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Review

Interplay of estrogen receptors and FOXA factors in the liver cancer

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ABSTRACT

Liver cancer is the fifth most common cancer in human with male dominance. Sexual dimorphism of liver cancer is conserved from rodents to humans, which was firstly found in mice in late 1930s and female mice were resistant to liver cancer. Sex hormones were found to affect the incidence of liver cancer in rodents. Estrogen receptor alpha (ERα)-mediated estrogen signaling or androgen receptor-mediated androgen signaling prevents or promotes the growth of rodent liver tumors, respectively. Forkhead box protein A (Foxa) factors, Foxa1 and Foxa2, also known as pioneer transcription factors in liver specification, are essential for both estrogen and androgen signaling by acting as central regulators of sexual dimorphism in liver cancer. This review mainly focuses on the interplay between ERα and FOXA factors in liver cancer, and summarizes recent breakthrough studies in elucidating the mechanisms of sexual dimorphism in liver cancer.

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1. Introduction

Sexual dimorphism has been found in the susceptibility of many cancers (Dorak and Karpuzoglu, 2012). Women show significantly lower incidence of HCC than men (Parkin et al., 2005). Sex hormones, estrogen in females and androgen in males, have been known to modulate sexual dimorphism of liver cancer, primarily hepatocellular carcinoma (HCC) since late 1930s (Andervont and Lorenz, 1937; Burns and Schenken, 1940; Tomita, 1937). Sexual dimorphism in other types of liver cancer has been barely studied, though their incidences showed clear sex difference and male dominance in human (SEER/NCI). Estrogen suppresses the tumorigenesis of HCC, whereas androgen promotes it (Ma et al., 2008; Shimizu et al., 1998; Tsutsui et al., 1992; Wu et al., 2010; Yamamoto et al., 1991). However, the molecular mechanism underlying sexual dimorphism of liver cancer has been poorly understood. Our recent breakthrough study revealed that forkhead box protein A (Foxa) factors, Foxa1 and Foxa2, acted as the central regulators of sexual dimorphism through steroid hormone receptors in a mouse model of carcinogen-induced HCC (Li et al., 2012). In this review, we focus on the estrogen regulation of liver cancer.

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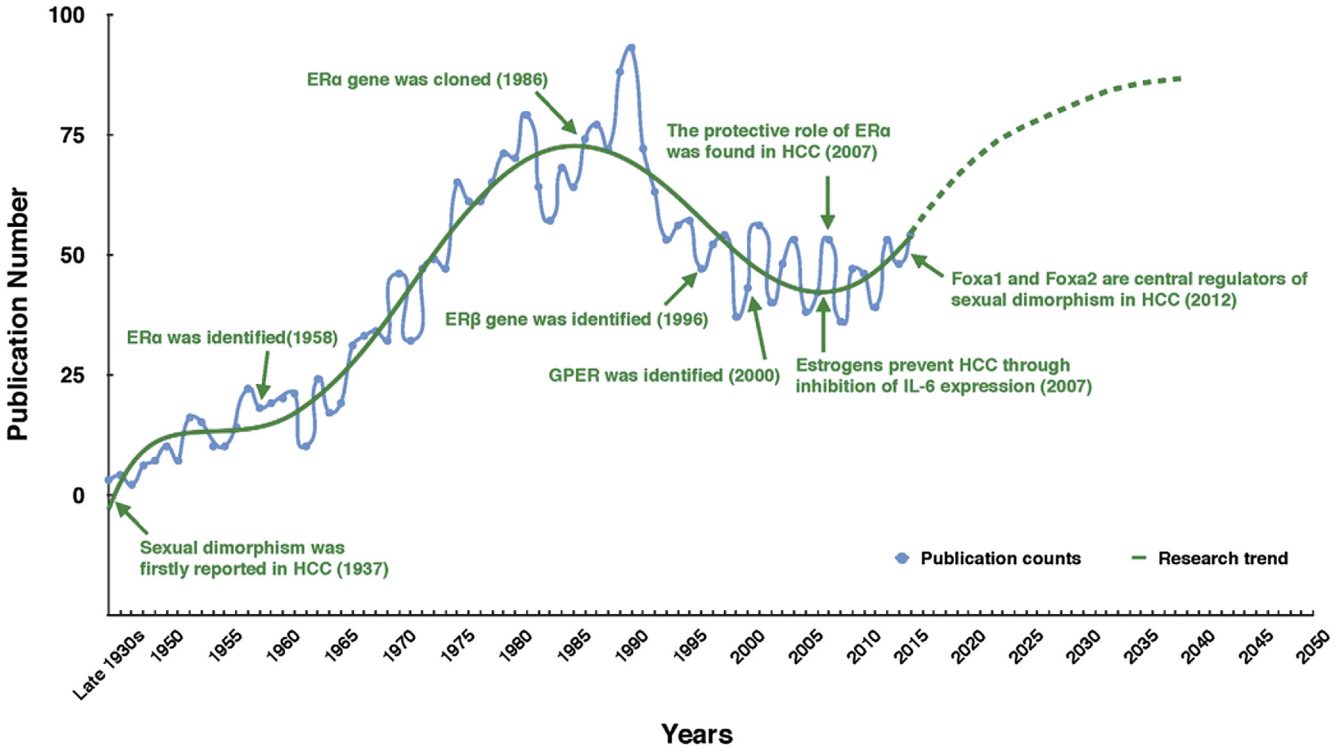

Fig. 1. The annual publication record and milestones for the research of estrogen action in liver cancer. Data were collected from PubMed with key words "estrogen", and "liver cancer" or "HCC" in title or abstract, and also manually selected.

2. Milestones in studying estrogen action in liver cancer

Based on a literature search, we summarized all published research articles regarding estrogen action in liver cancer and found that there were two peak times over the past 70 years. The first boom was a 20-year period from the 1970s to 1990s, and the second began in the late 2000s and has been on the rise today (Fig. 1).

The first study on sexual dimorphism in liver cancer was reported in late 1937, and sex hormones were believed to be the major players (Andervont and Lorenz, 1937; Tomita, 1937). Thereafter, more and more research activities were focused on sex hormone action in liver cancer. After the first estrogen receptor, estrogen receptor alpha (ERα), was identified in 1958 (Jensen and Jacobson, 1960), studies on estrogen regulation in liver cancer started to increase rapidly; the peak of this research interest appeared around the time when the ERα was cloned in 1986 (Green et al., 1986; Greene et al., 1986). But following the finding of the second nuclear estrogen receptor, estrogen receptor beta (ERβ) in 1996 (Kuiper et al., 1996) and the discovery of a novel membrane-localized estrogen receptor, G protein-coupled estrogen receptor (GPER), identified in 2000 (Filardo et al., 2000), related studies became less active. Two recent breakthroughs reignited the interest in the study of estrogen action in liver cancer: one was the discovery of the protective role of ERα in HCC found in 2007, which showed that estrogens prevented HCC through inhibition of IL-6 expression (Naugler et al., 2007); the other was the 2012 discovery that ERα-mediated estrogen signaling for the protection against the development of liver cancer in carcinogen-treated mice depended on Foxa factors, Foxa1 and Foxa2 (Li et al., 2012). Based on these recent breakthrough studies, we anticipate that there will be a spike in the investigation and clinical application of estrogen regulation in liver cancer in the coming years (Fig. 1).

3. Overview of estrogen receptors and estrogen action

In mammals, estrogen is an essential sex steroid hormone involved in many cellular processes, including cell metabolism, cell differentiation, and tissue development. In these processes, estrogen-targeted gene regulation generally requires the interaction between estrogen receptor (ER) proteins and genomic DNA, in which ER acts as a transcription factor (Deroo and Buensuceso, 2010). In addition, the activation of ERα requires the binding to its natural ligand, 17β-estradiol, which was first reported in rat uteri in 1958 (Jensen and Jacobson, 1960). Estradiol is mainly generated from female ovaries and also synthesized in liver (Yamamoto et al., 1984), fat (Grodin et al., 1973), testicular (Fritz et al., 1976), adrenal (Davies et al., 1970), breast (Miller and Forrest, 1974), and neural (Ryan et al., 1972) tissues. Thus, ER-mediated estrogen signaling has been observed in both males and females. The ERα gene *ESR1* was cloned and sequenced in 1986 (Green et al., 1986; Greene et al., 1986). Ten years later, another isoform of estrogen receptor, ERβ, was identified in rat prostates (Kuiper et al., 1996). Both ERα and ERβ are ligand-activated transcription factors, belonging to the nuclear hormone receptor protein family. Both of these receptors have five homologous domains, a highly-conserved ligand-binding domain (LBD, the amino acid identity ~55%), and a DNA-binding domain (DBD, the amino acid identity >95%), indicating that they could bind to the same *cis*-regulatory elements of genomic DNA (Dahlman-Wright et al., 2006; Kumar et al., 2011). The transcriptional activities of ERα and ERβ are mediated by the synergism between two distinct activation function (AF) domains, AF1 and AF2. AF1 is located at the N-terminal, and AF2 is located at the C-terminal of ERs (Dahlman-Wright et al., 2006). In ERα, the AF1 is constitutively active and AF2 is ligand-dependent, while the function of AF1 in ERβ is weaker than that in ERα, so the transcriptional activation of ERβ depends more on ligand-dependent AF2 domains (Delaunay et al., 2000). Both ERα and ERβ can shuttle between the