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Review

Steroid hormone influence on melanomagenesis

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ABSTRACT

Disparities in the prognosis and incidence of melanoma between male and female patients have led clinicians to explore the influence of steroid hormones on the development and progression of this malignancy. A better understanding of the disparities of melanoma behavior between sexes and ages could lead to improved prevention and treatment options. There are multiple themes in the literature that unify the physiologic functions of estrogen and androgen receptors; herein we discuss and map their pathways. Overall, it is important to understand that the differences in melanoma behavior between the sexes are multifactorial and likely involve interactions between the immune system, endocrine system, and environment, namely UV-radiation. Melanoma deserves a spot among hormone-sensitive tumors, and if tamoxifen is re-introduced for future therapy, tissue ratios of estrogen receptors should be obtained beforehand to assess their therapeutic predictive value. Because androgens, estrogens, and their receptors are involved in signaling of commonly mutated melanoma pathways, potential synergistic properties of the recently developed molecular kinase inhibitors that target those pathways may exist.

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1. Introduction

Scientists have attempted to classify estrogen receptors on melanocytic tumors in the skin by using immunohistochemistry to understand their utility in predicting prognosis, response to therapy, and tumor behavior; however, the early results were

Abbreviation: ER, estrogen receptor; AR, androgen receptor.

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inconsistent (Hakim, 1982; Flowers et al., 1987; Cohen et al., 1990). With the advent of more modern laboratory techniques, multiple isoforms of the estrogen receptor (ER) have been discovered (Hawkins et al., 2000; Mosselman et al., 1996). Specifically, the discovery of the predominant ER in the skin, ERβ, was monumental to furthering our understanding of the hormonal influence on melanocyte physiology (Mosselman et al., 1996).

This article will review the existing literature on α and β isoforms of estrogen and androgen receptors in malignant melanoma. We will also discuss estrogenic and androgenic influence on the expression, activity, and mechanisms of these receptors, which will then be correlated with tumor behavior and response to tamoxifen. Androgen- and estrogen-mediated cell signaling pathways emphasized in melanomagenesis will be described in the context of molecular therapeutic drugs targeted toward pathway-specific proteins. The interaction between the endocrine system and environment will also be discussed, specifically the regulation of steroid hormones and their receptors in response to UV radiation. Finally, the overall effects of steroid hormones on melanoma behavior will be summarized and compared to other hormone-sensitive malignancies.

1.1. Clinical observations of estrogen and androgen influence on melanocytes and melanomas

Historically, clinicians have observed that estrogens and androgens can influence melanocyte behavior and have put forth many conflicting theories explaining these phenomena. Melanocytic nevi have been noted to darken and grow during pregnancy under the influence of estrogen when observed from a gross and dermoscopic perspective (Zampino et al., 2006; Foucar et al., 1985; Sanchez et al., 1984). These changes are also more pronounced in dysplastic nevi of pregnant patients, although this may be confounded by the intrinsic volatile nature of these lesions (Ellis, 1991). Other observations during pregnancy include the hyperpigmentation of the face that is seen in melasma, which is also associated with the use of estrogen-altering agents such as oral contraceptives (Moin et al., 2006). Cutaneous pigment changes are also observed during other hormonally-influenced physiologic states, such as puberty where genital and areolar skin darken (Tadokoro et al., 1997).

In the early 1970's, Sadoff first proposed that melanoma should be grouped amongst the “estrogen-dependent” tumors based on noticeable patterns (Sadoff et al., 1973), and others have supported his observations. Travers and Mackie noted that melanomas diagnosed in pregnancy tend to be thicker than those diagnosed outside of pregnancy, even when controlled for site and age, although this does not translate to a worse prognosis for pregnant patients, suggesting a protective role of estrogen (Travers et al., 1995; MacKie et al., 1991b). Darvasula and Strouse noted that the incidence of melanoma peaks at menopause, which is a time when protective estrogen levels fall, although other factors likely play a role in contributing to melanomagenesis in this age group (Durvasula et al., 2002; Strouse et al., 2005). Gamba, Mackie, and Shaw noted the significant disparity in the prognosis of malignant melanoma between males and females. Population-based cohort studies show that although males comprise the minority of the melanoma cases, they comprise the majority of melanoma specific deaths (Gamba et al., 2013; Mackie et al., 1991a; Shaw et al., 1980, 1982). Notably, when matched for age and adjusted for tumor thickness, histologic subtype, anatomic site and extent of metastasis, males are still 55% more likely to die of melanoma than females (Gamba et al., 2013). Lastly, since 1975 the incidence of melanoma has been climbing in men at twice the rate that it has been climbing in women (Fig. 1) (NCI, 2012). Understanding the mechanisms by which estrogen and androgen exert their effects on benign and malignant melanocytes may help explain these phenomena.

2. Genomic and non-genomic signaling pathways

2.1. Estrogen receptor (ER) genomic and non-genomic pathways in melanomagenesis

Estrogen and estrogen receptors (ERs) mediate their effects through genomic and non-genomic pathways, which have diverse effects on hormone-responsive tissue by ultimately altering gene expression (Ribeiro et al., 1995; Ho and Liao, 2002; Gu et al., 2014). Notably, the proteins in these pathways are commonly mutated in malignant melanomas (Curtin et al., 2005, 2006). In the genomic pathway, liganded estrogen receptors dimerize and traffic from the cytoplasm to the nucleus, bind to estrogen response elements on the human genome, interact with various transcriptional protein coactivators, and augment target gene expression (Fig. 2) (Webb et al., 1999; Glass et al., 1997; Paech et al., 1997; Filardo, 2002; Zarich et al., 2006; Boriack-Sjodin et al., 1998; Migliaccio et al., 1996; Davies et al., 2002; Meierjohann and Schartl, 2006; Cantley, 2002; Salmena et al., 2008; Manning and Cantley, 2007; Madhunapantula and Robertson, 2009; Cato and Peterziel, 1998; Bai and Wilson, 2008; Minges et al., 2013; Xia et al., 2013; Wilson, 2010; Askew et al., 2010). In the non-genomic pathway, estrogen-influenced transcription is altered primarily through the RAS-RAF-MEK-ERK (MAPK) and phosphoinositide 3-kinases (PI3K) pathways, and is aided by rapid activation of intracellular signaling cascades using second messengers such as cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) (Ho and Liao, 2002; Nakhla et al., 1990; Harvey et al., 2002). The non-genomic pathway can be activated by ERs, androgen receptors (ARs), and epidermal growth factor receptor (EGFR) when liganded by estrogens or androgens.

The MAPK non-genomic pathway plays a significant role in cell growth, malignant transformation, and the development of neoplastic drug resistance; it is mutated in over 60% of human malignant melanomas (Davies et al., 2002; Kanda and Watanabe, 2003; Watters et al., 1997; vant Veer et al., 1989; McCubrey et al., 2007; Filardo et al., 2000; Ahola et al., 2002). Constitutively increased activity and expression of MAPK is a prominent feature of cutaneous malignant melanoma and other hormone-sensitive tumors, such as breast cancer (Migliaccio et al., 1996; Rodriguez and Setaluri, 2014). Estrogen binds directly to ER to stimulate MAPK activity, which activates cyclin-D and promotes the expression of the proto-oncogene c-fos resulting in cellular proliferation (Watters et al., 1997; McCubrey et al., 2007; Filardo et al., 2000; Ahola et al., 2002; Verdier-Sevrain et al., 2004). It has been shown that inactivation of cyclin-D in mice with melanoma xenografts leads to tumor apoptosis and shrinkage (Sauter et al., 2002). Alternatively EGFR-mediated activation of MAPK can occur when estrogen binds to this receptor. EGFR then mediates its effects through growth factor receptor-bound protein 2 (Grb2) and the son of sevenless protein (SOS), leading to proliferation and survival of hormone-sensitive breast cancer and melanoma cells (Fig. 2) (Filardo, 2002; Zarich et al., 2006; Boriack-Sjodin et al., 1998; Migliaccio et al., 1996; Davies et al., 2002; Meierjohann and Schartl, 2006).

Similarly to MAPK, the PI3K pathway can be activated through estrogen-mediated EGFR activation. This pathway is also frequently mutated, overexpressed, and constitutively activated in melanoma as well as other hormone-sensitive malignancies, leading to the proliferation of tumor cells (Madhunapantula and Robertson, 2009; Polsky and Cordon-Cardo, 2003; Blume-Jensen and Hunter, 2001; Bellacosa et al., 1995). Compared to melanomas without PI3K pathway mutations, those with mutations are associated with