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Xenoestrogens challenge 17β-estradiol protective effects in colon cancer

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Abstract

Several epidemiological, cellular, and molecular studies demonstrate the role of environmental chemicals with endocrine disrupting activities, typical of Westernized societies, in the pathogenesis of numerous diseases including cancer. Nonetheless this information, the design and execution of studies on endocrine disruptors are not yet cognizant that the specific actions of individual hormones often change with development and ageing, they may be different in males and females and may be mediated by different receptors isoforms expressed in different tissues or at different life stages. These statements are particularly true when assessing the hazard of endocrine disruptors against 17β-estradiol (E2) actions in that this hormone is crucial determinant of sex-related differences in anatomical, physiological, and behavioral traits which characterize male and female physiology. Moreover, E2 is also involved in carcinogenesis. The oncogenic effects of E2 have been investigated extensively in breast and ovarian cancers where hormone-receptor modulators are now an integral part of targeted treatment. Little is known about the E2 preventive signalling in colorectal cancer, although this disease is more common in men than women, the difference being more striking amongst pre-menopausal women and age-matched men. This review aims to dissect the role and action mechanisms of E2 in colorectal cancer evaluating the ability of estrogen disruptors (*i.e.*, xenoestrogens) in impair these E2 actions. Data discussed here lead to define the possible role of xenoestrogens in the impairment and/or activation of E2 signals important for colorectal cancer prevention.

Key words: 17β-Estradiol; Estrogen receptors; Xenoestrogens; Bisphenol A; Flavonoids; Colorectal cancer

Core tip: In this review, we will report recent data, including ours, on 17β-estradiol (E2) action in colon health and disease discussing on how environmental chemicals with endocrine disrupting activities could impact on these E2 effects in colon cancer. In particular, two plant-derived flavonoids (*i.e.*, naringenin, Nar, and quercetin, Que) and one synthetic food-contaminant bisphenol A will be reported as prototype molecules to evaluate how xenoestrogens can impact on cell proliferation/apoptosis balance, the critical physiological function of E2 in colon.

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INTRODUCTION

Since many years it was believed that the primary function of 17β-estradiol (E2) was in the development of female secondary sexual characteristics and subsequent regulation of reproductive function. However, this has been recognised as an over-simplification and now it is well known that this sex steroid hormone elicits a myriad of biological responses directed towards profoundly changing male and female physiology[1]. As a consequence, it is not surprising that E2 is also involved in

diseases including carcinogenesis. The oncogenic effects of E2 have been investigated extensively in breast[2] and ovarian[3] cancers where hormone-receptor modulators are now an integral part of targeted treatment. Little is known about the E2 preventive signalling in colorectal cancer although women are less susceptible to this cancer than men[4].

Both physiological and the contradictory pathologic actions of E2 are mediated by two receptor subtypes (*i.e.*, ERα and ERβ) members of the nuclear receptor superfamily which are defined as ligand-activated transcriptional factors. ERα and ERβ are localized in the cytoplasm and in the nucleus of E2-target cells where they are associated, in the resting state, to heat shock proteins. A small pool of these receptors is palmitoylated and localized at the plasma membrane in association with caveolin-1[5]. E2 binding to the cytosolic ER population (both ERα and ERβ) induces conformational changes that facilitate ER homo/heterodimerization, nuclear translocation, and binding to specific DNA recognition sequences (*i.e.*, estrogen responsive elements; ERE)[1]. In this classical/genomic mode of action, ERα and ERβ promote E2-sensitive gene transcription, ERβ being approximately 30% less efficient than ERα[6]. It is well established that the main role of the plasma membrane-localized ER population is to generate rapid/extranuclear signal transduction pathways that culminate in the activation of the protein kinase cascade[7]. The nature of these pathways as well as the role played in cell functions differs between ERα and ERβ[6]. In particular, rapid signals generated from the E2-ERα complex drive cells into the cell cycle and represent the main determinant for the E2 proliferative/survival effects[8,9]. By contrast, rapid effects generated by the E2-ERβ complex drive cells out of the cell cycle[10,11], representing the key to understanding the E2-induced antiproliferative effects working both during differentiative processes and in colon adenocarcinoma[11-17].

ERs are relatively promiscuous nuclear receptors with the ability to recognize, besides E2, different exogenous substances[18]. Several of these substances such as bisphenol A (BPA), diethyl hexyl phthalate, and the plant-derived polyphenols show estrogenic activity, thus they are collectively called xenoestrogens. Besides other impairment of E2 actions, the possible contribution of xenoestrogens in the incidence of E2-related cancers has only fairly recently received attention. In particular, only a few studies addressed the putative association between increased risk of colon cancer and environmental and occupational exposures to xenoestrogens have been reported[19].

In this review, we will report recent data, including ours, on E2 action in colon health and disease discussing on how xenoestrogens could impact on these E2 effects in colon cancer. In particular, two plant-derived flavonoids (*i.e.*, naringenin, Nar, and quercetin, Que) and one synthetic food-contaminant bisphenol A (BPA) will be reported as prototype molecules to evaluate how xenoestrogens can impact on cell proliferation/apoptosis balance, the critical physiological function of E2 in colon.

EFFECT OF 17β-ESTRADIOL IN COLON

Although the colon might not be considered one of "conventional" E2 target tissue, this pleiotropic hormone exerts various actions on the organs which assemble gastrointestinal apparatus. Whereas the role of E2 in colon malignancies is well established[20] (see below), less information are available on physiological functions of E2 in the colon[21]. The impact of E2 on colon physiology became evident when considering that several gastrointestinal disorders show considerable gender-specific incidence. As an example, the predominance of constipation in women is frequently reported with a female/male ratio approximately of 9:1. Also, the prevalence of irritable bowel syndrome is higher in women compared to men suggesting the involvement of E2 in the regulation of colon motility. This evidence is also supported by studies reporting delayed gastrointestinal transit time during pregnancy, characterized by high E2 and progesterone levels[22]. Both ERα and ERβ are present in enteric nerve cells[23] and in colonic smooth muscle cells[24] sustaining the E2 potential function as intestinal motility regulator. In addition, E2 also exerts profound actions on epithelial cells of intestinal wall. An E2-dependent up-regulation of sodium/hydrogen exchanger-3 in the plasma membrane of epithelial cells of the proximal colon has been reported in pregnant mice[21,25].

Knockout experiments targeting ER genes in mice have been useful in understanding the role played by ERα and ERβ in colon. Indeed, targeted disruption of ERβ in mice[26] and further investigation of tissue expression, have revealed that ERβ is the predominant ER expressed in colonic tissues[27-29] and that its expression is selectively lost in human malignant colon tissue[6,30-32].

To better understand the physiological role of ERβ in colonic tissue, Wada-Hiraike *et al*[33] compared morphology, proliferation, and differentiation of colonic epithelium in ERβ$^{-/-}$ mice and wild-type (wt) littermates. BrdUrd labeling revealed that the number of proliferating cells was higher in ERβ$^{-/-}$ mice and that the migration of labeled cells toward the luminal surface was faster in ERβ$^{-/-}$ mice than in wt littermates. Additionally, in the absence of ERβ, there was a decrease in apoptosis and in the expression of the differentiation markers. Finally, ERβ$^{-/-}$ mice display disrupted tight junction formation and abnormal colonic architecture[33]. As a whole, the loss of ERβ leads to hyperproliferation, loss of differentiation, and decreased apoptosis in the epithelium of colon suggesting a pivotal role for ERβ in the organization and architectural maintenance of the colon[32].

EFFECT OF 17β-ESTRADIOL IN COLORECTAL CANCER

Colorectal cancer is thought to develop as a sequence from aberrant crypt proliferation or benign hyperplasia to benign adenoma and then in most cases to adenocarcinoma. Epidemiological studies ascertained that this cancer is the second to fourth most common fatal malig-

nancy in industrialized countries[33-37]. Although colorectal cancer is a common malignancy in both sexes[38], several sex-related differences in incidence, certain molecular characteristics and response to chemotherapy have been reported. In particular, the difference between sexes are more striking amongst premenopausal women and age-matched men[29,38,39]. Based on a meta-analysis of 18 epidemiologic studies, the use of hormone replacement therapy by postmenopausal women was associated with a 20% decrease in colon cancer risk[40,41]. Other studies also demonstrated that women with a history of current or past hormone replacement therapy had a significantly decreased risk of colorectal cancer and showed that there are gender differences regarding cancer location and type within the colon[4,42].

These findings suggested that exposure to E2 and/or estrogenic compounds may underlie the differences between sexes leading many investigators to search for the ER subtype involved in this form of protection exerted by E2 against colorectal cancer. Since ERα is reported to be minimally expressed in normal colon mucosa and colon cancer cells[27,43], the effects of estrogen on colon cancer susceptibility could be mediated by ERβ[13]. ERβ1, 2 and 5 have been demonstrated in normal colorectal mucosa and at much higher levels than ERα[27,30]. Using semi-quantitative reverse transcription-polymerase chain reaction, Campbell-Thompson *et al*[27] showed that ERβ is the predominant ER subtype in the human colon, and that decreased ERβ1 (ERβwt) and ERβ2 (ERβcx) mRNA levels are associated with colonic tumorigenesis in women. In accordance, other authors[28,30] showed that ERβ expression was significantly lower in colon cancer cells than in normal colonic epithelium, and that there was a progressive decline in ERβ expression, which paralleled the loss of malignant colon cell dedifferentiation. A model of mice bearing germline mutations in murine Adenomatosis polyposis coli (APC) develops multiple intestinal tumors. In this model, E2-induced prevention of APC associated tumor formation was correlated with an increase in ERβ protein and a decrease in ERα expression[13,44].

Beside the previous models, also human colon cancer cell lines have been found to express primarily ERβ[45,46], where E2 stimulation (10-1000 nmol/L) consistently induced apoptosis in a dose-dependent manner[16,17,41,46]. Altogether, these results strongly suggest that the presence of ERβ could justify the E2 effects against colon carcinogenesis.

17β-estradiol action mechanism in colorectal cancer

The first mechanism in anti-proliferative action of ERβ was suggested by the papers of Paruthiyil *et al*[14] and Ström *et al*[15]. They showed that introducing ERβ into breast cancer cell line (MCF-7 and T47D), which also expresses ERα, caused an inhibition of proliferation *in vitro* and prevented tumor formation in a mouse xenograft model in response to E2. ERβ inhibited proliferation by repressing components of the cell cycle which are associated with proliferation, such as c-myc, cyclin D1, and cyclin A gene transcription, and by increasing the expression of Cdk inhibitor $p21^{Cip1}$ and $p27^{Kip1}$, which leads to a G_2 cell cycle arrest. These findings suggested a possible role for ERβ as tumor suppressor in breast cancer, impairing ERα-mediated proliferative effects of E2[14,15]. But in colon mucosa and colon cancer cells only ERβ is expressed[27,43], so the protective effects of estrogen on this tissue should be mediated by specific ERβ-activated signal transduction pathways.

To test this hypothesis, we used DLD-1 colon adenocarcinoma cancer cells in which only ERβ1 isoform is present. In these cells ERβ undergoes palmitoyl acyl transferase-dependent S-palmitoylation which allows to a small ERβ pool to localize at the plasma membrane and associate to caveolin-1 and the p38 member of mitogen activated protein kinase (MAPK) family[16]. Upon E2 stimulation, ERβ undergoes de-palmitoylation paralleled by an increased association of receptor to caveolin-1 and to p38. The physical association ERβ-caveolin-1 and p38 increase ERβ level at the plasma membrane, impairing its association to other signaling proteins which characterize E2-induced ERα-mediated cell survival and proliferation [*i.e.,* Src, extracellular regulated kinase/mitogen activated protein kinase (ERK/MAPK), and phosphatidyl inositol 3 kinase/serine-threonine protein kinase Akt (PI3K/AKT)][16]. On the other hand, the E2-induced ERβ association to p38 strongly impacts on DLD-1 colon cancer cells growth. In fact, p38 activation is required for the activation of downstream pro-apoptotic cascade involving the cleavage of caspase-3 and of its main substrate the poly-(ADP-ribose) polymerase (PARP). Further study of DLD-1 cells, revealed that ERβ activation of the p38-MAPK pathway leads to increased expression of ERβ itself by both genomic and nongenomic means[17] leading to a self-perpetuating cycle increasing its protective effect.

As a whole, the membrane-starting signal due to the presence of ERβ at the plasma membrane seems to be mainly involved in protective effects of E2 against colorectal cancer. In fact, the treatment of these cells with the palmitoylation inhibitor 2-Bromopalmitate (2Br) completely remove ERβ from the plasma membrane impairing p38 activation. This condition prevents the pro-apoptotic cascade activation without interfering with ERβ transcriptional activity which, indeed, is still able to promote ERE-dependent gene transcription[17].

Furthermore, experimental studies with nitric oxide (NO) support the E2 rapid signal involvement in protective effects of E2 mediated by ERβ against colon cancer. NO is a diatomic molecule whose presence, modulated by several hormones including E2, is important for gastrointestinal motility. NO mainly acts through *S*-nitrosylation of cysteine (Cys) residues in target proteins modulating their activity[47-49]. Among proteins regulated by NO, modulation of ERs has been demonstrated. This molecule is able to link to ER's zinc finger impairing their transcriptional activity without interfering with rapid signal pathways. S-nitrosylation seems to selectively modulate the bioactivity of ER, shifting the receptor from its role as a transcription factor toward rapid functions. For instance, in DLD-1 colon cancer cells, in the occurrence

of NO concentration in micromolar range, normally present during peristalsis, transcriptional activity of ERβ is inhibited, but ERβ maintains its capability to mediate pro-apoptotic effects of E2 inducing caspase-3 activation and the PARP cleavage. When over produced (*e.g.*, during inflammation processes) NO worsens its effects. Although the ERβ-dependent phosphorylation of p38/MAPK is still present, NO inhibits the caspase-3 catalytic activity by nitrosylation of enzyme's Cys residues[48].

Thus, besides its role as negative modulator of ERα activities above reported and its ability to decrease the transcription of anti-apoptotic genes[50], these findings indicate that ERβ triggers specific rapid signal cascade mainly involved in protective effect of E2 in colorectal cancer.

XENOESTROGEN EFFECT IN COLORECTAL CANCER

Xenoestrogens, like other endocrine disrupting substances, could interfere with the synthesis, secretion, transport, metabolism, binding, action or elimination of E2[51,52]. All these actions could affect the homeostasis maintenance, reproduction, and developmental processes regulated by this hormone in all organs and tissues including colon. Currently quite lot chemicals, containing halogen groups have been identified as xenoestrogens. They include: (1) synthetic chemicals used in industry, agriculture, and consumer products; (2) synthetic chemicals used as prescription drugs; and (3) chemical components of human and animal food. Xenoestrogens have very low water solubility, extremely high lipid solubility, and long environmental half-life resulting in a continue increase of their global concentration in the environment even at great distances from where they are produced, used or released. Exposure to xenoestrogens can occur from a number of different sources: water, air, food, soil or even in the workplace[53].

In a review embracing environmental and occupational causes of cancer, Clapp *et al*[19] identified only a few studies that found increased risk of colon cancer associated with environmental and occupational exposures. The researchers reported a study in a nested case-control study of female textile workers in Shanghai showing that long-term exposure (20 years or longer) to dye and dye metabolites resulted in nearly 4-fold elevation in colon cancer risk. In a cohort of aerospace workers exposed to hydrazine, a component of rocket fuels, colon cancer was elevated when exposures were lagged 20 years and risk significantly increased with increasing dose. Lastly, a significant increase in colon cancer risk was reported among pesticide applicators with increasing level of exposure to the herbicide dicamba. Although these limited studies indicate a positive correlation between colon cancer incidence and environmental pollutants, no information on the estrogenicity of these compounds was reported[19].

In a recent and very interesting review, Sokolosky and Wargovich[54] reported and commented the data by GLOBOCAN[36]. The researchers evidenced that the incidences for colorectal cancer, as well as most other cancers, were highest in Australia, Canada, Western Europe, Japan, and the United States, while the lowest incidences were reflected for the majority of the African continent (except for South Africa), India, the Middle East, and South American countries surrounding the Amazon basin[54]. Although the reduced risks of cancer and other chronic diseases reported in people from these low-income countries could be attributable in some ways to genetic disposition, it could be also related with environmental factors arising from their retention of preventive dietary and lifestyle practices. Thus, they concluded that the correlation between modernization, acculturation, and increased risk for chronic diseases such as colorectal cancer exists[54].

Recently, two Scientific Statement of The Endocrine Society focused on a demanding need to understand the basic mechanisms of action and the physiological consequences of endocrine disruptors. In particular, among other scientific recommendations for research, it is imperative to perform basic *in vitro* molecular studies to identify pathways for xenoestrogens influence on endocrine tissues[51,52]. Given the diverse repertoire of xenoestrogens present in the environment, it should not be surprising that these molecules exert their effects through several mechanisms. Indeed, xenoestrogens act directly *via* steroid hormone receptors or indirectly through non-steroid receptors (*e.g.*, neurotransmitter receptors such as the serotonin receptor, dopamine receptor, norepinephrine receptor), orphan receptors (*e.g.*, aryl hydrocarbon receptor AhR), and on enzymatic pathways involved in steroid biosynthesis and/or metabolism[53]. Therefore, such considerable structure heterogeneity and diverse potential mechanism of action make the characterization of the effects of these substances quite hard. Nonetheless, many xenoestrogens often have a phenolic moiety that mimics E2 enabling them to interact with ERs as agonists or antagonists[18]. However, xenoestrogens have been often, if not exclusively, tested for their ability to influence the ERs nuclear activities while xenoestrogens ability to participate in the extranuclear activities of the ERs has been rarely evaluated. It has been reported that BPA, a well known xenoestrogen, binds to ERα and ERβ with a lower affinity than E2 (*i.e.*, 10 μmol BPA *vs* 10 nmol E2) inducing E2-responsive gene expression. Interestingly, the set of genes induced by BPA and E2 seems to be quite different, most of them being unique for BPA[55-57]. Moreover, our recent experiments in colon cancer cells expressing only ERβ subtype indicates that BPA acts as a full E2 antagonist by blocking both genomic and extranuclear ERβ activities which drive colon cancer cells to apoptosis[57].

The plant-derived flavonoids represent a singular class of xenoestrogens. Indeed, over several decades, a combination of epidemiological and experimental indications has shown that these compounds have a protective potential on human health[58-61]. This evidence led to a substantial increase in flavonoid usage as dietary

components, even if the estrogen-like or the estrogen antagonistic effects are not yet fully clarified. Intriguingly, flavonoids are considered potentially able to exert also a protective role against the development of E2-dependent tumours by binding to ERα and ERβ[59,62-65]. Among others, nutritionally relevant concentrations of naringenin (5,7,4'-trihydroxyflavone, Nar), especially abundant in oranges and tomatoes, or of quercetin (2-(3,4-dihydroxyphenyl-3,5,7-trihydroxy-4*H*-1-benzopyran-4-one, Que) present in apples, onions, and other vegetables induce apoptosis in different cancer cell lines containing ERα or ERβ (*e.g.*, colon, breast, and uterus cancer cell lines)[62-64]. As an example, quercetin, at nutritionally relevant concentrations, mimic E2-induced apoptotic effect in ERβ-containing DLD-1 colon cancer cell lines by inducing the activation of p38/MAPK. In turn, p38 activation is responsible for the pro-apoptotic activation of caspase-3 and the cleavage of PARP. Notably, no inactivation or downregulation of the survival kinases (*i.e.*, PI3K/AKT and ERK/MAPK) or the antiapoptotic protein Bcl-2 was observed after quercetin stimulation[64]. On the contrary, quercetin acted similarly to E2 by increasing the levels of the oncosuppressor protein PTEN and by impeding ERβ-dependent cyclin D1 promoter activity, which subsequently resulted in the transcription of the estrogen-responsive element remaining unchanged[64]. As a whole, these data indicate that flavonoids mimic the E2 effects in the presence of ERβ1, thus maintaining the E2 anticarcinogenic potential against colorectal cancer. Intriguingly, even in the presence of BPA naringenin impairs cancer cell proliferation by activating caspase-3-dependent apoptosis, at least in E2-dependent breast cancer cell lines expressing ERα[66]. If similar mechanisms are working also in colorectal cancer cell lines is unknown at the present.

CONCLUSION

The increase in non-communicable diseases in humans and wildlife over the past 40 years indicates an important role of the modernization and its resulting life style trends in disease etiology. Over the years this concern grew with the advancement of biochemical, biomedical, and biotechnological industries and with the increasing possibility of bioterrorism and chemical-warfare. The man-made chemicals and, in particular xenoestrogens, are nowadays found abundantly in the environment on residential buildings, cars, furniture, plastics, products such as baby feeding bottles, lining, tin-food containers, and even in children's toys. Thus, xenoestrogens are important component of the environmental influences on disease, along with nutrition and other factors. This sentence is sustained by data obtained from epidemiologic evidence, *in vivo*, and *in vitro* studies which give us an alarming picture of the wide effect of xenoestrogens on human health[47,48,62]. In particular, the literature demonstrates a role of these substances in the pathogenesis of obesity, diabetes mellitus, cardiovascular disease, and cancer the major epidemics of the modern world[67-69].

Here, we explored the idea that the increased incidence of diseases such as colorectal cancer could be the result of physiological and molecular imbalances of E2 signals. Flavonoid-deprived diets combined with low-dose exposures to xenoestrogens could be linked to increasing incidences of this type of cancer in Westernized societies and developing countries. In order to address a disease multi-factorial, case-specific, and remarkably adaptive as colorectal cancer, research must focus on its root causes in order to elucidate the molecular mechanisms by which they can be prevented or counteracted *via* plant-derived compounds such as naringenin and quercetin. As a whole, the research on the impact of xenoestrogens on E2-induced protection against colorectal cancer represents an area that requires further investigation.

At the present, a huge amount of literature assembles tissue culture, animal studies (*in vivo* and *ex vivo*), and epidemiological data only on the effect of xenoestrogens on gynaecological cancers (*i.e.*, breast, ovary, and endometrial cancers) whereas only few address the role of these compounds on colorectal cancer. In addition, data on xenoestrogen action mechanisms in colorectal cancer are still unclear and confused. Molecular studies *in vitro* and with *in vivo* animal models are needed to identify pathways for xenoestrogen influence on this E2 target tissue. In addition, studies on xenoestrogens on gastrointestinal and colon are much underrepresented, and these fields need to be expanded.

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