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REVIEW ARTICLES

Effect of estrogen in malignant melanoma

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Abstract

Background: Melanoma is associated with poor prognosis in its advanced stages. Potential influence of estrogen and its metabolites on melanoma growth has been suggested.

Aims: The objective of this review was to provide an overview on the evidence related to estrogen in malignant melanoma.

Materials and Methods: Literature search using PubMed, Google Scholar and relevant cross-references of the retrieved articles was performed to review relevant published articles related to estrogen and its effects in malignant melanoma.

Results: Effect of estrogen signaling on a tissue largely depends on the relative expression of estrogen receptors (ER) α and β. Gender differences in melanoma may be explained by the difference in expression of these receptors. ERβ is the principal ER in melanoma.

Discussion: Although there is uncertainty about role of estrogen in pathogenesis and progression of melanoma, evidence suggests that its growth and metastasis are influenced by estrogen stimulation. Role ER on the proliferation of melanoma cells is well described.

Conclusion: There is a need of safe and effective therapy for melanoma, especially for advanced cases. After the establishment of specific role of estrogen and its receptor, analysis of specific genetic mutation can be performed for proper utilization of targeted therapies.

KEYWORDS
estrogen, melanocytes, melanoma

1 | INTRODUCTION

The ultimate effect of estrogen signaling on a tissue largely depends on the relative expression of estrogen receptors (ER) α and β. The latter are members of the nuclear receptor family of transcription factors. They are involved in the formation of a multi-protein complex and can form homo/heterodimers that upon activation, they move into the nucleus to bind with their coregulatory proteins. Through the binding to specific ER response element regions, they control the transcription of specific target genes. This is the genomic effect of ER. These receptors are produced by ESR1 and ESR2 genes, located on chromosomes 6 and 14, respectively. ERα and ERβ are

soluble receptors predominantly found in the nucleus, but can also shuttle between cytoplasm and nucleus.[1] Both the receptors contain multi-domain structures and are comprised of very specific DNA-binding segments, two transcription activation functions (AF1 and AF2) and a ligand-binding site. The DNA-binding domain is located in the center of the ER protein and is involved in the recognition activity, followed by the binding of DNA. On the other hand, the ligand-binding domain is located in the COOH terminal and takes part in the receptor-ligand interactions. The NH2 terminal site is the most variable domain in terms of its length and sequence. AF2 is found in the COOH terminal, while the AF1 is present in NH2 terminal area. AF1 is constitutively active and AF2 has hormone-dependent activation.[2] Both the ERs are synthesized in multiple splice variants; however, the biological function of these variants has not yet been completely elucidated. For example, there are a few short ERα isoforms that lack the NH2 terminal AF1, named hERα-36 and 46, and have been found in various cells, but not isolated from tissue samples. Their function in the regulation of estrogen effects is still vague, although they constitute a convenient research tool *in vitro* because they are capable of hetero-dimerizing with the full length of ERα, which ultimately leads to downregulation of AF1. It is also hypothesized that they can move to cell membrane and hence may play a role in rapid non-genomic estrogen effects.[3,4] Despite the almost identical general structure of these receptors, they have major differences in ligand-binding domain that are responsible for the differences in the final effect. ER has been shown to be present in various estrogen-responsive tissue samples, such as brain, prostate, and others. Estrogen acts indirectly on these tissues. In contrast to breast, characterized by a preponderance of ERα, ERβ is the chief ER in skin. The activity/expression of aromatase enzyme in a tissue is also an important factor guiding the influence of estrogen on a tissue.[5-7] However, there is no concrete evidence of the expression level of aromatase enzyme and its clinical outcome, since aminoglutethimide (a first-generation aromatase inhibitor) was not found to be effective in decreasing the spread of melanoma.[8] Estrogen has non-genomic effects as well, through regulation of various signaling pathways, such as G protein-coupled receptor (GPCR) mediated signaling. The activation of the GPCR after estrogen stimulation suggests that it might represent another ER. It is currently considered as a very popular ER, hence described by the new acronym GPER. It seems to be mostly intracellular and mediates a wide range of responses to estrogen molecule in variable tissues. Its functions are different from those of the classical nuclear ER, although these may interact/overlap in a few cases.[9] Its activation leads to the production of cyclic AMP, which is responsible for the rapid estrogen-dependent activation of Src-dependent signaling pathway that finally leads to extracellular signal-regulated kinases (ERKs) activation and hence to the final effects.[10] It has been hypothesized that GPCR cross-talks with α5β1 integrin, epidermal growth factor receptor, and insulin-like growth factor receptor facilitating signaling pathway activation and its effects.[11,12] The estrogenic activity of GPCR is not well understood, and there are still objections regarding the role of GPER as an ER at all.[13]

ERα has a pro-proliferative and ERβ has an antiproliferative effect on estrogen-sensitive tissue; hence, imbalance between these receptors favoring ERα predominance leads to tumor formation.[14-16]

ERβ is known to have a suppressive effect on tumor progression in patients with breast, prostate, colon, and ovary cancers and has shown therapeutic potential in management of these malignancies.[17-20] Experimental and research studies have indicated a similar role of ERβ in melanoma cells and in the disease progression. A study by Neil et al. demonstrated the inhibitory role of estrogenic steroid on the invasion of melanoma cells in in vitro models.[21]Further studies on animal models showed anti-apoptotic effects of estrogen metabolites on melanoma cells reducing the progression and thickness of the tumor.[22] Studies using real-time transcription assay and immunohistochemistry have shown decreased ERβ expression in advanced stages of melanoma, concluding that ERβ expression can be considered as a prognostic marker in melanoma.[23]

Schmidt et al.[24] evaluated the immunohistochemical expression of ERβ receptors in various benign and malignant melanocytic growths and established that the expression level corresponded with tumor surroundings and invasion capacity of the tumor cells, thus acting as a prognostic marker in melanoma. They also found that the levels of ERβ mRNA and the protein derived from it were lower in more aggressive and thicker tumors. The level of this receptor and protein was lower in tumor cells as compared to nearby normal skin as well. An inverse correlation was found between Breslow thickness and ERβ levels in their study.[24] Giorgi et al reported that there was lower expression of ERβ in affected cells of patients of melanoma with lymph node metastases as compared to surrounding normal skin cells.[23] In a study, a polymorphism at the AluI restriction site of ERβ was detected in exceedingly large numbers of melanoma cells, proposing that this polymorphism could predispose to the development of melanoma.[25] ERβ which is the ER expressed in human melanoma cells can harbor various genetic mutations like WM1552, WM115, and BLM. Also, the pattern of expression of various isoforms of ERβ was similar in BLM (BRAF-wild type, NRAS mutant) and WM115 (BRAF V600D-mutant) melanoma cells: ERβ2 had higher expression level while ERβ1 and ERβ5 were found to be expressed at similar levels. In A375 (BRAF V600E-mutant) cells, ERβ1 had lower expression while both ERβ2 and β5 were expressed at quite a higher level.[26] When considered together, these findings suggest that ERβ is expressed in melanoma cells and it might have a role in progression and prognosis of melanoma.

2 | GENDER DIFFERENCES IN MELANOMA

The distribution of ERβ is age- and sex-dependent. Females have higher skin levels of ERβ as compared to males, while the expression decreases with age in both genders but more drastically in postmenopause phase, as the positive effect of estrogen is lost.[15] There are gender-related differences in the metabolism of and the response

to sex hormones in men and women.[27] Estrogens are found to facilitate wound healing and increase epidermal thickness, improve inflammatory conditions, and protect against sun-induced damage of the skin.[28]

The gender-related influence in melanoma progression has been studied by various authors since the late 1960s. Studies performed in a melanoma fish model (Xiphophorus couchianus) depicted a 2-fold higher incidence of melanoma in males than in females after acute UVB radiation exposure, and this was associated with a sex-specific genetic response.[29] It has been stated that there is a more rapid development of melanoma in males than in females and that females have better prognosis than men in the majority of cases.[6] Various studies have investigated the presence of in-transit and satellite metastasis in female and male patients with melanomas. As an example, in a study held by Meier et al., there was a difference in percentages of in-transit and satellite metastases between women (26.4%) and men (16.7%).[30] The regional lymph node was the commonest site of metastasis, seen more often in men than in women. This observation was consistent with earlier reports in which males had stronger tendency for tumor spread, from the stage of the primary cutaneous growth into the metastasis.[30]

Considering the observed difference in incidence and progression of melanoma in the different genders, a potential role of hormones (mainly estrogen) was speculated. In this context, there were suggestions of classifying melanoma as an hormone-related neoplasm.[27] Besides, a difference in the ER concentrations was found to be statistically significant in melanoma specimens derived from male versus female patients.[31] However, these studies are in opposition to older studies stating that the incidence of melanoma with detectable estrogen receptor (refers to ERα which was the only discovered ER during that time) is low, emphasizing that the usefulness of the estrogen receptor assays in melanoma might not be important.[32] However, the latter statement was released before the recognition of the second ER, that is ERβ. Although there is evidence that favors a potential role of estrogen in improved melanoma prognosis in women, some evidence is against this hypothesis which suggest that low incidence of melanoma and favorable outcome in females can be also attributed to various other factors, including the higher rate of IgG, IgM, and CD3-positive T cells,[33] the less susceptibility to ultraviolet rays induced immunosuppression, the role of other environmental factors,[34] the higher level of antioxidant enzyme,[35] the higher estrogen level that own an antioxidant property,[36] genetic factors,[37] and the most frequent visit to health care providers and total-body skin checks.[38] Though most of the authors have suggested that females have better survival over males with increasing age for localized as well as regional melanoma, some investigators have found no survival difference, mainly due to increasing risk of death with age in women.[39,40]

Based on some case reports mentioning melanoma development during and post-pregnancy, there are some presumptions of the association between ER expression and hormone status in melanoma cases. In 1998, Grin et al. reviewed the literature (controlled trials) in an effort to figure out the effect of hormonal changes in pregnancy on the prognosis of melanoma. Studies assessing the risk of development of melanoma after exposure to oral contraceptive pills (OCPs)/hormonal replacement therapy (HRT) were also included.[41] The 5-year survival rate was not influenced by pregnancy in melanoma patients according to their review. In the same context, exposure to OCPs/HRT did not appear to predispose to melanoma, opposed to other hormone-dependent malignancies like prostate, breast, or endometrial.[41] Auriemma et al.[42] studied the possible changes in nevi in women who were undergoing ovarian stimulation in a controlled manner for assisted reproduction technologies. The authors concluded that their findings do not support a causal association between the clinical changes of moles and the high (above normal) hormone levels in the body. The prime role of estrogen in favorable outcomes in female melanoma patients is disregarded by many indicating a similar outcome in women on OCPs, hormone replacement therapy, or pregnancy as compared to those not being under these treatments and not being pregnant.[43] Ohata et al.[44] also suggested that melanoma cells predominantly express ERβ through immunohistochemical analysis and that the intensity of ERβ staining is not influenced by sex, age of women, and serum levels of estrogen.

3 | PATHOGENESIS AT MOLECULAR LEVEL

Estrogen suppresses melanoma tissue growth by inhibiting interleukin 8.[45] Non-genetic effects of estrogen receptor ligands are arbitrated by two important signaling pathways: RAS/MEK/ERK and PI3K/Akt. Explicitly, the antitumor activity of ERβ is mediated by PI3K/Akt pathway in various cancers.[46,47] Melanoma lines expressing the BRAF oncogene are known to downregulate phosphodiesterase type 5, leading to vasodilation and melanoma metastases.[48] Current melanoma treatment mostly includes modalities targeting BRAF mutation and the downstream pathway, and biologics acting over the immune checkpoints. However, treatment-related mild to life-threatening side effects and resistance is not uncommon. ERβ is the principal ER in melanoma so the ratio of ERβ/ERα is high, possessing various types of genetic mutations. This receptor can be utilized for melanoma therapy. The first oncogene to be unveiled in melanoma was RAS. NRAS (one of the RAS members) is one of the commonest mutations in melanomas. In recent times, it has been found that NRAS mutant allele is associated with melanoma progression and metastasis. This mutation leads to increased proliferation and metastasis of melanoma cells.[49] Marzagalli et al. found that in BLM (NRAS mutant) melanoma cells, ERβ agonists (17β-estradiol, KB1, etc.) remarkably impeded proliferation of cells induced by an ER antagonist. There is an alteration in the expression of various proteins involved in the G1/S phase of cell cycle (decreased activity of cyclin D1 and cyclin D3, and increased activity of CDK inhibitor) by ERβ agonists.[26] Genomic instability in BLM cells due to global DNA hypomethylation was reversed by the use of ERβ agonists. Hence, ERβ has an antitumor effect in NRAS mutant melanoma cells by causing cell cycle arrest and through the regulation of cell cycle-associated

proteins, like cyclin and CDK inhibitor. BRAF mutation occurs in approximately 50% of melanomas, the majority of which involve a single substitution of valine with glutamic acid at 600th position (V600E). Other mutations are the V600K (lysine substituting valine) and the V600D (aspartic acid substituting valine). BRAF mutations activate the regulatory domain of the receptor protein, leading to increased kinase activity and hence activation of the downstream molecules including MEK and ERK. Increases in the activity of this pathway stimulate the G1/S transition of the cell cycle by activation of cyclin D1 synthesis and downregulation of p27 protein. In their study, ERβ agonists were not effective in curtailing the growth of V600E BRAF-mutated melanoma cells, expressing the ER isoform. Thus, it was postulated that the ultimate effect of ERβ ligand in the tumor cells might be allied to a specific mutation (RAS/BRAF).[26,50,51] Gene effects and role of an ERβ agonist on tumor cells have been depicted in the Figure 1.

ERβ agonists can be combined with specific MEK cascade inhibitors (trametinib, cobimetinib) to inhibit the activity of the PI3K/Akt, as well as the MEK/ERK signaling pathways in the melanoma cells, increasing in this way the efficacy of treatment. Tamoxifen, an antiestrogen drug, remarkably impedes the growth, as well as the metastasis, of melanoma cells in mouse.[52] Tamoxifen restrains protein kinase C, IGF-1, and various other molecular pathways in murine melanoma cells (B16BL6).[52,53] In human melanoma, it probably acts through inhibition of the IGF-1 receptor. However, usage of tamoxifen failed to render positive results in patients with melanoma.[54] Various studies documented that co-treatment (specific chemotherapy and tamoxifen combination) may cause improvement in response to therapy, but is often associated with an unfavorable toxicity profile and almost no survival benefit.[54-57] It is hypothesized that this is attributed to a nonspecific binding of tamoxifen to ERs (ERα and ERβ), hence increasing cell proliferation by binding to ERα, vice versa on binding to Erβ.[58] Thus, the eventual outcome of the use of tamoxifen largely depends on the Erα/Erβ ratio in a particular tissue.[59] Also, owing to nonselective ER binding, tamoxifen decreases and increases proliferation of cells when bound, respectively, to ERα and ERβ. Thus, resistance to tamoxifen therapy is intelligible in melanomas possessing ERβ preponderance, in which tamoxifen inhibits the defensive effect of ERβ that ultimately leads to tumor proliferation. An ideal hormonal therapy in melanoma should inhibit the ERα protein with proliferative action and increase the activity of ERβ protein (antiproliferative). If future studies confirm that ERβ levels correlate inversely with Breslow thickness and the rate of metastases, then ER loss may be of paramount importance to melanoma tumor spread and be regarded as a factor of adverse prognostic significance and a specific target for estrogen receptor agonism as a therapy in melanoma.[55]

4 | NATURAL ERB LIGANDS IN MELANOMA

Phytoestrogens are plant-extract, estrogenic, natural molecules that behave like natural estrogen and favorably bind to ERβ than estrogen receptor α, hence also called as estrogen receptor subtype agonists.[60] They have been found to be effective molecules in the prevention of various diseases including cardiac diseases, postmenopausal syndrome, and osteoporosis. They are found to have antitumor effects on various cancers, such as prostate and colorectal cancer, due to their antiproliferative activities mediated by various pathways.[61,62] The antitumor action of these phytoestrogens mainly depends on the specific ER expression, its activity, and the hormone environment near the tumor cells.[26] Like estrogen, phytoestrogens also exert their effects through genomic and non-genomic (effect on signaling pathways) mechanisms. These effects comprise epigenetic effects, antioxidant mechanisms, and changes in AKT pathways, and they are also affecting coregulators involved in chromatin binding activities, suggesting in this context the role of epigenetics in estrogen activity. Flavonoids are polyphenolic compounds found in various medicinal herbs and vegetables. Some of these compounds have been found to be effective in various tumors by interfering with cancer progression through regulation of apoptosis, proliferation, invasion, and metastasis.[26]

Phytoestrogens undergo glycosidic binding to carbohydrates to form products that are difficult to absorb. Hence, this binding must be regulated by glycosidases found in the gastrointestinal tract, produced by the intestine microflora that convert glycosidic molecules into the corresponding easily absorbed forms: "aglicones."[26] Table 1 depicts natural ERβ ligands with their effects on melanoma cells.

The isoflavones like daidzein and genistein are found in soybean, an important part of Asian diet. Various epidemiological studies have emphasized that soybean-containing diet is an important factor related to lower incidence of certain malignancies in Asian countries.[26]

Russo et al.[63] found that genistin has a repressive effect on human malignant melanoma cells. Ultraviolet light-induced DNA and lipid membrane damage is also inhibited by this agent. Furthermore, genistin and daidzin (the glycosidic forms of the two isoflavones) resulted in a shielding effect on oxidative DNA damage; however, only genistin was found to have antiproliferative effects on human melanoma cells (M14).

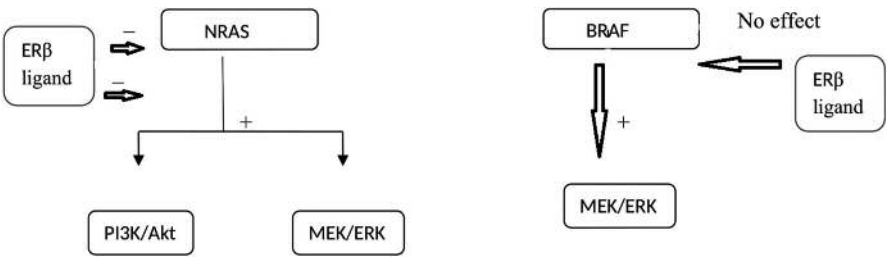

FIGURE 1 Gene effects and role of ERβ agonist on tumor cells

TABLE 1 Natural ERβ ligands and their effects on melanoma cells

Serial No.	ERβ ligand	Mechanism	Evidence	Comments
1	Genistein[66,67]	Interacts with ER (ERα<ERβ) Modulates the activity of various enzymes involved in the degradation of the extracellular matrix (ECM) like urokinase-type tissue plasminogen activator	Reduces the growth, angiogenesis, and the motility of mouse B16 melanoma cells Reduces the growth and metastasis in human melanoma cells.	It is partly absorbed without cleavage and does not require hydrolyzation to produce the biologically active form
2	Flavanone LQ[51,68,69]	Selective ERβ agonist Recruits ERβ coactivators It binds to Erβ-responsive elements in the promoter region of specific genes Inhibits PI3K/Akt pathway	Enhances the anti-invasive/anti-migratory effects of CDDP (cis-diamine dichloroplatinum) in melanoma cells of mouse (B16F10) It increased the CDDP-induced repression of metastasis in mice with B16F10 xenografts In temozolomide-resistant glioma cells, LQ increases ERβ expression and sensitizes tumor cells to drug-induced inhibition. Also, it downregulates PI3K/Akt pathway	Extracted from well-known herbal medicine glycyrrhizae It has lower affinity for ERβ than estradiol hence may require higher dose for therapeutic effects
3	Liquiritigenin[70]	Selective estrogen receptor modulator, behaving as ERα agonists and antagonists in various cell types	Unclear role. Increases antiproliferative, antimetastatic effects of chemotherapy on murine melanoma cells	Component of licorice roots
4	Isoangustone A[71]	Inhibits cell cycle progression. It also downregulates PI3K/Akt pathway	Impedes the growth of human melanoma cells	
5	Glycyrrhizin[72]	Conjugates free radicals	Protects human melanoma cells from UVB irradiation	
6	Licochalcone A[73]	? ERβ agonism	Decreases cancer cell growth	
7	Apigenin[74,75]	Chemopreventive action and suppresses cancer growth Causes accumulation of ROS in mitochondria of tumor cells, upregulates Bax, caspase 3, 9, and PARP, and downregulates Bcl−2 leading to induction of apoptosis in mitochondria. Antimetastatic: downregulation of signal transducer and activator of transcription 3 (STAT3) phosphorylation and suppression of STAT3 target genes VEGF MMP−2,9, and Twist1 Increases p53 (proapoptotic) levels and, ultimately, upregulates the p53 target gene, TRAIL receptor 2	Causes apoptosis and has antimetastatic effects in A375 human melanoma cells	It cross-reacts with progesterone receptor, but the activity of the progesterone receptor in melanoma cells and its cross-reaction with apigenin still needs to be elucidated

(Continues)

TABLE 1 (Continued)

Serial No.	ERβ ligand	Mechanism	Evidence	Comments
8	Silymarin	Selectively binds to ERβ[76] Induces cell cycle arrest in melanoma cells by directly targeting the MEK1/2 pathway[77]	Inhibits the proliferation of melanoma cells both in vitro and vivo Also has chemopreventive and antimetastatic effects (through effect on Wnt/β-catenin pathway) on melanoma cells Prevents UV irradiation-induced apoptosis of human A375-S2 melanoma cells, through the activation of the SIRT1 and Akt pathways[78-80]	It is extracted from Silybum marianum, a mixture of four flavolignans (silydianin,silybinin, silychristin, and isosilybinin) and the isoflavone taxifolin Silymarin can also bind the androgen receptor, and specifically in prostate cancer cells, it upregulates the pathways involved in the ERβ signaling. However, the role of this receptor in cutaneous melanoma has not been elucidated till now[81]

Thus, the isoflavone aglycons and their corresponding glycosides may possess notable anticancer activity in human melanoma cells.[63]

Licorice root extracts including glabridin, liquiritigenin, glabrene, glycycoumarin, vestitol, calycosin, glycyrrhizin, and methoxychalcone are used by postmenopausal females to fight against postmenopausal syndrome like flushing. These compounds act as SERMs (selective estrogen receptor modulators), specifically behaving as ERα agonists in some cells and acting as ERα antagonists in other tissues. Hence, they might have antiproliferative effect on melanoma cells.[64]

Apigenin is a phytoestrogen inducing apoptosis in prostate tumor by down-regulating proteasomal function, hence saving ERβ from destruction and therefore increasing its level inside the tumor cells increasing the antitumor effects of ERs.[65]

5 | CONCLUSION

Although there is a high degree of uncertainty in the results regarding the role of estrogen in the causation and course of melanoma, there is ongoing preclinical and clinical evidence suggesting that the growth and metastasis of melanoma are influenced by estrogen stimulation. There is cumulative evidence for the role of ER on the proliferation of melanoma cells. The biology of melanoma occurrence and growth is complex with primary melanomas or their metastases sometimes arising many years following excision of the primary melanoma, suggesting a delicate interaction between growth and surveillance.[48] With time, any enhanced understanding of tumor milieu in melanoma progression may facilitate the development of future therapy. Despite the numerous therapies being tested and employed in advanced melanoma, therapeutic outcomes are still far of being optimal. Hence, we are in a dire need of safe and effective therapy for melanoma, especially for advanced cases. Once the role of estrogen and its receptor gets clear, analysis of specific genetic mutation (BRAF/RAS) and proportion of ER subtype (ERβ/ERα) can also be performed in melanoma patients for proper utilization of targeted therapeutic modalities. The efficacy and safety of various natural ERβ can be properly analyzed by well-designed studies and clinical trials, paving the way for newer potent therapies for melanoma.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Neetu Bhari: writing the manuscript. **Robert A. Schwaertz:** review and revising the manuscript. **Zoe Apalla**: review and revising the manuscript, **Gabriel Salerni:** review and revising the manuscript. **Anant Patil:** review and revising the manuscript. **Stephan Grabbe:** review and revising the manuscript. **Mohamad Goldust:** review and revising the manuscript.

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