risk is lower in women than in men (7, 8). Women who took HRT for an average of 5.6 years had a 44% lower relative risk of CRC compared with nonusers. This was the only positive cancer-related Women’s Health Initiative finding on HRT (9); some HRT results involving breast cancer are discussed later (10). Several studies also indicate an inverse association between use of combined oral contraceptives and CRC risk (11). Compared with the rather ambiguous role of diet, strong data points to a protective role for female hormones against CRC development.

In this issue of the journal, Jin et al. (12) describe a novel mechanism by which estrogens induce mismatch repair gene expression in colonic epithelial cells in vitro and in vivo. The DNA mismatch repair system is an evolutionarily conserved system with a key role in recognizing and repairing mismatches generated during DNA replication and recombination. Hence, the finding of Jin et al. could be an important explanation for estrogen-mediated protection against colon carcinogenesis. Of interest, hereditary nonpolyposis CRC is a result of mutated genes within the mismatch repair system.

We now know that estrogen functions are mediated by two nuclear receptor subtypes, estrogen receptor (ER) α and ERβ. These subtypes bind to estrogen response elements as homodimers or heterodimers either directly in promoter regions or indirectly through alternative DNA elements such as regions of activator protein 1 or specificity protein 1 (13, 14). The transcriptional activity of ERs, however, depends on direct interactions with nuclear receptor cofactors with chromatin-remodeling abilities. Cofactors could be of two types—coactivators or corepressors. Under normal conditions, estrogen-bound ERα activates transcription through the recruitment of coactivators. In tamoxifen-treated breast cancer cells, however, tamoxifen-bound ERα inhibits transcription through the recruitment of corepressors (15). ERα and ERβ have different tissue distributions and are sometimes coexpressed within the same tissue and cell type. ERβ is the only estrogen receptor in the normal colonic epithelium and declines dramatically in expression levels in CRC cells (16). Furthermore, ERβ expression decreases in correlation with higher grades of CRC (17). Consequently, one could infer that epithelial ERβ is responsible for the protective effect of estrogens against colorectal carcinogenesis.

A similar pattern of ERβ expression occurs in the breast, where ERβ is the only subtype in normal breast epithelial cells and is downregulated in breast cancer cells. On the other hand, ERα expression differs between the breast,
where it is coexpressed with ERβ in cancer cells, and the colon-rectum, where it is lacking in both the normal epithelium and cancer cells. Most of the numerous in vitro studies of human ERβ function have involved breast cancer cells (18). Based on these studies, one can conclude that ERβ has an overall antiproliferative effect, thereby inhibiting cancer cell proliferation and antagonizing ERα function in the breast (19, 20). Because estrogen signaling has such a central role in breast cancer progression, it generally has been thought that estrogens could even initiate breast cancer. Nevertheless, HRT with estrogen alone did not increase the risk of breast cancer in the Women’s Health Initiative clinical trials program (21).

As mentioned above, colorectal normal or cancer epithelium does not coexpress ERα and ERβ, and thus, does not allow any possibilities for ERβ to antagonize ERα function through heterodimerization. One could therefore expect a different expression profile and mechanism of ERβ-mediated transcriptional regulation in colorectal normal or cancer cells. Our group recently used lentiviral transduction of an ERβ expression vector to characterize ERβ function in colon cancer cells (22). ERβ expression resulted in the inhibition of proliferation and G1 phase cell-cycle arrest, and this effect depended on a functional DNA-binding region within ERβ. We also observed that ERβ expression strongly inhibited cMyc and tumor growth in a xenograft mouse model. These data suggest that induced ERβ in CRC cells has an antiproliferative, tumor-suppressive function that is independent of ERα. This conclusion raises the important question of whether ERβ could be activated in a more specific manner to prevent CRC carcinogenesis and even repress CRC progression? Perhaps this effect could be achieved by using synthetic, ER subtype-specific ligands. The selective ER modulators are a class of synthetic ER ligands with tissue-specific pharmacology. Tamoxifen is the best-known selective ER modulator, having an overall antagonistic function in breast epithelium aside from being used as a standard adjuvant treatment for ER-positive breast cancers (23). Tamoxifen has a strong affinity for ERα and works as an agonist or antagonist depending on cofactor expression within a particular cell and organ. Considering this variability, could tamoxifen be chemopreventive against CRC? A number of published studies have examined the effect of tamoxifen on CRC incidence (24, 25). Although the results of these studies are inconsistent, they provide little evidence that tamoxifen prevents CRC.

Based on the molecular character of their ligand-binding domains, ERα and ERβ have a binding preference for estradiol. On the other hand, ERs also have the ability to bind many other compounds with an estrogen-like structure, including phytoestrogens and xenoestrogens (or endocrine disruptors). In recent years, substantial efforts have been made to identify the adverse effects of xenoestrogens in the environment and their potential to affect estrogen signaling in normal physiology. Today, there is a serious concern that exposure to these substances could affect human health, including the risk of CRC and other cancers. Xenoestrogens comprise a wide range of structurally diverse compounds (26), including the industrial chemicals polychlorinated biphenyls and dioxins, which have well-known adverse health effects and potential to disrupt estrogen-signaling, and pesticides such as chlordecone, which have a strong carcinogenic effect. Little is known, however, about the potential role of xenoestrogens in CRC initiation.

Phytoestrogens are a diverse class of natural compounds with structural similarity to estradiol. These compounds generally have a binding preference for ERβ over ERα. Several phytoestrogens such as the isoflavone genistein, however, have ER-independent effects as well and should not be considered as ERβ-specific ligands. High phytoestrogen intake has long been associated with a lower incidence of CRC. Few clinical trials, however, have tested this hypothesis. Fruits, vegetables, and other foods considered rich in phytoestrogens contain different types and different levels of phytoestrogens, and therefore, it is difficult to draw conclusions concerning the significance of individual phytoestrogens and CRC. Barone et al. recently found that two ERβ-selective phytoestrogens effectively counteracted CRC tumorigenesis and surprisingly increased ERβ expression in mice with mutations of the tumor-suppressor gene adenomatous polyposis coli (APC; ref. 27). Other tumor models show similar effects of phytoestrogens. Treatment with phytoestrogen dietary soy isoflavones of an azoxymethane-induced colon cancer in rats reduced the burden of and increased ERβ expression within the tumor (28).

We can conclude that estrogens are important in protecting against CRC initiation and progression, and that the protective effect most likely is mediated by ERβ. Several clinical trials of ERβ-specific ligands are ongoing for different indications such as the prevention of menopausal symptoms. To our knowledge, however, no clinical trials of ERβ-specific ligands are being or have been performed for the prevention or treatment of CRC. Such trials are needed to finally establish the significance of ERβ as a target of CRC prevention or therapy.

Disclosure of Potential Conflicts of Interest

J.-Å. Gustafsson is a consultant of KaroBio, Sweden and Bionovo, Inc. No other potential conflicts of interest were disclosed.

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