Opinion

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The role of estrogens and estrogen receptor signaling pathways in cancer and infertility: the case of schistosomes

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***Schistosoma haematobium*, a parasitic flatworm that infects more than 100 million people, mostly in the developing world, is the causative agent of urogenital schistosomiasis, and is associated with a high incidence of squamous cell carcinoma (SCC) of the bladder. Schistosomiasis haematobia also appears to negatively influence fertility, and is particularly associated with female infertility. Given that estrogens and estrogen receptors are key players in human reproduction, we speculate that schistosome estrogen-like molecules may contribute to infertility through hormonal imbalances. Here, we review recent findings on the role of estrogens and estrogen receptors on both carcinogenesis and infertility associated with urogenital schistosomiasis and discuss the basic hormonal mechanisms that might be common in cancer and infertility.**

The case of schistosomiasis

Schistosomiasis is a neglected tropical disease transmitted to humans from freshwater snails. It is caused by a blood fluke of the genus *Schistosoma*. Schistosomiasis is considered the most important of the helminthiases and the second most important parasitosis, after malaria, causing high rates of morbidity and mortality. Schistosomes affect at least 76 countries and 200 million people worldwide. From these, 20 million have severe disease and 120 million are considered symptomatic. Risk of infection affects 600 million others including travelers from developed countries [1].

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This opinion focuses on estrogen metabolism and estrogen receptor (ER) signaling pathways associated with cancer induction and female infertility in the context of *Schistosoma haematobium* infection. The present work attempts to integrate a variety of studies and experimental approaches with *S. haematobium* models, while giving particular emphasis to the *in vitro* studies that have contributed to expanding our understanding of the mechanisms of action of estrogen metabolism and ER signaling pathways associated with schistosomiasis. In particular, we suggest that hormonal imbalance resulting from *S. haematobium* may promote cancer and infertility.

Urogenital schistosomiasis

Three major species of schistosomes are the agents of human schistosomiasis – *Schistosoma japonicum* and *Schistosoma mansoni* cause intestinal schistosomiasis in East Asia, Africa, South America and the Caribbean, while *S. haematobium*, occurring widely throughout Africa and the Middle East, causes urogenital schistosomiasis. Recent recalibration of health burdens revealed that in the range of 4.5–70 million disability adjusted life years (DALYs) are lost to schistosomiasis. More people are infected with *S. haematobium* than with the other schistosomes combined. Of ~112 million cases of *S. haematobium* infection in sub-Saharan Africa, 70 million are associated with hematuria, 18 million with major bladder wall pathology, and 10 million with hydronephrosis leading to kidney damage [2–4]. In many patients, deposition of *S. haematobium* parasite ova eventually leads to squamous cell carcinoma (SCC) of the bladder [5,6]. Accordingly, *S. haematobium* has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) [7,8]. In addition, as many as 75% of women infected with *S. haematobium* suffer from female genital schistosomiasis (FGS) of the lower genital tract [3]. FGS results from

deposition of schistosome eggs in the uterus, cervix, vagina, and/or vulva, with ensuing inflammatory responses; it also increases susceptibility of the woman to HIV [9–11]. The resulting FGS is associated with contact bleeding, discharge, pain on intercourse, as well as diminished fertility, besides being a source of shame and stigma [12].

The cellular and molecular mechanisms linking *S. haematobium* infection either with both cancer induction and female infertility remain to be deciphered [12,13]. However, estrogen-derived molecules and estrogen receptor signaling pathways have been described for both associations. Accordingly, we review and discuss the general molecular mechanisms underlying estrogen metabolism, focusing on the hormones and receptors involved.

Molecular mechanism underlying estrogen metabolism

Estrogens are steroid hormones produced in the ovaries, adrenal glands, and placenta during pregnancy. The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH induce the production of estrogen in the form of estradiol and estrone by the ovaries. These estrogens bind to ERs in target tissues of the breast, uterus, brain, bone, liver, and heart [14]. When the estrogen molecule binds to its receptor, a conformational change in the ER permits its interaction with a specific regulatory sequence of the ER gene (estrogen responsive element), inducing the transcription of this target coding sequence. The resulting ER protein promotes changes in the cell according to tissue type and underlying conditions. The cycle is completed when high levels of estrogen in the blood send negative feedback to the hypothalamus to suppress the release of GnRH [14].

By the 1950s, most of the basic actions of the estrogenic hormones were recognized, such as their stimulation on the growth and function of tissues of the female reproductive tract. However, the biochemical processes involved were not entirely clear [15]. The generally accepted hypothesis was that the 17-hydroxyl group of estradiol underwent enzymatic oxidation from a cholesterol molecule using one coenzyme (NADH), and the resulting estrone was reduced using another (NADPH) [15]. The identification of the ER provided a mechanism to describe the target site specificity of estrogen action in the uterus, vagina, pituitary gland, and breast tissue [16]. Most importantly, a test was established to predict the outcome of antihormonal therapy in breast cancer, and a target was identified to develop new drugs for the treatment and prevention of breast cancer [16].

ERs and action of estrogen

Nuclear hormone receptors belong to a family of hormone-activated transcription factors that can initiate or enhance the transcription of genes containing specific hormone response elements [17]. The human ER, which belongs to this family, was cloned and sequenced from MCF-7 human breast cancer cells [17]. The human ER locus is located on chromosome 6q sub-band 25.1 [18] and the mouse ER is located on chromosome 10 [19,20]. The ER consists of 595 amino acids with a molecular mass of 66 kDa and includes six functional domains [20–22]; two of the domains are highly conserved among the members of the nuclear hormone receptor superfamily [20–22]. Two zinc fingers at the DNA-binding domain (DBD) of ER mediate receptor binding to hormone-response elements in the promoter regions of hormone-responsive genes. The hormone-binding domain (HBD), located at the ER C terminus, exhibits two regions of sequence homology with other hormone receptors. These regions confer hormone specificity and selectivity to ER [22–26].

More recently, another sequence belonging to the nuclear hormone receptor superfamily was cloned from a rat prostate cDNA library [27,28]. This sequence was named ERβ (as opposed to ERα). ERβ contains 485 amino acid residues and has a molecular weight of 54.2 kDa (Figure 1). There is a high homology between ERα and ERβ, mainly in the DBD (95%) and the HBD (55%), and both proteins bind estrogen with high affinity, bestowing functional homology. The latter has been determined by the activation of transcription of a vitellogenin A2, an estrogen-response element (ERE)-containing reporter plasmid in the presence and absence of estrogen [20,27].

The mechanism of target site specificity and selectivity seen with anti-estrogens, such as raloxifene, could be explained by the existence of two different ERs [29]. The receptor-specific regions are probably responsible for the differences seen between ERα and ERβ, in spite of the high homology in the conserved regions of both ERs [20].

Estrogen diffuses through the plasma membrane of cells where it binds to the ER. Once estrogen binds to the inactive ER, the receptor is activated, a conformational change and homodimerization occurs, and two receptor–ligand monomers dimerize and bind to the ERE. Once bound to the ERE, the ER uses activation functions (AFs) (AF-1 and AF-2) to stimulate transcription from

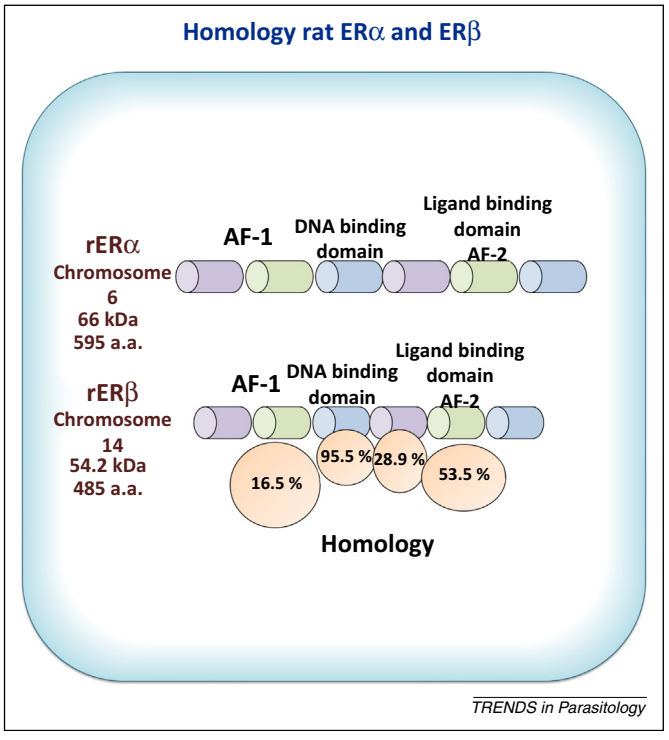

Figure 1. Comparison of the rat (r) ERα and rERβ proteins and percent amino acid homology in the functional regions (Adapted from [20]). Abbreviation: ER, estrogen receptor.

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