

## Perspective

Perspective on Jin et al., p. 910

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

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## 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  $\beta$  (ER $\beta$ ), which is the predominant ER in the colorectal epithelium. The importance of ER $\beta$  in breast cancer is well described in the literature, and recent studies reveal that ER $\beta$  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 ER $\beta$  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 rath-

er 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)  $\alpha$  and ER $\beta$ . 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 ER $\alpha$  activates transcription through the recruitment of coactivators. In tamoxifen-treated breast cancer cells, however, tamoxifen-bound ER $\alpha$  inhibits transcription through the recruitment of corepressors (15). ER $\alpha$  and ER $\beta$  have different tissue distributions and are sometimes coexpressed within the same tissue and cell type. ER $\beta$  is the only estrogen receptor in the normal colonic epithelium and declines dramatically in expression levels in CRC cells (16). Furthermore, ER $\beta$  expression decreases in correlation with higher grades of CRC (17). Consequently, one could infer that epithelial ER $\beta$  is responsible for the protective effect of estrogens against colorectal carcinogenesis.

A similar pattern of ER $\beta$  expression occurs in the breast, where ER $\beta$  is the only subtype in normal breast epithelial cells and is downregulated in breast cancer cells. On the other hand, ER $\alpha$  expression differs between the breast,

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where it is coexpressed with ER $\beta$  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 ER $\beta$  function have involved breast cancer cells (18). Based on these studies, one can conclude that ER $\beta$  has an overall antiproliferative effect, thereby inhibiting cancer cell proliferation and antagonizing ER $\alpha$  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 ER $\alpha$  and ER $\beta$ , and thus, does not allow any possibilities for ER $\beta$  to antagonize ER $\alpha$  function through heterodimerization. One could therefore expect a different expression profile and mechanism of ER $\beta$ -mediated transcriptional regulation in colorectal normal or cancer cells. Our group recently used lentiviral transduction of an ER $\beta$  expression vector to characterize ER $\beta$  function in colon cancer cells (22). ER $\beta$  expression resulted in the inhibition of proliferation and G<sub>1</sub> phase cell-cycle arrest, and this effect depended on a functional DNA-binding region within ER $\beta$ . We also observed that ER $\beta$  expression strongly inhibited cMyc and tumor growth in a xenograft mouse model. These data suggest that induced ER $\beta$  in CRC cells has an antiproliferative, tumor-suppressive function that is independent of ER $\alpha$ . This conclusion raises the important question of whether ER $\beta$  could be activated in a more specific manner to prevent CRC carcinogenesis and even reverse 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 ER $\beta$  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, ER $\alpha$  and ER $\beta$  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 ER $\beta$  over ER $\alpha$ . Several phytoestrogens such as the isoflavone genistein, however, have ER-independent effects as well and should not be considered as ER $\beta$ -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 ER $\beta$ -selective phytoestrogens effectively counteracted CRC tumorigenesis and surprisingly increased ER $\beta$  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 ER $\beta$  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 ER $\beta$ . Several clinical trials of ER $\beta$ -specific ligands are ongoing for different indications such as the prevention of menopausal symptoms. To our knowledge, however, no clinical trials of ER $\beta$ -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 ER $\beta$  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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