Narrative Review Article

The Influence of Estrogen and Estrogen Receptors on the Sex-Based Differences of the Immune Response to Melanoma

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ABSTRACT

Melanoma is a highly mutagenic cancer that disproportionately affects men in comparison to women. Women have been found to be diagnosed less often than men, recover significantly better, and have a lower mortality rate that is almost half that of men for cutaneous melanoma, which is melanoma of the skin. This paper reviews the underlying biological factors for these sex differences. It was found that these differences can be attributed to the influence of estrogen signaling on melanoma tumor cells as well as innate and adaptive immune compartments. Estrogen suppresses tumor proliferation and enhances the development and activity of the immune system. This could be part of why women have an advantage since estrogen is their primary sex hormone. Together, these findings display that estrogen pathways may be an effective target to treat melanoma patients. Further research is required to test this hypothesis and these findings highlight the importance of incorporating sex-based biology into future melanoma studies.

Keywords: Melanoma; Immune System; Hormones; Cancer; Sex-Based Differences

INTRODUCTION

Cutaneous melanoma is a cancer that is caused by the mutation of pigment producing cells called melanocytes in the skin. It primarily affects white individuals and is often caused by double strand breaks by ultraviolet radiation. Melanoma is also extremely mutagenic; in some cases this can help cancer to evade the immune system, but in other cases, it can actually facilitate recognition by immune cells. Current treatments to combat melanoma include surgical resection, chemotherapy, targeted therapies, and immunotherapies (1).

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Another characteristic of melanoma is that it disproportionately affects men in comparison to women. In all age groups except young people under the age of forty, melanoma is more predominant among men (2). It is estimated that in 2025 itself, melanoma cases in men will outnumber female cases by 36.34% (estimated 16,140 extra cases), while the estimated deaths in men will be 84.8% more than those of women (estimated 2,510 more deaths) (3). This matches previous patterns, as between 2018 and 2022, the mortality rate in men was over double that of women (3).

Despite a number of environmental and social factors that could lead to these differences, an underlying factor to cause this disparity still remains (4, 5) Studies have emerged pointing to the role of sex based hormones, such as estrogen, playing a role in immune system function. By binding to the G protein-coupled estrogen receptor (GPER), estrogen often induces a stronger immune response. Research suggests that the lack of estrogen

in men leads to the active presence of various immune checkpoints leading to T cell inhibition. In turn, this leads to the overall higher occurrence and mortality of men diagnosed with melanoma (6).

By examining the role of estrogen in both melanoma cells and the immune system, this paper aims to understand how estrogen and estrogen receptors affect the immune system's response to melanoma in men versus women.

MELANOMA AND THE IMMUNE SYSTEM

Melanoma tumors are highly immunogenic and easily lead to immune responses. Their strength depends on factors such as the amount of tumor and immune cells, the immune evasion ability of the tumor, and immune surveillance (7).

The main cells involved in immune response to cancer are T-cells. T cell activation begins with the recruitment of antigen presenting cells (APCs) such as dendritic cells (DCs) to find antigens, break them down into antigenic peptides, and present these peptides through MHC molecules. Then, the CD80 surface protein on APCs binds to the CD28 surface protein on T cells. Both of these steps combined lead to T cell activation. However, the absence of one of these steps can lead to tolerance of tumor cells (8). After this, T cell immune response itself occurs in three simple steps starting with the homing of T cells to the tumor microenvironment, the recognition of melanoma cells, and finally the destruction of the melanoma cells through apoptosis (9).

The process of homing directs T cells to the tumor site. This happens through a few mechanisms. Activated T cells and surrounding blood vessels produce adhesion molecules to guide the T cells. Blood vessels also produce chemokines for the same. This process relies on integrins, with specific types of integrins even being expressed to keep T cells in the tumor. The other factor is chemokines, as T cell infiltration in melanoma has been found to correspond with specific chemokine patterns. Overall, effective infiltration is based on successful T cell homing and can be associated with the signature left by the presence of adhesion molecules, the ability of the integrins to keep T cells at the tumor, and chemokine activity (9).

Once homing happens, tumor-specific T cells will infiltrate the tumor and search for melanoma cells expressing their tumor-specific antigen. Melanoma itself has a long list of melanoma-associated antigens (MAGEs), which are recognized by cytotoxic T cells (CTLs) and other immune cells (10). By recognizing antigens, T cells can be directed to the MHC-1 receptor on the surface of tumor cells, where these tumor antigens are presented. When T cells come into contact with MHC-1, they initiate cytotoxic T cell (CTLs) activity to destroy the cell (9).

To actually destroy the tumor, these cells follow one of two main pathways. The first is granule exocytosis. First, cytotoxic T cells and natural killers (NKs) release perforins to create pores in the tumor cell membrane. Then, granzymes enter the cell and trigger caspases, which leads to apoptosis. In other cases, granzymes lead to inflammatory death, necroptosis (death due to injury), and autophagy. The other pathway is through death ligands. Fas ligand (FasL) or TRAIL on CTLs or NKs bind to receptors such as the Fas receptor that are present on tumor cell surfaces. This recruits and activates caspases, leading and leads to cell death via apoptosis (11).

To avoid this destruction, melanoma tumors are adept at evading an immune response. In fact, in many cases, melanoma survives and metastasizes simply due to its evasion ability. The tumor cells employ various strategies to evade antigenic detection by the immune system, effectively deceiving the immune system (12).

A major mechanism is through defective immune recognition. For T cells to recognize antigens, they have to recognize processed antigens on the MHC-1 receptor. This process relies on mature DCs to process and present them. However, as melanoma progresses, it promotes immunosuppressive signals such as interleukin-8 (IL-8) and interleukin-10 (IL-10) which block DC maturation. By leaving them immature, these DC cells lack costimulators such as CD80 and weakens T cell activation. Additionally, immune cells employ their own suppression mechanisms. Myeloid-derived suppressor cells (MDSCs) release reactive oxygen species (ROS) like nitric oxide (NO), which suppress cytotoxic T cells and NK cells. Regulatory T cells (Tregs) release IL-10 and IDO to suppress the response from NKs and T cells alike. Melanoma cells contribute to evasion of NK recognition by shedding MICA/B ligands and by reducing arginine production, a substance essential for T cells to survive and multiply (12).

The second approach is by using immune checkpoints as a control to inhibit the immune response. One major checkpoint that has been studied extensively surrounding this topic is PD-1. PD-1 is a programmed death ligand that is expressed on T cells and binds to the PD-L1 receptor on tumor cells. By doing so, immune responses

are inhibited. Though the purpose of this mechanism is to prevent autoimmune responses, melanoma cells overexpress PD-L1, leading to severe T cell inhibition and preventing cancer cell death. It has been demonstrated that higher PD-1 expression on T cells is associated with lower T cell infiltration and poorer survival rates (12). Other inhibitory receptors include CTLA-4, TIM-3, LAG-3, VISTA, and CD160. The activation of these receptors eventually leads to T cell exhaustion. They stop producing various cytokines and lose their ability to kill cancer cells, which causes immune evasion (12).

SEX DIFFERENCES IN THE IMMUNE SYSTEM

Genetic sex is determined by the state of the twenty-third chromosome pair. An XX pair determines a female while an XY pair determines a male (13). Despite chromosomal aneuploidies that can sometimes alter the number of chromosomes in this pair, this rule of XX and XY generally applies to most of the human population (14). It is important to understand the difference between gender and sex, where sex corresponds to one's chromosomal make-up while gender comprises social constructs regarding behaviors, dress, and identities expected for a particular sex. This differentiation is essential when collecting data, allowing for the collection of data on different demographics (15).

Biological sex is an important factor in response to melanoma. The difference in immune response between women and men is often attributed to X chromosome genes and sex hormones (16). Many common viral infections affect women less than men, and those affected often have a lesser viral load (17). Women also exhibit better memory T cell responses and vaccine responses (17). These advantages also come with a flip side, as women have a higher risk of developing an autoimmune disease (17). Together, all these factors help demonstrate and reflect that women have stronger immune responses.

One explanation for the better immune response in women is the result of a higher androgen presence in men. Androgen is the primary sex hormone in males and is also a transcription enhancer for genes such as transmembrane protease serine 2 (TMPRSS2), which the SARS-CoV-2 virus uses to enter cells. The higher amount of androgens like testosterone in males led to more TMPRSS2 and made men more vulnerable to SARS-CoV-2 (18). Genes like TMPRSS2, which are activated by androgens, could lead to similar situations. Another possible reason is the fact that the primary sex hormone in women, estrogen, plays a vital role in activating pro-inflammatory cytokines, inhibiting anti-inflammatory cytokines, and regulating apoptosis. These two factors lead to lesser prevalence of viruses in women and lesser viral load (18).

Better T cell response and vaccine response can also be attributed to estrogen, as estrogen increases the expression of Vitamin D receptors on T cells and reduces the expression of the cytochrome P450 component of the 25-hydroxyvitamin D(3)-24-hydroxylase enzyme that inactivates Vitamin D. Furthermore, estrogen activates various adaptive and innate immune cells, as most immune cells express estrogen receptors. This enhances the immune response (18). Additionally, genetic and chromosomal factors contribute to this response. Toll-like receptor (TLR) activation, retinoic acid-inducible gene (RIG), IFN-1 release, cytokine production, and macrophage and APC activity are all higher in women due to differences in sex cells. The response of lymphoid cells is also higher in women, but a lack of regulation is what leads to autoimmune disease (18).

Testosterone has the opposite effect in men, suppressing aspects of the innate immune response such as NK cells and inflammatory markers. Testosterone can be an essential player in regulating the immune response to prevent damage to healthy cells or tissues. However, in some cases, androgens can inhibit immune responses too early, thereby affecting the ability of the immune system to fight infections or cancer. However, testosterone promotes T helper 1 cells (Th1) and in turn cytotoxic T cell activity, showing a higher reliance on adaptive immune responses for men (19). Androgens have also been shown to suppress pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. Conversely, they also increase anti-inflammatory cytokines like IL-10 (20).

Estrogen regulates B cell differentiation and function and impairs the removal of self-reactive B cells (20, 19). Estrogen also modulates all T cell subsets and helps prevent autoimmunity by suppressing immune responses from follicular helper T cells (20). It also promotes T helper 2 cell (Th2) activity and enhances T cell homing through increased expression of the CCR5 homing marker (19).

On the opposite end of the spectrum, androgens usually do not have much influence. Mature B cells do not display androgen receptors (ARs), and only immature B cells do (20). Moreover, higher presence of testosterone leads to fewer B cells, as testosterone downregulates the B cell activating factor (BAFF) cytokine responsible for B cell maturation, survival, and homeostasis (21).

Interestingly, young women and girls have fewer B cells in some subsets compared to young men and boys despite these differences, but that number flips as they age. Similar to B cells, mature T cells do not have ARs, but immature T cells do (20). This leads to androgens playing a more regulatory role in both sexes. Despite the lack of ARs in mature immune cells, androgens still play a crucial role in the maturation of immature immune cells (22). To top that, androgens can influence the adaptive immune system as thymic epithelial cells, which help T cells mature in the thymus, and bone marrow stromal cells, which support hematopoiesis, both express ARs. It is also suggested that androgens play an important role in preventing autoimmunity as autoimmune disorders are more common in women, who have less androgens (20).

Androgen-estrogen cross talk plays a role in sex differences as well. Oftentimes, this cross talk has led to antagonistic responses, with AR activation or overexpression being found to suppress estrogen signaling. This is because ARs directly compete with ERs for estrogen response elements (ERE), therefore mitigating the effects of ERs. The AR DNA-binding domain (DBD) itself can inhibit ER activity. Due to this role of androgen and its receptors as an inhibitor of estrogen signaling, the immune response is slowed or blocked; since men have more androgens and androgen receptors, this creates a significant disadvantage for them (23).

ESTROGEN AND ESTROGEN RECEPTORS

Estrogen is one of the two primary female sex hormones produced in the ovaries. Men also have estrogen, but at significantly lower levels than women, as their primary sex hormones are androgens like testosterone. As a primary sex hormone in females, estrogen plays a crucial role in the functioning of the female reproductive system, skeletal system, cardiovascular system, nervous system, and immune system (24).

Before puberty, estrogen levels in girls are low, and they start producing more estrogen afterwards. As puberty begins, the hypothalamus also begins producing gonadotropin-releasing hormone. This triggers the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. These hormones lead the ovarian follicle to produce large amounts of estrogen by converting androgens to estrogens through the P450 aromatase enzyme (25).

Premenopausal women continue producing estrogen in this manner. However, ovarian production of estrogen in postmenopausal women declines, and they produce estrogen through extra-gonadal sites such as adipose tissue, bone, blood vessels, and the brain. Tissue-specific estrogen synthesis is controlled by distinct promoters of the CYP19 gene, which codes for aromatase. This gene is itself activated by various hormones, including FSH, glucocorticoids, and others (Figure 1) (26).

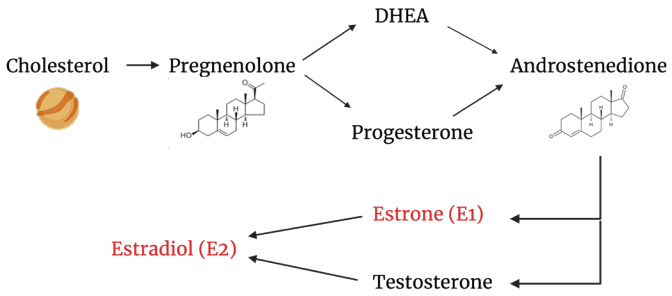

Figure 1. Diagram outlining process of estrogen biosynthesis through the conversion of various hormones. Each arrow signifies one substance being converted to another.

Similarly to how women in different stages have different methods of making estrogen, they use different types of estrogen. The three main endogenous estrogens are estrone (E1), estradiol (E2), and estriol (E3). Premenopausal women often use E1 and the stronger E2, while postmenopausal women switch to E1. E3 is more common in pregnancy (25).

To act, estrogen binds to estrogen receptors. The main and most common estrogen receptors are ERα, ERβ, and the G protein-coupled estrogen receptor (GPER). ERα is 595 amino acids long and is encoded by the ESR1 gene on chromosome 6. The same gene encodes ERβ, which is 530 amino acids in length. There are also many isoforms of these receptors, which result from gene splicing. ERα is primarily found in reproductive organs, bones, fat tissue, kidneys, and liver. ERβ is found in the central nervous system, cardiovascular system, immune system, kidney, lungs, and colon. ERβ is also found in male reproductive organs. The gene for GPER is located on chromosome 7 and is approximately 375 amino acids in length. GPER is structurally distinct from ERα and ERβ, and has a weaker affinity for estrogen. GPER is found

in blood vessels, skeletal muscles, neurons, and immune cells (27). In the context of melanoma, ERβ and GPER are highly expressed in tumor cells (2). ERα is most common in immune cells and often binds to E2 (28).

Estrogen itself acts through two main pathways: genomic and non-genomic mechanisms. Genomic signaling can be direct or indirect (Figure 2). Direct genomic signaling is the main method of estrogen action and occurs when estrogen binds to estrogen receptors, leading to receptor dimerization and creating a dimer complex. That dimer complex moves to the nucleus where it binds to DNA at ERE promoters or untranslated regions of a gene. This initiates the process of transcription. Indirect genomic signaling occurs when estrogen itself does not necessarily bind to DNA. Instead, the dimer complex interacts with other proteins, such as stimulating protein-1 (Sp-1) or nuclear transcription factor-Y, to induce genomic actions that can suppress or activate the transcription of a gene (29).

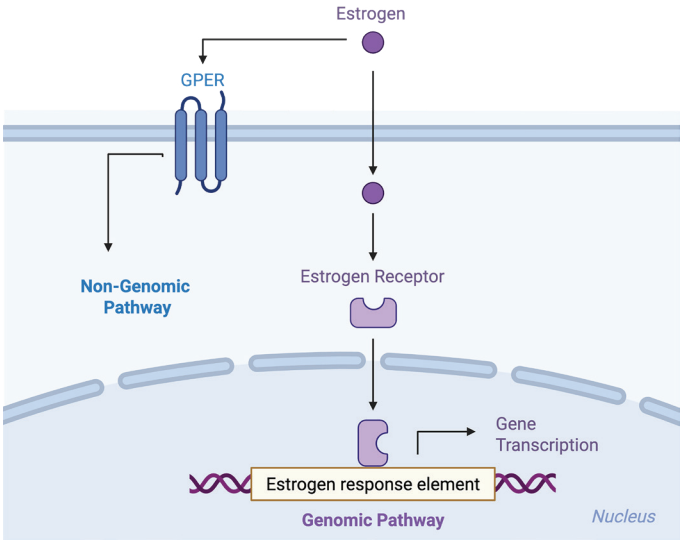

Figure 2. Processes of genomic and nongenomic estrogen signaling pathways.

Nongenomic signaling itself is an indirect mechanism and commonly happens by binding to GPER. After this binding, intracellular signaling cascades are activated, which generate second messengers, activate kinases, and ultimately regulate gene expression. These kinases can phosphorylate transcription factors, thereby altering their ability to regulate gene transcription. ERα and ERβ can also mediate non-genomic signaling by interacting with scaffold proteins, growth factor receptors, and signaling molecules, which trigger MAP kinase (MAPK) and Akt pathways that influence transcription. ERα and ERβ can also be phosphorylated, suggesting that they are involved in feedback regulation of receptors (29).

The last method is through ligand-independent activation. This process is triggered through phosphorylation of different substances that make up estrogen receptors and requires the action of regulatory molecules (29). Phosphorylation can be triggered by growth factors and is mediated by kinases. A common mechanism is using coactivators. For example, MAPK-mediated phosphorylation of activation function 1 (AF-1) in ERβ is triggered by the epidermal growth factor (EGF). It leads to the recruitment of steroid receptor coactivator-1 (SRC-1), eventually causing ligand-independent activation (30).

ESTROGEN RECEPTOR SIGNALING AND ITS EFFECTS ON THE IMMUNE RESPONSE TO MELANOMA

As mentioned in an earlier section, ERβ and GPER are more commonly found in melanoma cells. The high presence of ERβ and GPER in dysplastic nevi, a type of skin lesion that has a high risk of developing into melanoma, suggests that they play a role in suppressing the pathogenesis of melanoma (31). Further studies have shown that these receptors slow the progression of melanoma and lead to a better prognosis (32).

Activation of ERβ through E2 or ERβ agonists modulates cell cycle proteins by decreasing cyclin levels and increasing levels of cyclin-dependent kinase inhibitors (CDKIs), such as p27. This prevents uncontrolled growth and deviation from the cell cycle. ERβ also stops DNA hypomethylation. DNA hypomethylation could lead to gene silencing and cause rapid proliferation. By halting this gene silencing from happening, the activation of ERβ suppresses proliferation of melanoma cells. The effects were most noticeable in the BLM and WM115 melanoma tumor cells, which are caused by the mutation of NRAS and BRAF V600D respectively (33).

On the other hand, GPER tumor suppression acts more through immune checkpoints. When estrogen binds to GPER, the cAMP-activated Protein Kinase A (PKA) is activated and more expressed. This destabilizes and inhibits c-Myc levels. Ultimately, this results in the expression of HLA and the inhibition of PD-L1 on the surface of the melanoma cell. Both these actions

lead to tumor cell recognition by immune cells and can trigger an immune response. PKA activation also leads to melanoma cell differentiation, making it more recognizable by immune cells (6). This finding that GPER activation leads to better immune response was also observed in mice (6). In contrast, without GPER activation, c-Myc remains active, resulting in the display of PD-L1 and the downregulation of HLA on melanoma cells (Figure 3) (5).

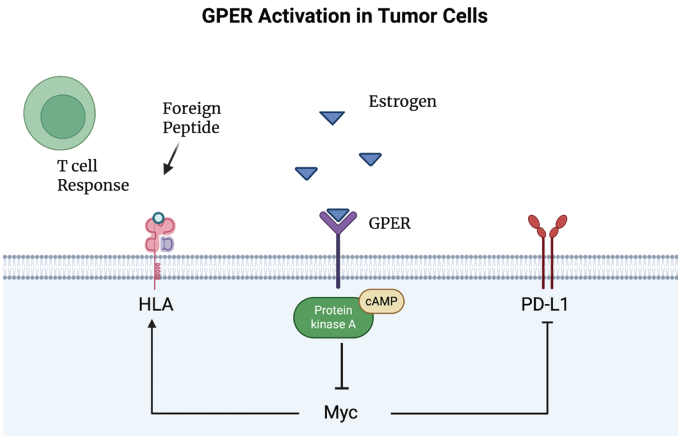

Figure 3. Pathway of estrogen signaling through GPER in melanoma cells.

Estrogen has a positive role in the innate immune response to melanoma too. Although it inhibits NF-κB signaling, it induces proinflammatory cytokines, such as IL-6, IL-23, IL-12, and IL-1β, through ERα signaling triggered by the stimulation of TLR ligands in DCs and macrophages. E2 enhances TLR signaling, which in turn increases cytokine production. However, when estrogen levels are too high, like during pregnancy, proinflammatory cytokine production can decrease (34). Estrogen receptor activation in immune cells also leads to the increased output of IFN-1 in macrophages. It has been found that female PMBCs and pDCs produce more IFN-1 than male cells due to long-term exposure to E2 (34).

Furthermore, estrogen helps regulate the functions of innate immune cells. To begin, estrogen and estrogen signaling play a crucial role in the development and maturation of innate immune cells. It regulates the maturation of various hematopoietic stem cells (HSCs) and DCs in response to E2 and ERα signaling (34). By binding to HSC-intrinsic ERα, E2 influences development, maturation, and differentiation by activating the transcription factor E2F1 and other cell cycle genes. This is not possible through male sex hormones, such as testosterone, since HSCs lack androgen receptors (34). E2 promotes GM-CSF-mediated differentiation of DCs and is essential early on by increasing the levels of interferon regulatory factor 4 (IRF4), a transcription factor crucial for GM-CSF-driven DC development (34). However, estrogen does decrease the cytotoxic activity of NK cells. Conversely, even though cytotoxic activity is reduced, estrogen promotes NK cell proliferation and rapidly increases its numbers in the tumor microenvironment (35). Overall, these actions in the tumor microenvironment lead to proinflammatory responses, prevent tumor escape by promoting innate immune cell maturation, and enhance the innate immune response's ability to combat cancer.

Estrogen plays a vital role in enhancing the adaptive immune response against tumors. As mentioned earlier, immature DCs cannot stimulate helper T cells, and this weakens the adaptive immune response (12). By promoting the maturation of dendritic cells (DCs), estrogen effectively blocks a major pathway of tumor immune evasion, as mature DCs are capable of presenting antigens and activating T cells. This activation initiates a cascade in which helper T cells can now be stimulated, leading to the subsequent activation and proliferation of cytotoxic T lymphocytes. This results in a more robust immune response, characterized by increased infiltration of activated cytotoxic T cells into the tumor microenvironment, which improves the immune system's ability to recognize and destroy tumor cells.

Estrogen also aids cytotoxic T cell responses. In cytotoxic T cells, estrogen acts through non-genomic pathways by affecting early TCR signaling. By binding to the ERβ and utilizing ERβ signaling, estrogen can regulate the antitumor activity of these T cells. This includes decreasing the migratory capacity of tumor cells, limiting their ability to spread while simultaneously enhancing the migration and infiltration of immune cells into the tumor microenvironment. Moreover, estrogen regulates the antitumor immunity of cytotoxic T cells through a tumor-extrinsic phosphotyrosine switch on ERβ, which serves as a control for immune activation (36).

Therefore, estrogen strengthens the immune response and suppresses melanoma cell proliferation, and this provides women with a sex based advantage to fight melanoma in comparison to men.

CLINICAL IMPLICATIONS AND TREATMENT PERSPECTIVES

Sex based differences in melanoma due to estrogen show that this pathway could be targeted to develop novel treatments in both men and women. As mentioned earlier, the binding of estrogen to melanoma cells and the subsequent estrogen signaling lead to an increased immune response against these cells. Therefore, this information suggests that even though the use of hormone therapy in melanoma still displays unclear results, targeted estrogen therapy should be explored as a therapy for melanoma. Combining it with immunotherapy or other treatments may also lead to better results. This is because a stronger immune response, combined with improved tumor recognition for immune cells, will optimize the effectiveness of the treatment.

Additionally, personalized treatments can be more effective for melanoma patients. Instead of a "one for all" type of treatment, personal treatments will give patients what they need. This may reduce side effects of the treatment and will be more effective in the long term against cancer. One specific treatment that has emerged is a personalized neoantigen-specific T cell therapy that began phase 1 testing earlier this year for metastatic melanoma. Researchers designed an autologous T cell named BNT221 from the patient's peripheral blood. This study was successful as it was well tolerated and did not display significant toxicities. Multiple patients saw substantial tumor regression and reached a stable state of disease (37). Emerging treatments such as these show the potential for personalized treatments based on immune profiles to make an impact in melanoma treatment, especially in bridging the sex-based differences in the response to melanoma.

The higher survival rate observed in female melanoma patients further highlights the importance of including sex as a biological variable in clinical trials. Men and women have differences in their immune responses. The influence of hormones in melanoma and the antitumor immune response are simply examples of this. Differences can extend beyond this, including variations in genes located on sex chromosomes and the influence of environmental factors.

CURRENT GAPS AND FUTURE STUDIES

Current gaps in melanoma studies are mainly shown in the effects of estrogen on melanoma tumor cells. The mechanisms of estrogen signaling in melanoma tumor cells are not entirely understood. Studies on melanoma tumors can be conducted to investigate the effects of ER signaling in various types of melanoma cells originating from different mutations, thereby understanding the impact of estrogen on different types of melanoma tumors. This could lead to the development of new treatments for melanoma patients.

Gaps also exist in the area of receptor polymorphisms and how they affect the immune system or risk for melanoma. Most research surrounding estrogen receptor polymorphisms have surrounded the ESR1 receptor, with cancer-related research being directed primarily towards breast cancer. Still results remain inconsistent or inconclusive. Furthermore, much of the research available about estrogen receptor polymorphisms is outdated, with many papers being fifteen to twenty years old. Newer research and research focused on melanoma or the immune system can create a better understanding on the topic of the influence of polymorphisms.

Lastly, there is a need for more research on novel melanoma treatments. Areas such as the use of hormone therapy in melanoma and personalized therapy can be explored and improved as treatment options. Current data for these treatments have yielded varied results, with some studies reporting positive outcomes, others indicating negative results, and a third group of studies concluding that the results for these treatments remain unclear. Future studies can investigate ways to enhance these treatments, aiming to achieve more consistent and positive outcomes in these areas.

CONCLUSION

All in all, women are better protected from melanoma compared to men, partly due to the protective effects of estrogen. Through activation of ERβ and GPER, estrogen directly suppresses tumor growth by regulating the cell cycle, preventing abnormal DNA hypomethylation, and making melanoma cells more visible to immune surveillance. Estrogen also amplifies both innate and adaptive immune responses by promoting dendritic cell maturation, hematopoietic stem cell differentiation, proinflammatory cytokine production, type 1 interferon output, and immune cell infiltration into tumors among other effects. Even when certain cytotoxic activities are reduced, estrogen compensates by increasing immune cell numbers in the human body. Additionally, it boosts T cell response and blocks tumor escape pathways, such as those that involve inhibitory ligands or T cell inactivation. These advantages create a tumor environment that

decreases chances of melanoma survival and spread, giving women a stronger defense against melanoma.

These findings suggest that therapies targeting estrogen, especially when combined immunotherapy, could be good options. At the same time, immune checkpoint therapies can also work for men, who often respond better to them than women. New personalized treatments, like BNT221 T cell therapy, are also showing promise by tailoring care to each patient's needs.

Together, these express that sex differences in biology matter in clinical trials and will lead to more effective treatments for melanoma as well as for other diseases in both men and women. Continued studies about estrogen in melanoma only increase the potential for advancement and importance of understanding sex-based differences.

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CONFLICT OF INTEREST

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