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A Review on Trends in Cancer Immunotherapy

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Abstract

The incidence, malignancy, and mortality rates of various types of cancer differ significantly between genders, indicating a growing global burden of the disease. Understanding the impact of sex and gender on cancer management is crucial, with sex hormones, particularly estrogens, playing a significant role in driving these differences. These hormones influence gene expression, molecular changes, and the varying effectiveness and side effects of anticancer therapies. Recently, there has been a paradigm shift in cancer treatment with the introduction of immunotherapy, which aims to enhance treatment strategies by minimizing off-target effects of chemotherapy and directly targeting cancer cells. This groundbreaking approach harnesses the immune system to combat cancer and has shown immense promise, revolutionizing our perception and approach to cancer treatment. This article seeks to highlight the latest advancements in cancer immunotherapy and shed light on the role of sex and gender in this field, providing valuable insights to clinicians and researchers in adopting a gender perspective when developing new cancer treatment strategies.

Keywords: Cancer, Immunotherapy, Gene expression, Molecular changes

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Introduction

Sex, as a biological factor, has an impact on the progress and development of various illnesses, including cancer. Although sex and gender are often used interchangeably, they have different meanings. Sex refers to biological characteristics, while gender encompasses roles, behaviors, activities, and attributes that society deems appropriate for males and females based on cultural beliefs. In terms of health, a gender perspective should examine people's circumstances in relation to their economic, social, cultural, and working conditions [1]. These factors have a significant influence on the development, diagnosis, and response to treatment. Some experts propose using the term "sex-gender" to better capture the combined biological and social context, as gender and sex are often intertwined and have multiple dimensions. However, it's important to note that conflating the two terms can create challenges, especially since most data primarily reports sex. Currently, immunotherapy is revolutionizing cancer treatment and offering new possibilities for patients with advanced malignancies, delivering unprecedented therapeutic advantages. As part of immunotherapy, immune cells interact with cancer cells in the tumor microenvironment [2-4]. Through immune checkpoint blockade (ICB) or engineering T cells, tumor killing is achieved by reactivating depleted immune cells and restoring or enhancing their effector functions. A significant amount of progress has been made in cancer immunotherapy over the past few months.

This article aims to provide a concise overview of notable advancements. In an effort to present a perspective on sex and gender and the response to immunotherapy within this subject, we will summarize the understanding of the immunological mechanisms influenced by sex. Additionally, we will analyze the available literature based on different types of immunotherapies, incorporating epidemiological data, experimental discoveries, clinical observations, and therapeutic outcomes [5]. Unfortunately, at times, the outcome may involve simply listing contradictory published information, while other instances may involve engaging in speculative discussions. By considering the existing knowledge, our objective is to encourage further research as a crucial step towards enhancing the development of personalized and patient-centered care in cancer immunotherapy.

Immune Responses to Sex, Gender, and Age

Distinct immune systems are possessed by males and females, which are influenced by various factors. These factors encompass genetic mediators like sex chromosomes (X, Y), hormonal mediators such as estradiol, progesterone, and androgens, environmental mediators like the microbiome, social behaviors associated with sex (e.g., smoking and alcohol consumption), and age. In females, mosaicism results from the random inactivation of one X chromosome in each cell, leading to genetic heterogeneity and the advantages it brings. This inactivation aids in balancing the expression of X-linked genes, although some genes are exempted from this process. It is conceivable that harboring mutations in tumor suppressor genes on one allele while retaining two functional copies could serve as a protective mechanism [6, 7]. In comparison to

the Y chromosome and the autosomes, the X chromosome harbors a larger number of immune-related microRNAs. To be precise, the X chromosome contains approximately 120 microRNAs, while the Y chromosome only has four, and the autosomes have an average of 40 - 50 microRNAs. MicroRNAs regulate gene expression at the post-transcriptional level. Although the functions of most microRNAs have not been fully elucidated, those located on the X chromosome are implicated in immunity and cancer. Ultimately, the unique inheritance pattern of the X chromosome is accountable for the observed immune disadvantage in males as compared to females [8] (Figure 1).

The immune system and sexual hormones

The immune response is influenced by sex hormones: progesterone has substantial anti-inflammatory effects; androgens suppress immune cell activity; and estradiol enhances cell-mediated and humoral immune responses. Females exhibit stronger innate and adaptive immune responses compared to males. They display a superior response to various vaccines and are more resistant to several types of infectious agents. Females generate more robust humoral immune reactions than males; estrogens stimulate plasma cells to produce immunoglobulins. When cultured in vitro with 17-beta-estradiol (E2), peripheral blood mononuclear cells from healthy male and female individuals secrete higher levels of immunoglobulins (Ig), but their proliferation rate and viability remain unaffected [9-11].

E2 has the ability to enhance the synthesis of human peripheral blood mononuclear cell immunoglobulins primarily through the augmentation of Interleukin (IL)-10 release from monocytes, which subsequently triggers the secretion of IgG and IgM by B cells. Administration of estrogen elevates the frequency of IL-6 and IL-10-secreting cells in an animal model. When bone marrow-derived dendritic cells are treated with increasing concentrations of dihydrotestosterone, but not E2, there is a gradual decrease in IL-6 production, whereas the levels of IL-10 initially decrease and then increase with higher concentrations of dihydrotestosterone and E2. In contrast, testosterone

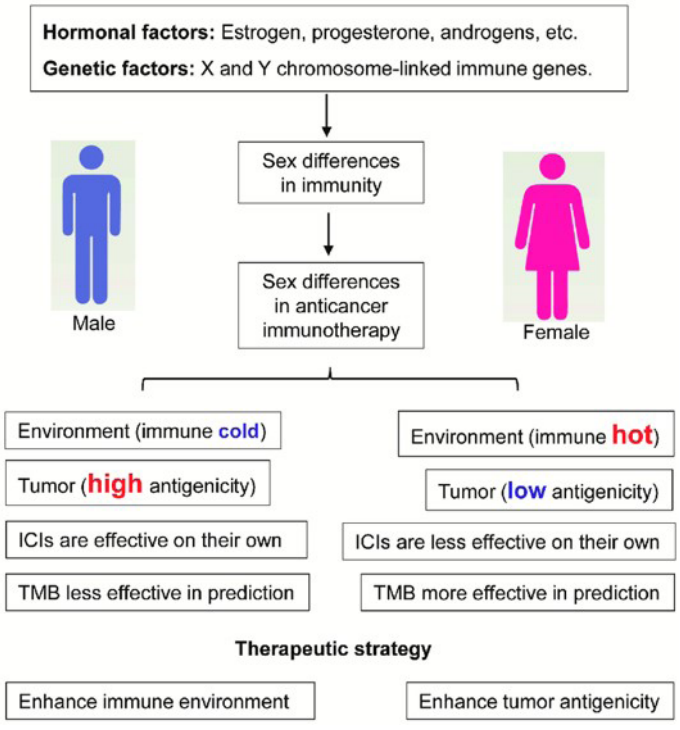

Figure 1: Sex differences in cancer immunotherapy [8].

reduces immunoglobulin production by more than 50% through a mechanism distinct from estrogen [12-16]. Testosterone directly impairs the secretion of IgG and IgM in B lymphocytes, while also diminishing the production of IL-6 by monocytes and increasing the expression of the anti-inflammatory cytokine IL-10. Estrogen has also been demonstrated to directly enhance the expression of survival mediators in B cells, such as CD22, SHP-1, and Bcl-2, as well as alter apoptosis mediators, like PD-1. It should be noted that not only B lymphocytes, but also dendritic cells (DC), macrophages, neutrophils, and natural killer cells (NK) are affected by sex hormones [17, 18].

T-regulatory cells (T-reg) are affected by fluctuations in sex hormone levels throughout the ovarian cycle [19]. The frequency and quantity of T-regs increase during the follicular phase due to elevated estrogen levels, whereas they decrease during the luteinic phase when estrogen is low, and progesterone is high. Given that T-regs regulate the expansion of the peripheral T cell pool and play a key role in maintaining self-tolerance by suppressing self-reactive T cell clones, it can be postulated that the impact of sex hormones on T-reg contributes to the development of autoimmune diseases in women. Estrogen also selectively regulates the expression of certain chemokine receptors on T cells. Specifically, estrogen stimulates the CCR5 and CCR1 receptors, which are CC-chemokine receptors, on CD4+ T cells. This has implications for the migratory abilities of reactive T cells, not only during infection but also in the context of autoimmunity [20-24].

The precise mechanism through which estrogen influences the biology of T cells remains incompletely understood. Reduced levels of estrogen shift the T helper (Th) response towards Th1 differentiation, thereby promoting cellular immunity. Conversely, elevated concentrations of estrogen disrupt the differentiation of Th cells towards the Th2 phenotype, consequently enhancing humoral immunity [25,26]. Estrogen's impact on various immune parameters is contingent upon its concentration. ESTROGENS HIGH LOW Augmented Treg Reduced Treg Th2 differentiation Th1 differentiation highlighting certain variations in immune response between males and females.

Estrogens increase the production of immunoglobulins mainly by increasing the production by monocytes of IL-10, which in turn triggers the secretion of IgG and IgM by B cells; in contrast, testosterone has been found to reduce immunoglobulin production directly damaging the secretion of IgG and IgM in B lymphocytes, and indirectly by reducing the production of IL-6and increasing IL-10 from monocytes; estrogen increase the expression regulation of B cell survival mediators, such as CD22, SHP-1 and Bcl-2, and change the expression of the PD-1, an apoptosis mediator; T-regulatory cells (T-reg) are sensitive to changes in sex hormone levels during the ovarian cycle: increase with high estrogen levels and decrease with low estrogens and high progesterone; low estrogens means T helper (Th) differentiation towards Th1 while high doses of estrogen towards the Th2 phenotype. T-regulatory cells (T-reg) are sensitive to changes in sex hormone levels during the ovarian cycle [27-34].

The amount and occurrence of T-regs rise during the follicular phase due to the escalation in estrogen levels, while they decline during the luteinic phase in which estrogen is low and progesterone is elevated. Considering that T-regs regulate the expansion of the peripheral T cell pool and have a key role in maintaining self-tolerance by suppressing self-reactive T cell clones, it can be presumed that the impact of sex hormones on T-regs contributes to the initiation of autoimmune diseases in women [35-39]. Estrogen also selectively manages the expression of certain chemokine receptors on T cells. In the case of the CC-chemokine receptors, estrogen stimulates the CCR5 and CCR1 on CD4 + T cells.

The migratory capabilities of reactive T cells are influenced by this, not only during infection but also in cases of autoimmunity. The exact mechanism through which estrogen impacts T cell biology remains incompletely understood. Reduced levels of estrogen bias the Th response towards differentiation into Th1, enhancing cellular immunity. Conversely, high levels of estrogen disrupt the differentiation of Th cells towards the Th2 phenotype, resulting in a stronger humoral immune response. Additionally, estrogen has a suppressive effect on the innate immune system [40]. Fcγ RIIIA is one of the primary activating receptors found on monocytes. Estrogen signaling suppresses the transcription of the Fcγ RIIIA gene, thereby diminishing the ability of monocytes to secrete IL-1β, IL-6, and TNF.

Moreover, studies have demonstrated a decrease in the production of these cytokines during the follicular stage of the ovarian cycle (when the level of estrogen is elevated) and an increase during the luteal stage (when the level of estrogen is lower) [41]. Females have a higher phagocytic activity in neutrophils and macrophages compared to males. As stated in several studies, the quantity of neutrophils varies throughout the menstrual cycle in females: they decrease during the follicular stage and increase during the luteal stage [42, 43].

There is a significant increase when estrogens are present as well as progesterone in pregnant women. Different studies have described estradiol's dose-dependent effect on degranulation differently based on the release of glucuronidase, lysozyme, and myeloperoxidase from cytoplasmic neutrophil granules [45]. There is also some evidence that estrogens influence the intracellular oxygen-dependent killing mechanism, but the results are still unclear.

Immunity, microbiome, and aging

The recognition of the microbiome's influence on immunity is acknowledged. However, determining the exact contribution of the microbiome is challenging due to the potential impact of sex on its composition in relation to body mass [46]. Sex hormones, specifically androgens, play a crucial role in shaping the makeup of the gut microbiota, which can also be affected by dietary factors and the use of antibiotics. The microbiota of the stomach and vagina undergo changes with age, such as gastric atrophy and menopause-related vaginal alterations [47]. Bacteria are capable of metabolizing sex hormones through hydroxy steroidal dehydrogenase enzymes, which regulate the balance between active and inactive steroids. Aging has a notable effect on estrogen and androgen levels in both males and females. While estrogen levels decrease solely in menopausal women, androgen levels gradually decline in both sexes starting around the age of thirty [48-52]. Moreover, the heightened risk of cancer associated with aging is linked to the senescence of stromal fibroblasts and the activation of cancer-associated fibroblasts. The activity of cancer-associated fibroblasts is also influenced by sex hormones, yielding varying outcomes depending on the specific tissue (Figure 2).

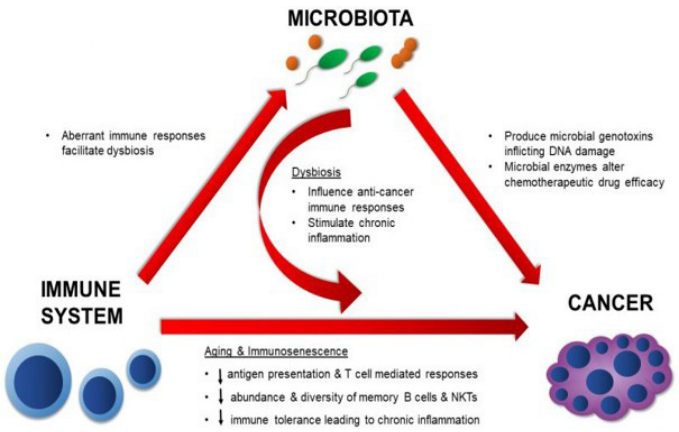

Figure 2: Microbiota and immune system influence cancer development during aging [52].

Sex, genes, immunity, and cancer

Numerous genes on the X chromosome control the immune system, while the Y chromosome also possesses genes that regulate responses. X chromosome genes associated with immunity produce proteins that play a role in innate immunity regulation, including Toll-like receptors (TLR), as well as proteins involved in adaptive immunity regulation, such as cytokine receptors and transcription factors. These genes on the X chromosome can evade X inactivation, resulting in higher expression levels in females compared to males. Sexual disparities in immunity are influenced by sex hormones, which impact the development and function of various immune cell populations [53].

They have a significant impact on the control of numerous genes associated with the immune system. Androgen response elements and estrogen response elements are promoters found on multiple genes linked to natural and acquired immunity, suggesting that sex hormones can directly control the expression of factors that influence immunity. Female cells seem to possess a more effective epigenetic mechanism compared to their male counterparts [54]. Specifically, the X chromosome contains a substantial number of non-coding microRNAs (miRs), currently surpassing the mere two miRs found on the Y chromosome and an average of 40 - 50 on the autosomes. The regulatory influence of miRs is widely acknowledged, as they target approximately 30 - 50% of all protein-coding genes and their impact on cell fate has been extensively proven.

Stimuli elicit contrasting responses in male (XY) and female (XX) cells, likely attributable to their distinct cellular stress management capabilities. This discrepancy is likely attributed to the superior capacity of XX cells to prevent and rectify damage, in comparison to XY cells [55]. Biological DNA repair mechanisms display sexual variations. While males exhibit a higher degree of DNA damage, females possess a lower capacity for DNA repair. Additionally, research has demonstrated elevated levels of oxidative stress biomarkers in males, as opposed to females of matching age, and male cells exhibit a higher production of reactive oxygen species than female cells. Women exhibit a relatively lower susceptibility to oxidative stress in comparison to men.

The female immune system appears to be more efficient in diverse species, including humans. The enzyme aromatase (CYP19A1) transforms androgens into estrogens, which then engage with either the estrogen receptor α (ERα) or the estrogen receptor β (ERβ) to generate both genomic and non-genomic physiological impacts [56]. Although the two forms of ER are encoded by distinct genes, they exhibit similar interactions with natural hormones. ERs can be located in both the nucleus and cytoplasm of cancer cells, enabling the control of genes implicated in cell survival, proliferation, and communication. Significantly, E2 seems to play a crucial function in the growth and malignant advancement of various types of tumors, such as breast, prostate, endometrium, ovary, colon, and lung tumors.

Development and Susceptibility to Cancer

Incidence of cancer by gender and sex

As per the Italian Cancer Registry (AIRTUM), the likelihood of developing cancer is 50% for men and 33.33% for women, while the chance of dying from cancer is 33.33% for men and 16.67% for women. The reason for this can be attributed to the intricate interplay among sex hormones, sex chromosomes, cancer cells, the

tumor microenvironment, and the immune system. Female cells have demonstrated a greater capacity to withstand cellular stress by activating protective mechanisms like autophagy and possessing more antioxidant defenses compared to male cells [57]. Several research papers have been published that examine patient groups based on their gender: studies that compare the genetic material of cancer patients with that of healthy individuals (controls) to identify specific genetic variations associated with cancer risk; gene expression studies that employ microarray or RNA-seq techniques to analyze the expression patterns of sex chromosome genes; studies that identify gender-specific changes in body cells (e.g., alterations in the number of gene copies or mutations that occur after birth). Various factors related to gender, such as smoking and other behaviors (including alcohol consumption and sun exposure), exposure to environmental toxins in the workplace, body weight, dietary choices, and physical activity, have varying effects on men and women in this context [58]. In terms of most types of cancer, males have a higher likelihood of developing malignancies during their lifetime compared to females and experience poorer outcomes. Males face an almost twofold increase in mortality risk for all types of cancer compared to females, especially for cancers affecting the larynx, esophagus, bladder, and lungs. This higher mortality rate in males is not only due to differences in cancer causes but also to sexual disparities in hormonal regulation and immune system functioning. Females generally exhibit stronger innate and adaptive immune responses, which helps lower the risk of cancer-related deaths.

The dissimilarities arise from the interplay of epigenetic and genetic elements, as well as the influence of sex hormones and psychosocial factors. The X chromosome harbors crucial genes that regulate immune response, such as those responsible for IL-2 receptor gamma subunit, TLR-7 and TLR8, CD40L, and the forkhead box P3 (FoxP3). Sex hormones play a role in modulating the development, maturation, lifespan, and functional capabilities of various components of the innate immune system, including dendritic cells, neutrophils, natural killer cells, macrophages, B lymphocytes, and T lymphocytes [59, 60]. The presence of sex chromosomes and the effects of hormones impact the self-renewal of systemic factors associated with carcinogenesis, stem cell populations, and the microenvironments within tumors. As a consequence of mounting a more robust immune response, women are more prone to autoimmune and inflammatory diseases [61]. Women possess an immune system that exhibits a Th1 bias. Sex hormones have been found to impact the regulation of the balance within the Th cell network in various manners. The homeostasis of Th1 and Th2 cell network functions in the immune response is dependent on the roles played by Th1 and Th2 cytokines (Th1/Th2). The production pathway of IL-6 is specific to women and contributes to immune response homeostasis, while the interferon (IFN)-γ production pathway is specific to men [62]. The IL-10 pathway, which is controlled by gender-specific pathways, plays a role in restoring immune system resting homeostasis. In mice, adult females produce higher levels of Th1-type cytokines like IFNγ compared to males [63]. However, the Th1-Th2 dichotomy may not always hold true for human males and females. In post-puberty adulthood, females exhibit higher CD4/CD8 ratios and CD4+ T lymphocytes, increased T cell activation and proliferation, and lower CD8+, Treg, and NK cells. B cells and immunoglobulins are also elevated in human females [64]. With the exception of certain cases, Th1 cells, through their immune functions, can generally be considered beneficial in inducing an effective antitumor immune response. As previously mentioned, the Th1 phenotype plays a pivotal role in the development of an effective immune response against tumors through various means, particularly by inducing the activation of CTL activity [65]. It is hypothesized that PDL1 might impact the adaptability of the Th1 phenotype. The preservation of the Th1 phenotype could be directly achieved through PD1 blockade, which demonstrates notable clinical benefits in the treatment of cancer. Hence, an intriguing approach to fully restore the Th1 phenotype could involve the transfer of Th1 cells combined with an anti-PD1 blocking antibody. In females, cancer must evade more robust immune surveillance mechanisms and undergo a heightened process of immune editing in order to become metastatic. This ability of female tumors to evade immune surveillance reduces their immunogenicity and enhances their capacity to escape the immune system, thereby potentially leading to resistance against immunotherapy.

Cancer by viral infections

Approximately 10% to 15% of human malignancies are caused by viral infections, and the currently available immunizations effectively prevent both infection and neoplastic conditions [66]. Vaccines exploit humoral immunity, and the discrepancy in vaccination response between genders may be attributed to higher levels of CD4+ lymphocytes and the production of Th1 cytokines in women following immunization. It has been observed that women who receive the anti-hepatitis B virus vaccine experience higher rates of seroconversion, leading to a reduced prevalence of liver cancer development. Diseases related to human papillomavirus (HPV), including oncological ailments, exhibit sex and gender discrepancies [67]. Females and males exhibit different inflammatory reactions to HPV, with estrogen inhibiting viral clearance and testosterone facilitating faster clearance in men. HPV affects genital organs differently, with the cervix being the most affected in women while the genital area is rarely involved in males. Additionally, different behaviors impact the epidemiology of HPV-related diseases, placing certain groups of men (such as homosexuals, individuals with human immunodeficiency virus, smokers, and alcoholics) at a higher risk of developing tumors in sites like the oropharynx and anus. The distribution of HPV-related diseases is also influenced by socio-economic conditions. On the other hand, viruses also present a therapeutic opportunity. Since 2015, oncolytic viral therapy, which involves selective infection and replication of genetically engineered viruses in cancer cells to induce immune-mediated death, has been approved by the Food and Drug Administration [68].

mTOR as a Link Between the Immune System and Sex Hormones

mTOR, also known as mammalian target of rapamycin, is an essential protein involved in the creation of two complexes called mTORC1 and mTORC2. mTORC2 is responsible for regulating cell survival, growth, and aging, while mTORC1 controls cellular metabolic processes, specifically the synthesis of proteins and the utilization of glucose. By inhibiting mTOR, it can enhance the immune system's vigilance by influencing the interaction between the tumor microenvironment and immune cells such as macrophages, natural killer cells, neutrophils, helper T lymphocytes, cytotoxic T lymphocytes, and regulatory T lymphocytes. Moreover, the inhibition of mTOR disrupts the proper functioning of natural killer cells and influences the differentiation of cytotoxic T lymphocytes. Blocking mTOR also limits the proliferation of regulatory T lymphocytes but has minimal impact on helper T lymphocytes and cytotoxic T lymphocytes. Additionally, mTOR plays a role in regulating PD-L1. Upon activation, mTOR, through mTORC1, triggers the activation of S6K1, resulting in the phosphorylation of the ribosomal protein S6 (S6rp) and increased translation of mRNA, ultimately leading to cell proliferation [69].

The S6K1 can also be activated by the Ras/MEK/MAPK cascade. S6K1 activates ER via phosphorylation, resulting in ligand-independent activation. Furthermore, phosphorylated ER can also activate S6K1.

By triggering downstream PI3K-mTOR signaling and hepatocyte proliferation, E2 promotes liver carcinogenesis by binding to the G-protein-coupled estrogen receptor 1.

Previous research and Chaturanta et al. have reported a sex-specific mTOR activity in the liver. They suggested that this sex-specific activity is mediated by G-protein-coupled estrogen receptor 1, which activates PI3K-mTOR during liver regeneration. The androgen receptor (AR) pathway is known to interact with the PI3K/Akt/mTOR pathway, as well as other receptors such as the estrogen receptor and human epidermal growth factor receptor 2. Chen et al. demonstrated that suppressing androgen and PI3K/Akt signaling leads to cell proliferation in prostate cancer. The growth and survival of prostate cancer cells are supported by a reprogramming of cellular metabolism through AR signaling. Specifically, androgen-induced aerobic glycolysis and mitochondrial respiration require the activation of mTOR-dependent metabolic gene networks after an AR-mediated reprogramming of mTOR-chromatin associations [70].

Recent Highlights in Immune Therapy

In recent years, the use of ICB therapy, encompassing drugs like anti-PD-1, PD-L1, and CTLA-4, has revolutionized the treatment of advanced cancer patients. It has demonstrated remarkable effectiveness in various types of cancer, including melanoma and non-small cell lung cancer. Nevertheless, a subset of patients fails to respond to ICB treatment, and others experience hyper progressive disease (HPD), leading to rapid cancer advancement. Hence, it is essential to conduct further investigations to comprehend the complex interconnection between cancer and the immune system (Figure 3) [71].

Dendritic cells (DCs)

In ICB conventionally, the activation of the immune system in the fight against cancer through ICB therapy typically involves the direct stimulation of CD8+ T cells within the tumor microenvironment (TME), enabling them to carry out their cytotoxic functions. A recent investigation has brought attention to the participation of CD5+ DCs in initiating CD8+ T cell responses during ICB therapy. In this process, the presence of minimal levels of IL-6 encourages a higher proportion of CD5+ DCs, which then interact with T cells and trigger T cell activation. This discovery implies that CD5 may serve as a potential target for enhancing the efficacy of ICB therapy. Additionally, the expression of CD5 on DCs can function as a biomarker for predicting patient responses to ICB therapy.

γ-δ T cells in ICB

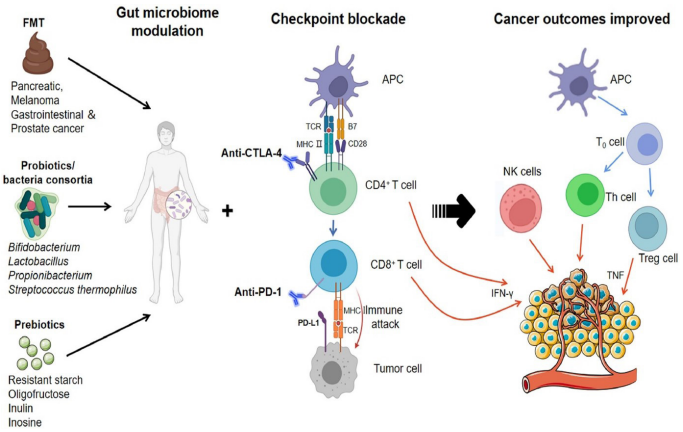

Figure 3: Efficiency of cancer immunotherapy [71].

CD8+ T cells, the main cells that carry out the effects of ICB, depend on binding to antigenic epitopes presented by HLA Class I molecules to perform their function. However, in colorectal cancer, defective DNA mismatch repair often results in the loss of HLA Class I-mediated antigen delivery due to impaired mechanisms for processing antigens. Despite this, some patients with these cancers can still respond to PD-1 blocking, and some even have long-lasting responses [72]. This suggests that other subsets of immune cells, aside from CD8+ T cells, are involved in fighting against tumors. Research has shown that γ-δ T cells are the key effector cells responsible for post-ICB activation in cancers with HLA Class I molecular defects, and their ability to fight against tumors partly relies on interactions between NKG2D and NKG2D-ligands. This funding further enhances our understanding of how ICB treatment leads to a response.

B cells in ICB

The function of B-cell reactions in cancer immunotherapy has additionally been clarified. The scientists discovered that levels of antibodies linked to endogenous retroviruses (ERV) are noticeably increased in the bloodstream and tumor tissue of patients with lung cancer. Despite ERV-derived antigens being autoantigens, their significant upregulation in cancer leads to immune acceptance. Further investigations revealed that ERV-linked antibodies exhibit anti-tumor action, trigger a tumor immune response, and amplify the impact of anti-PD-1/PD-L1 immunotherapy [73]. This research offers fresh concepts for the development of innovative immunotherapeutic approaches for lung cancer. Furthermore, ERV antibodies possess the potential to emerge as an original immunotherapeutic approach for lung cancer, holding the promise of augmenting the efficacy of PD-1/PD-L1 immune checkpoint inhibitor therapy.

Tumor draining lymph nodes in ICB

Besides the tumor environment, a research group has discovered that tumor lymph nodes play a crucial role in the response to ICBs. The presence of CD8+ T cells in tumor-draining lymph nodes is vital for ICB therapy. Following ICB treatment, there were observed variations in the ratio of different CD8+ T cell subtypes in unaffected areas. Specifically, precursor exhausted CD8+ T cells (Tpex cells) in lymph nodes differentiate into intermediate-exhausted CD8+ T cells (Tex-int), which are then transported via the bloodstream to the cancer site [74]. However, changes in the immune cell composition within the lymph nodes hosting the tumor hinder this essential process. In line with this discovery, there was also an increase in the proportion of Tex-int cells in the blood after ICB treatment, and a significant increase in this proportion indicated a more favorable prognosis. Consequently, Tex-int cells may serve as a biomarker to evaluate the effectiveness and prognosis of ICB therapy.

Bacteria in ICB

Bacteria have been found in various tumors. Lactobacillus royale (Lr), a commonly used probiotic, was recently discovered to migrate and inhabit melanoma from the gut through the bloodstream and lymphatic vessels. Lr breaks down tryptophan to create indole-3-aldehyde (I3A), which triggers the Aryl hydrocarbon receptor (AhR) pathway. This activation stimulates the proliferation of CD8+ T cells and improves their performance within the tumor immune environment, leading to increased IFN-γ production and heightened response to ICB therapy. Additionally, patients with elevated levels of serum I3A have a more favorable prognosis compared to those with lower I3A levels [75]. This underscores the significance of microbial metabolism in controlling tumor growth, and it is anticipated that Lr therapy will be combined with ICB therapy. However, the mechanisms governing the migration

of Lr from the gut to the TME and its exact localization within the TME are still unknown, necessitating further investigation in these areas. It is worth mentioning that previous studies have demonstrated that tumor cells have the ability to generate kynurenine by metabolizing tryptophan, thereby activating the AhR pathway and suppressing the body's immune response against tumors. This highlights the complexity of the effect of AhR on cancer. Variations in the type of cancer and the TME can lead to different or even contradictory outcomes following activation of the AhR pathway, which should be considered in future research endeavors.

Circadian rhythms in ICB

Interestingly, the role of circadian rhythms in immunotherapy has become increasingly important. A study comparing different times of the day found that immune cell delivery was more active in the afternoon, leading to a greater reduction in cancer volume when anti-immunotherapy was administered. The expression of the co-stimulatory molecule CD80 in DCs is regulated by circadian rhythms, as well as the rhythmicity of antigen specific CD8+ T cells that are transported by DCs to cancer sites [76]. These recent findings indicate that the duration of treatment could impact the effectiveness of immunotherapy in patients, and aligning treatment with the function of DCs could enhance the effectiveness of cancer immunotherapy. By timing interventions appropriately, the therapeutic effect can be maximized while improving treatment safety [77].

Mechanisms of ICB tolerance

PD-L1, a factor that suppresses the immune system, is present in various cancer cells and immune cells. Recent studies have found a significant amount of PD-L1 in the nucleus of uveal melanoma samples, which is linked to unfavorable clinical outcomes. They also discovered that nPDL1 enhances the binding of phosphorylated signal transducer and activator of transcription 3 to the early growth response 1 (EGR1) promoter, promoting EGR1-mediated angiogenesis. Moreover, the use of HDAC2 inhibitors can restore the acetylation level of PD-L1 in UM and prevent its movement into the nucleus. As a result, it reduces EGR1 expression levels, inhibiting angiogenesis in UM. Consequently, combining anti-PD-L1 immunotherapy with HDAC2 inhibitors offers a potential treatment approach for UM patients. Another study identified TANK-binding kinase 1 (TBK1), an innate immune kinase, as a gene associated with evading the immune system in tumors [77-81].

TBK1 hinders the signal transmission of cell death after the TNF receptor, which can be focused on to increase the vulnerability of tumors to TNF and IFN-γ toxicity, therefore enhancing the effectiveness of PD-1 blockade treatment. Nonetheless, there are presently no approved inhibitors for TBK1. The experiments are currently confined to the animal phase and further inquiry is still required. Conversely, the mechanism behind the emergence of HPD has been clarified. By means of IFN-γ, CD8+ T cells stimulate the increase of fibroblast growth factor 2 in cancer cells, commencing a metabolic restructuring that inhibits PKM2 activity and reduces NAD levels. This consequently stimulates the acetylation of β-actin and ultimately amplifies the stem-like characteristics of tumor cells [82]. This process can be concisely portrayed as immune alterations causing metabolic restructuring in cancer cells, which subsequently propels tumor advancement following ICB treatment. Patients with a "triple high" pattern of IFN-γ, fibroblast growth factor 2, and β-catenin are more prone to accelerated progression after ICB treatment. This pivotal finding not only assists in the pre-treatment assessment of patients to avoid direct ICB treatment for those with the "triple high" pattern, possibly averting HPD, but also provides insights into a new objective and theoretical basis for merging immunotherapy with targeted metabolic therapy [83].

The new generation of checkpoint inhibitors

Resistance to current immunotherapy regimens in some patients may lead to the need for additional co-blockade targeting new inhibitory receptors (IRs) and ligands. Promising results have been observed in early study findings of a new generation of checkpoint inhibitors currently undergoing clinical trials. T-cell IRs like LAG-3, TIM-3, and TIGIT, as well as inhibitory ligands within the B7 family such as B7-H3, B7-H4, and B7-H5, are emerging clinical immunotherapeutic targets [84]. Although the mechanisms of many of these targets are complex and not yet fully understood, they have shown remarkable therapeutic efficacy. Recent research indicates that LAG3 (CD223) accumulates at the immunological synapse, resulting in acidic conditions that disrupt the interaction between the tyrosine kinase Lack and the CD4 or CD8 co-receptor, thereby hindering a crucial requirement for T-cell activation and signaling. This challenges the previous consensus that LAG3 functions as a signal disruptor in a manner dependent on major histocompatibility complex class II [85]. These innovative findings may enhance the effectiveness of IRs and provide new theoretical grounds for the development of a new generation of checkpoint inhibitors.

Chimeric Antigen Receptor (CAR) T cell therapy

CAR T cell therapy is an important form of immunotherapy that offers high rates of complete response in hematologic tumors like acute lymphoblastic leukemia and lymphoma. However, many patients still experience disease recurrence, and CAR T therapy is not as effective in solid tumors. Presently, it is only used for hematologic tumors. Consequently, the focus of research is on improving the response rate of CAR T therapy and reducing relapse and adverse reactions [86]. Overcoming these limitations could open up the possibility of using CAR T therapy for solid tumors. Ark313, a variant of adeno-associated virus vectors (AAV6), is highly efficient in transducing mice T cells and can be genetically modified to enhance the cytotoxicity of CAR T cells. Ark313 facilitates the delivery of large DNA fragments for efficient transgene transfer. Furthermore, Ark313 expands the scope of T-cell genetic engineering studies to include mice and is not restricted to immunodeficient murine and human T cells.

The discovery of Ark313's potential in tumor immunotherapy greatly facilitates research in experimental T-cell immunology. Epigenetic regulation plays a role in T cell differentiation and functional status. An innovative study revealed that TET2 editing, which reduces 5-methylcytosine oxidation in DNA, boosts the cloning amplification and effectiveness of CAR T cells in an antigen-independent manner, thereby improving the antitumor impact. This discovery implies that epigenetic intervention holds promise for clinical application in CAR T therapy. It is important to acknowledge, however, that this technique also carries the risk of CAR T cell overexpansion in vivo, which can lead to secondary mutations. Immune evasion and resistance in CAR T therapies are often caused by antigenic variability and antigen loss. Recent research proposes a new strategy, known as vaccine-enhanced CAR T, to overcome this challenge [87].

The researchers developed a vaccine-enhanced strategy for CAR T cells with the goal of promoting CAR T cell growth and increasing their ability to fight against tumors through CAR ligands. To their surprise, they found that this approach also triggers the spread of antigens and initiates anti-tumor responses in native T cells. As a result, the effectiveness of CAR T therapy in fighting cancer is significantly improved, and the chances of tumor recurrence are reduced. The use of Boolean logic in CAR T cells allows them to distinguish between normal tissue and tumor tissue, which is crucial in expanding the

application of CAR T therapy to solid tumors.

By substituting the CD3ζ domain in CAR with LAT and SLP-76, the scientists developed Boolean-logic AND-gate CAR T cells. These modified CAR T cells selectively target cancer cells that possess both antigens, sparing single antigen-positive normal cells and minimizing systemic toxicity [88]. The incorporation of this AND-gate mechanism enables more precise control over CAR T cell activation, enhancing killing specificity and reducing unintended effects. Beyond cancer immunotherapy, the funding for this research holds promise for extending the use of CAR T cells to investigate autoimmune diseases. However, it is important to acknowledge that this double positive killing approach mediated by the AND-gate may heighten the risk of immune evasion by tumor cells.

T Cell Receptor (TCR) - Gene Engineered T cell therapy

TCR T-cell treatment involves modifying TCR from the patient's own T cells in the lab and then reintroducing them into the patient's body. This allows these T cells to specifically attack cancerous substances. Unlike CAR T-cell treatment, TCR T cells rely on MHC molecules to recognize antigens. This characteristic means that TCR T cells can target antigens not only on the cell surface, which makes them more effective in treating solid tumors compared to CAR T therapies. However, there are numerous challenges in TCR T cell treatment. The level of affinity is a key obstacle to the success of TCR T treatment. Insufficient affinity can result in off-target effects, causing T cells to mistakenly attack normal tissues that express tumor-associated antigens or similar binding molecules [89].

On the other hand, an excessively high level of attraction could result in abnormal immune activation, increasing the likelihood of triggering a cytokine storm. Hence, it is crucial to attain the ideal level of attraction to ensure the safety and effectiveness of TCR T therapy. Moreover, unresolved issues such as T cell depletion, dysfunction during application, evasion of tumor immunity, and the limited availability of tumor-specific antigens for targeting in most cancer patients present significant challenges. Overcoming these obstacles will play a vital role in achieving greater clinical success in the future [90-92]. A recent advancement involves the utilization of neoantigen specific TCR (neoTCR), which entails the non-viral CRISPR-Cas9 gene modification of the patients' own T cells TCR chain to express neoTCR.

The initial step involved the isolation and cloning of multiple neoTCRs that recognize the tumor antigens of the patient. Subsequently, the endogenous TCRs of T cells were removed and replaced with the neoTCRs using non-viral CRISPR-Cas9 gene editing techniques *in vitro*. Subsequently, the modified T cells were reintroduced into the patient's body. The Phase I clinical trial demonstrated the safety and feasibility of these personalized engineered T cells [93]. Furthermore, a subsequent study conducted by the same research team revealed that gene editing-mediated reconstruction of neoTCR in T cells resulted in specific recognition of tumors and displayed cytotoxicity in patients who did not respond to PD-1 blocking therapy. This innovative technology not only facilitates the advancement of TCR T therapies but also offers an alternative treatment option for individuals with advanced solid tumors who do not respond to ICB therapy. This technology also holds the potential to enable the knockout or insertion of specific genes in T cells in order to prevent T cell exhaustion and enhance the long-term effectiveness of immunotherapy.

Tumor Vaccines

Therapeutic cancer vaccinations elicit innate T cell immune responses against tumor antigens through the internalization, processing, and exhibition by dendritic cells. Tumor antigens can either be universal across various cancer variants, such as prevalent mutated forms of KRAS or p53, or they can be tailored neoantigens designed to target unique somatic mutations specific to individual tumors [93]. Merck and Moderna carried out a randomized trial involving patients diagnosed with advanced melanoma who had previously undergone surgical removal of their melanomas. All patients were administered ICB therapy, while two-thirds of them also received the mRNA tumor vaccination, directing cells to generate tumor-specific antigens [94]. Remarkably, the documented data revealed a 44 percent decrease in the mortality and recurrence rates among immunized patients. This signifies an encouraging milestone in clinical assessments of tumor vaccinations, showcasing the healing capabilities of personalized immunotherapeutic medications and tumor vaccinations.

The Role of Gender in Cancer Immunotherapy

The complexity lies in discussing how gender influences cancer immunotherapy compared to sex. This topic is intriguing and has many aspects to consider, making it challenging to evaluate [95]. Moreover, the absence of reliable tools for assessing gender adds another layer of difficulty, making it difficult to compare studies. Stress-related disorders can have long-term consequences on health outcomes and are another significant effect of sex and gender. Persistent exposure to stress is linked to increased vulnerability in cancer, which can impact the outcome. If we consider the role of the behavioral immune system in the effectiveness of immunotherapy, which is influenced by affective and emotional factors and has a more proactive function than the biological system, we anticipate notable gender variations that warrant investigation [95-98].

This subject is practically non-existent in the literary world and remains an area that lacks extensive research. Due to the fact that gender is highly dependent on specific circumstances and shaped by socio-cultural factors, it is challenging to observe and quantify. Broad considerations can be made that spark valuable insights for further investigations. It is widely accepted that the consumption of alcohol, poor dietary choices, limited physical activity, and tobacco use are linked to a higher risk of various cancers, as well as worse outcomes following diagnosis [99]. It is also recognized that there are disparities in cancer prevalence and outcomes based on geographic location. Furthermore, cancer survivors often experience a lower quality of life and diminished psychosocial well-being. For instance, there is a well-documented divide in health outcomes between major urban areas and regional or remote regions in Australia. These geographical disparities and the influence of gender may be explained by factors such as larger populations of older individuals, social and economic disadvantages, limited access to healthcare outside major cities, variations in health behaviors across different environmental contexts, and participation in cancer screening programs [100]. Fourteen out of twenty-three biomedical factors may impact all of these elements. Gender has a pervasive influence on every aspect of our well-being, deeply intertwined with our everyday realities. Social dynamics, health behaviors, cultural and educational factors, work, and work environments are just a few variables within this intricate subject, all interconnected. Social behavioral models have proven to be powerful tools in elucidating disparities in mortality and morbidity based on gender [101-105].

Cancer patients represent a specific subset of individuals who face intense emotional, existential, and physical challenges. They require specialized attention with regards to their quality of life, personal goals, requirements, principles, and connections. Variations based on gender are evident in terms of cognition, memory, problem-solving abilities, and sensitivity to potential harm or danger. Noteworthy gender-related

disparities have been observed in healthcare between females and males, particularly in terms of seeking support during times of crisis, communication styles, coping mechanisms for illness-related distress, involvement in medical decision-making, and the need for psychosocial assistance [106]. Women tend to actively seek out health information and care, while men are less inclined to report negative reactions to treatments. Lifestyle habits, which are themselves influenced by gender, play a role in the onset and progression of chronic diseases, including cancer [107]. Unhealthy and healthy lifestyle patterns vary among men and women based on gender-specific behaviors and attitudes. Gender dimorphism is evident in a range of health-related behaviors, including dietary choices and intake, physical activity levels, habits such as smoking and alcohol consumption, personal grooming and hygiene practices, attention to overall health status, occupational circumstances and associated conditions, adherence to prescribed medications, and use of sun protection measures [108-110].

These attitudes can vary over time due to age or specific personal experiences. Each of these factors can have additional effects. For instance, dietary habits can alter the microbiota, leading to obesity, and we are aware of how both of these factors impact an individual's immune status and can have consequences for neoplastic diseases, their treatment, and outcomes [111]. The exposure to various mutagenic causes, such as ultraviolet light for melanoma and tobacco smoke for non-small-cell lung cancer, has been observed to result in strong positive associations with increased tumor mutational burden and the efficacy of immune checkpoint inhibitors. Cancer patients who have a better psychosocial quality of life are found to have subjective feelings such as self-concept, happiness, optimism, the use of coping strategies, family functioning, and social support. These feelings may differ between genders [112]. Interestingly, while women experience stress-related psychiatric disorders more often, paradoxically, they appear to be better at coping with cancer and positively influencing its outcome. Two studies have shown a significant connection between being female and experiencing psychological distress related to kidney cancer.

Patients' Sex and Adverse Events of Cancer Immunotherapy

Sex-specific adverse reactions to cancer therapy are well-documented; moreover, it has been observed that women experience multiple adverse events with immunotherapy (known as immune-related adverse events or irAEs), specifically endocrinopathies, arthritis, and pneumonia, resulting in a higher discontinuation rate of treatment [113, 114]. Premenopausal women had higher rates of irAEs compared to postmenopausal women and men. Although there was no difference in the occurrence of grade 3 irAEs between the two genders, women were more likely to be prescribed oral or intravenous steroids, suggesting that they may receive different treatment for immunotherapy complications. One possible explanation for this disparity in irAE treatment is the variation in the types of irAEs experienced by each gender. Pneumonia, which is more common in women, is typically treated with oral or intravenous steroids, while men have higher rates of dermatological toxicity, which is usually managed with topical steroids. Factors such as ethnicity, body mass index, and genetic predisposition to autoimmune disorders may also contribute to the risk of developing irAEs [115].

The use of steroids could potentially reduce the effectiveness of the immune checkpoint inhibitors due to the possible suppression of IL-2 and the increase in immunosuppressive regulatory T cells. However, findings from other research studies have indicated that treating irAEs with steroids does not impact the outcome. Higher grade (Grade 2 or above) irAEs have been associated with improved progression-free survival and overall survival [116-118]. Nevertheless, there is currently no substantial evidence from large-scale perspective studies to establish a strong correlation between irAEs and treatment efficacy. Most clinical trials involving immune checkpoint inhibitors have excluded patients with known or suspected active autoimmune diseases, except for vitiligo. Particularly, patients who are currently taking immunosuppressant drugs or have clinically relevant symptoms have been excluded from these studies. In the absence of a clear association between autoimmunity and immunotherapy efficacy and safety, pharmaceutical companies have decided to exclude patients with an increased risk of adverse events from studies because these drugs can induce a variety of serious autoimmune adverse events. Using immune checkpoint inhibitors to treat patients with underlying autoimmune diseases is safe and effective, according to some data from retrospective studies [119].

Contrarily, the negative effects caused by the immune system may hold a favorable predictive significance, as evidenced by the correlation between vitiligo development and the most effective responses to immunotherapy in metastatic melanoma [120-122]. Numerous ongoing investigations are examining the factors linked to the likelihood of immune-related adverse events (e.g., hereditary genetic background and gut microbiota) and their function as prognostic indicators. The occurrence of autoimmune disorders is significantly skewed towards females. It is approximated that autoimmune disorders affect 6% of the general populace, with females making up 80% of this percentage. Moreover, the emergence, intensity, and outcome of various autoimmune diseases are associated with gender [123-126]. Factors contributing to the disparity in adverse reactions between genders are often attributed to gender-related factors such as cultural, psychosocial, or behavioral distinctions. Behaviors related to seeking healthcare, societal roles, and even gender-based bias in medication prescription can influence the perception of adverse reactions differently between genders. For instance, self-image (or body perception) may impact the perception of certain adverse reactions in a dissimilar manner between genders [127-129].

Conclusions

Sex is determined by the presence of sex chromosomes and the levels of sex hormones. It is a factor that impacts both the innate and adaptive immune responses. Surprisingly, less than 10% of studies in immunology consider the gender of the patients when analyzing their data. When it comes to clinical trials for immunotherapy, women are not adequately represented compared to men. This may be because historically, men have been used as the standard representation of the human species. There is also concern that the cyclic hormonal fluctuations in a woman's body could potentially affect the outcomes of clinical trials. However, it would be incorrect to assume that the findings in male patients can be applied to female patients and vice versa. Therefore, it is important for clinical trials on cancer immunotherapy to focus on identifying differences between the sexes. Future research should aim to increase the participation of women in studies and improve the effectiveness of immunotherapies in women. This could involve exploring different approaches to immunotherapy for both men and women. It is crucial to conduct prospective studies to gain a better understanding of these observations and determine if there is a link between irAE and response to immunotherapy. All cancer-related matters require greater attention to gender, including the inclusion of individuals who identify as lesbian, gay, bisexual, transgender, and intersex. Achieving a truly inclusive model of precision medicine may be challenging due to the relatively small numbers of these minorities, but it is necessary. In addition to biological sex, considering gender

identity is vital for a comprehensive understanding and description of cancer and for making treatment decisions.

References

1. Klinge I (2008) Gender perspectives in European research. Pharmacol Res 58: 183-189. https://doi.org/10.1016/j.phrs.2008.07.011
2. Straface E, Gambardella L, Brandani M, Malorni W (2012) Sex differences at cellular level:"cells have a sex". Sex and Gender Differences in Pharmacology. 49-65.
3. Irelli A, Sirufo MM, D'Ugo C, Ginaldi L, De Martinis M (2020) Sex and gender influences on cancer immunotherapy response. Biomedicines. 8: 232. https://doi.org/10.3390/biomedicines8070232.
4. Massimini M, Palmieri C, De Maria R, Romanucci M, Malatesta D, et al. (2017) 17-AAG and apoptosis, autophagy, and mitophagy in canine osteosarcoma cell lines. Vet Pathol 54: 405-412. https://doi.org/10.1177/030098581668140
5. Lista P, Straface E, Brunelleschi S, Franconi F, Malorni W (2011) On the role of autophagy in human diseases: a gender perspective. J Cell Mol Med 15: 1443-1457. https://doi.org/10.1111/j.1582-4934.2011.01293.x
6. Zhu Y, Shao X, Wang X, Liu L, Liang H (2019) Sex disparities in cancer. Cancer Lett 466: 35-38. https://doi.org/10.1016/j.canlet.2019.08.017
7. Kim SY, Lee S, Lee E, Lim H, Shin JY, et al. (2019) Sex-biased differences in the correlation between epithelial-to-mesenchymal transition-associated genes in cancer cell lines. Oncol Lett 18: 6852-6868. https://doi.org/10.3892/ol.2019.11016
8. Wang S, Cowley LA, Liu XS (2019) Sex differences in cancer immunotherapy efficacy, biomarkers, and therapeutic strategy. Molecules 24(18): 3214. https://doi.org/10.3390/molecules24183214
9. Jaillon S, Berthenet K, Garlanda C (2019) Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol 56: 308-321. https://doi.org/10.1007/s12016-017-8648-x
10. Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF (2011) Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev 20: 1629-1637. https://doi.org/10.1158/1055-9965.EPI-11-0246
11. Wang S, He Z, Wang X, Li H, Wu T, et al. (2019) Can tumor mutational burden determine the most effective treatment for lung cancer patients? Lung Cancer Manag 8: LMT21. https://doi.org/10.1158/1055-9965.EPI-11-0246
12. Ortona E, Pierdominici M, Rider V (2019) Sex hormones and gender differences in immune responses. Front Immunol 10: 1076. https://doi.org/10.3389/fimmu.2019.01076
13. Pellegrini P, Contasta I, Del Beato T, Ciccone F, Berghella AM (2011) Gender-specific cytokine pathways, targets, and biomarkers for the switch from health to adenoma and colorectal cancer. Clin Dev Immunol 2011: 819724. https://doi.org/10.1155/2011/819724
14. Klein SL, Flanagan KL (2016) Sex differences in immune responses. Nat Rev Immunol 16: 626-638. https://doi.org/10.1038/nri.2016.90
15. Konishi N, Miki C, Yoshida T, Tanaka K, Toiyama Y, et al. (2005) Interleukin-1 receptor antagonist inhibits the expression of vascular endothelial growth factor in colorectal carcinoma. Oncology 68: 138-145. https://doi.org/10.1159/000086768
16. Wetzler M, Kurzrock R, Estrov Z, Kantarjian H, Gisslinger H, et al. (1994) Altered levels of interleukin-1 beta and interleukin-1 receptor antagonist in chronic myelogenous leukemia: clinical and prognostic correlates. Blood 84: 3142–3147.
17. Chraa D, Naim A, Olive D, Badou A (2019) T lymphocyte subsets in cancer immunity: friends or foes. J Leukoc Biol 105: 243-255. https://doi.org/10.1002/JLB.MR0318-097R
18. Furman D, Hejblum BP, Simon N, Jojic V, Dekker CL, et al. (2014) Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc Natl Acad Sci 111: 869-874. https://doi.org/10.1073/pnas.1321060111
19. Conforti F, Pala L, Bagnardi V, De Pas T, Martinetti M, et al. (2018) Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 19: 737-746. https://doi.org/10.1016/S1470-2045(18)30261-4
20. Ruggieri A, Malorni W, Ricciardi W (2016) Gender disparity in response to anti-viral vaccines: new clues toward personalized vaccinology. *J* Sex Gend Specif Med 2(3): 93-98. https://doi.org/10.1723/2625.26991
21. Garutti P, Montori S, Bazzan E, Tarabbia C (2018) Gender differences in the epidemiology and prevention of human papillomavirus (HPV) and HPV-related diseases. Ital J Gend -Specif Med 4: 152-156. https://doi.org/10.1723/3091.30836
22. Carrel L, Willard HF (2005) X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 434: 400-404. https://doi.org/10.1038/nature03479
23. Pinheiro I, Dejager L, Libert C (2011) X-chromosome-located microRNAs in immunity: might they explain male/female differences? The X chromosome-genomic context may affect X-located miRNAs and downstream signaling, thereby contributing to the enhanced immune response of females. Bioessays 33: 791-802. https://doi.org/10.1002/bies.201100047
24. Kanda N, Tamaki K (1999) Estrogen enhances immunoglobulin production by human PBMCs. J Allergy Clin Immunol 103: 282-288. https://doi.org/10.1016/S0091-6749(99)70503-8
25. Mirandola L, Wade R, Verma R, Pena C, Hosiriluck N, et al. (2015) Sex-driven differences in immunological responses: challenges and opportunities for the immunotherapies of the third millennium. Int Rev Immunol 34: 134-142. https://doi.org/10.3109/08830185.2015.1018417
26. Verthelyi D (2001) Sex hormones as immunomodulators in health and disease. Int Immunopharmacol 1: 983-993. https://doi.org/10.1016/S1567-5769(01)00044-3
27. Canellada A, Alvarez I, Berod L, Gentile T (2008) Estrogen and progesterone regulate the IL-6 signal transduction pathway in antibody secreting cells. J Steroid Biochem Mol Biol 111: 255-261. https://doi.org/10.1016/j.jsbmb.2008.06.009
28. Salem ML (2004) Estrogen, a double-edged sword: modulation of TH1-and TH2-mediated inflammations by differential regulation of TH1/TH2 cytokine production. Curr Drug Targets Inflamm Allergy 3: 97-104. https://doi.org/10.2174/1568010043483944
29. Thompson MG, Peiffer DS, Larson M, Navarro F, Watkins SK (2017) FOXO3, estrogen receptor alpha, and androgen receptor impact tumor growth rate and infiltration of dendritic cell subsets differentially between male and female mice. Cancer Immunol Immunother. 66: 615-625. https://doi.org/10.1007/s00262-017-1972-4
30. Kanda N, Tsuchida T, Tamaki K (1996) Testosterone inhibits immunoglobulin production by human peripheral blood mononuclear cells. Clin Exp Immunol 106: 410-415. https://doi.org/10.1046/j.1365-2249.1996.d01-842.x
31. Mohamad NV, Wong SK, Hasan WN, Jolly JJ, Nur-Farhana MF, et al. (2018) The relationship between circulating testosterone and inflammatory cytokines in men. The Aging Male 22: 12-140. https://doi.org/10.1080/13685538.2018.1482487
32. De Martinis M, Sirufo MM, Suppa M, Di Silvestre D, Ginaldi L (2020) Sex and gender aspects for patient stratification in allergy prevention and treatment. Int J Mol Sci 21: 1535. https://doi.org/10.3390/ijms21041535
33. Wagner AD, Oertelt-Prigione S, Adjei A, Buclin T, Cristina V, et al. (2019) Gender medicine and oncology: report and consensus of an ESMO workshop. Ann Oncol. 30: 1914-1924. https://doi.org/10.1093/annonc/mdz414
34. Springer KW, Hankivsky O, Bates LM (2012) Gender and health: relational, intersectional, and biosocial approaches. Soc sci med 74: 1661-1666. https://doi.org/10.1016/j.socscimed.2012.03.001
35. Marino M, Masella R, Bulzomi P, Campesi I, Malorni W, et al. (2011) Nutrition and human health from a sex–gender perspective. Mol Aspects Med. 32: 1-70. https://doi.org/10.1016/j.mam.2011.02.001
36. Franconi F, Campesi I, Colombo D, Antonini P (2019) Sex-gender variable: methodological recommendations for increasing scientific value of clinical studies. Cells 8: 476.. https://doi.org/10.3390/cells8050476
37. Ribas A, Wolchok JD (2018) Cancer immunotherapy using checkpoint blockade. Science. 359: (6382): 1350-1355. https://doi.org/10.1126/science.aar4060
38. Wang PF, Song HF, Zhang Q, Yan CX (2020) Pan-cancer immunogenomic analyses reveal sex disparity in the efficacy of cancer immunotherapy. Eur J Cancer 126: 136-138. https://doi.org/10.1016/j.ejca.2019.12.008
39. Prakash VS, Mansukhani NA, Helenowski IB, Woodruff TK, Kibbe MR (2018) Sex bias in interventional clinical trials. J Womens Health 27: 1342-1348. https://doi.org/10.1089/jwh.2017.6873
40. Gemmati D, Varani K, Bramanti B, Piva R, Bonaccorsi G, et al. (2019) "Bridging the gap" everything that could have been avoided if we had applied gender medicine, pharmacogenetics and personalized medicine in the gender-omics and sex-omics era. Int J Mol Sci 21: 296. https://doi.org/10.3390/ijms21010296
41. Legato MJ (2011) The "biological sex or gender?" Debate: "everything flows, nothing stands still. Nothing endures but change." Gender medicine 8: 161-163. https://doi.org/10.1016/j.genm.2011.02.004

42. Conforti F, Pala L, Bagnardi V, Viale G, De Pas T, et al. (2019) Sex-based heterogeneity in response to lung cancer immunotherapy: a systematic review and meta-analysis. J Natl Cancer Inst 111: 772-781. https://doi.org/10.1093/jnci/djz094

43. Carè A, Bellenghi M, Matarrese P, Gabriele L, Salvioli S, et al. (2018) Sex disparity in cancer: roles of microRNAs and related functional players. Cell Death Differ 25: 477-485. https://doi.org/10.1038/s41418-017-0051-x

44. Delaunay F, Pettersson K, Tujague M, Gustafsson JÅ (2000) Functional differences between the amino-terminal domains of estrogen receptors α and β. Mol Pharmacol 58: 584-590. https://doi.org/10.1124/mol.58.3.584

45. Frasor J, Danes JM, Komm B, Chang KC, Lyttle CR, et al. (2003) Profiling of estrogen up-and down-regulated gene expression in human breast cancer cells: insights into gene networks and pathways underlying estrogenic control of proliferation and cell phenotype. Endocrinology 144: 4562-4574. https://doi.org/10.1210/en.2003-0567

46. Trzeciak AR, Barnes J, Ejiogu N, Foster K, Brant LJ, et al. (2008) Age, sex, and race influence single-strand break repair capacity in a human population. Free Radic Biol Med 45: 1631-1641. https://doi.org/10.1016/j.freeradbiomed.2008.08.031

47. Ide T, Tsutsui H, Ohashi N, Hayashidani S, Suematsu N, et al. (2002) Greater oxidative stress in healthy young men compared with premenopausal women. Arterioscler Thromb Vasc Biol 22: 438-442. https://doi.org/10.1161/hq0302.104515

48. Matarrese P, Colasanti T, Ascione B, Margutti P, Franconi F, et al. (2011) Gender disparity in susceptibility to oxidative stress and apoptosis induced by autoantibodies specific to RLIP76 in vascular cells. Antioxid Redox Signal 15: 2825-2836. https://doi.org/10.1089/ars.2011.3942

49. Hewagama A, Patel D, Yarlagadda S, Strickland FM, Richardson BC (2009) Stronger inflammatory/cytotoxic T-cell response in women identified by microarray analysis. Genes Immun 10: 509-516. https://doi.org/10.1038/gene.2009.12

50. Rothenberger NJ, Somasundaram A, Stabile LP (2018) The role of the estrogen pathway in the tumor microenvironment. Int J Mol Sci 19: 611. https://doi.org/10.3390/ijms19020611

51. De Martinis M, Sirufo MM, Suppa M, Ginaldi L (2020) New perspectives in food allergy. Int J Mol Sci 21: 1474. https://doi.org/10.3390/ijms21041474

52. Irelli A, Sirufo MM, Scipioni T, De Pietro F, Pancotti A, et al. (2019) mTOR links tumor immunity and bone metabolism: what are the clinical implications? Int J Mol Sci 20: 5841. https://doi.org/10.3390/ijms20235841

53. Tibbs TN, Lopez LR, Arthur JC (2019) The influence of the microbiota on immune development, chronic inflammation, and cancer in the context of aging. Microbial Cell 6: 324. https://doi.org/10.15698/mic2019.08.685

54. Zeng H (2017) mTOR signaling in immune cells and its implications for cancer immunotherapy. Cancer lett 408: 182-189. https://doi.org/10.1016/j.canlet.2017.08.038

55. O'Donnell JS, Massi D, Teng MW, Mandala M (2018) PI3K-AKT-mTOR inhibition in cancer immunotherapy, redux. Semin Cancer Biol 48: 91-103. Academic Press https://doi.org/10.1016/j.semcancer.2017.04.015

56. Xue G, Zippelius A, Wicki A, Mandalà M, Tang F, et al. (2015) Integrated Akt/PKB signaling in immunomodulation and its potential role in cancer immunotherapy. J Natl Cancer Inst 107: 171. https://doi.org/10.1093/jnci/djv171

57. Conciatori F, Bazzichetto C, Falcone I, Pilotto S, Bria E, et al. (2018) Role of mTOR signaling in tumor microenvironment: an overview. Int J Mol Sci 19: 2453. https://doi.org/10.3390/ijms19082453

58. Aaltonen KE, Rosendahl AH, Olsson H, Malmström P, Hartman L, et al. (2014) Association between insulin-like growth factor-1 receptor (IGF1R) negativity and poor prognosis in a cohort of women with primary breast cancer. BMC cancer 14: 1-3. https://doi.org/10.1186/1471-2407-14-794

59. Sobhani N, Generali D, Zanconati F, Bortul M, Scaggiante B (2018) Current status of PI3K-mTOR inhibition in hormone-receptor positive, HER2-negative breast cancer. World J Clin Oncol 9: 172. https://doi.org/10.5306/wjco.v9.i8.172

60. Alayev A, Salamon RS, Berger SM, Schwartz NS, Cuesta R, et al. (2016) mTORC1 directly phosphorylates and activates ERα upon estrogen stimulation. Oncogene 35: 3535-3543. https://doi.org/10.1038/onc.2015.414

61. Botticelli A, Onesti CE, Zizzari I, Cerbelli B, Sciattella P, et al. (2017) The sexist behaviour of immune checkpoint inhibitors in cancer therapy? Oncotarget 8: 99336. https://doi.org/ 10.18632/oncotarget.22242

62. Baar EL, Carbajal KA, Ong IM, Lamming DW (2016) Sex-and tissue-specific changes in mTOR signaling with age in C57 BL/6J mice. Aging cell 15: 155-166. https://doi.org/10.1111/acel.12425

63. Tsai SY, Rodriguez AA, Dastidar SG, Del Greco E, Carr KL, et al. (2016) Increased 4E-BP1 expression protects against diet-induced obesity and insulin resistance in male mice. Cell rep 16: 1903-1914. http://dx.doi.org/10.1016/j.celrep.2016.07.029

64. Chaturantabut S, Shwartz A, Evason KJ, Cox AG, Labella K, et al. (2019) Estrogen activation of G-protein–coupled estrogen receptor 1 regulates phosphoinositide 3-kinase and mTOR signaling to promote liver growth in zebrafish and proliferation of human hepatocytes. Gastroenterology 156: 1788-1804. https://doi.org/10.1053/j.gastro.2019.01.010

65. Kono M, Fujii T, Lim B, Karuturi MS, Tripathy D, et al. 2017. Androgen receptor function and androgen receptor–targeted therapies in breast cancer: a review. JAMA Oncol 3: 1266-1273. https://doi.org/10.1001/jamaoncol.2016.4975

66. Chen H, Zhou L, Wu X, Li R, Wen J, et al. (2016) The PI3K/AKT pathway in the pathogenesis of prostate cancer. Front Biosci 21: 1084-1091.

67. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, et al. (2018) Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 379: 2108-2121. https://doi.org/10.1056/NEJMoa1809615

68. Calles A, Riess JW, Brahmer JR (2020) Checkpoint blockade in lung cancer with driver mutation: choose the road wisely. Am Soc Clin Oncol 40: 372-84. https://doi.org/10.1200/EDBK_280795

69. Arab A, Yazdian-Robati R, Behravan J (2020) HER2-positive breast cancer immunotherapy: A focus on vaccine development. Arch Immunol Ther Exp 68: 1-8. https://doi.org/10.1007/s00005-019-00566-1

70. Aldous AR, Dong JZ (2018) Personalized neoantigen vaccines: a new approach to cancer immunotherapy. Bioorg Med Chem 26: 2842-2849. https://doi.org/10.1016/j.bmc.2017.10.021

71. Mandal R, Chan TA (2016) Personalized oncology meets immunology: the path toward precision immunotherapy. Cancer Discov 6: 703-713. https://doi.org/10.1158/2159-8290.CD-16-0146

72. Li X, Zhang S, Guo G, Han J, Yu J (2022) Gut microbiome in modulating immune checkpoint inhibitors. EBioMedicine 82: 104163. https://doi.org/10.1016/j.ebiom.2022.104163

73. Fan X (2023) Recent highlights of cancer immunotherapy. Holist Integ Oncol 2: 37. https://doi.org/10.1007/s44178-023-00057-6

74. Lotter H, Altfeld M. (2019) Sex differences in immunity. Semin Immunopathol. 41: 133-135.. https://doi.org/10.1007/s00281-018-00728-x

75. Fischinger S, Boudreau CM, Butler AL, Streeck H, Alter G. (2019) Sex differences in vaccine-induced humoral immunity. Semin Immunopathol 41: 239-249. https://doi.org/10.1007/s00281-018-0726-5

76. Gubbels Bupp MR, Potluri T, Fink AL, Klein SL (2018) The confluence of sex hormones and aging on immunity. Front Immunol 9: 1269. https://doi.org/10.3389/fimmu.2018.01269

77. Özdemir BC, Dotto GP (2019) Sex hormones and anticancer immunity. Clin Cancer Res. 25: 4603-4610. https://doi.org/10.1158/1078-0432.CCR-19-0137

78. Irelli A, Sirufo MM, Morelli L, D'Ugo C, Ginaldi L, et al. (2020) Neuroendocrine cancer of the breast: a rare entity. J Clin Med 9:1452. https://doi.org/10.3390/jcm9051452

79. Klein SL (2000) The effects of hormones on sex differences in infection: from genes to behavior. Neurosci Biobehav Rev 24: 627-638. https://doi.org/10.1016/S0149-7634(00)00027-0

80. Sánchez-Rodríguez C, Cruces KP, Ayora JR, Martín-Sanz E, Sanz-Fernández R. (2017) BCG immune activation reduces growth and angiogenesis in an *in vitro* model of head and neck squamous cell carcinoma. Vaccine 35: 6395-6403. https://doi.org/10.1016/j.vaccine.2017.10.008

81. De Bree LC, Janssen R, Aaby P, van Crevel R, Joosten LA, et al. (2018) The impact of sex hormones on BCG-induced trained immunity. J Leukoc Biol 104: 573-578. https://doi.org/10.1002/JLB.5MA0118-027R

82. Pampena MB, Cartar HC, Cueto GR, Levy EM, Blanco PA, et al. (2018) Dissecting the immune stimulation promoted by CSF-470 vaccine plus adjuvants in cutaneous melanoma patients: long term antitumor immunity and short term release of acute inflammatory reactants. Front Immunol 9: 2531. https://doi.org/10.3389/fimmu.2018.02531

83. Uhlig A, Strauss A, Hosseini AS, Lotz J, Trojan L, et al. (2018) Gender-specific differences in recurrence of non–muscle-invasive bladder cancer: a systematic review and meta-analysis. Eur Urol Focus 4: 924-936. https://doi.org/10.1016/j.euf.2017.08.007

84. Sirufo MM, De Martinis M, Ginaldi L (2018) Omalizumab an effective and safe alternative therapy in severe refractory atopic dermatitis: a case report. Medicine 97: e10897. https://doi.org/10.1097/MD.0000000000010897

85. De Martinis M, Sirufo MM, Ginaldi L (2019) A "stadium" urticaria, cold urticaria is still a mostly unknown disease, with a wide spectrum of severity degrees and few therapeutic certainties: is omalizumab one of these? reflections from a clinical case report. Iran Red Crescent Med J 21: 84250. https://doi.org/10.5812/ircmj.84250.

86. De Martinis M, Sirufo MM, Ginaldi L (2019) Solar urticaria, a disease with many dark sides: is omalizumab the right therapeutic response? Reflections from a clinical case report. Open Med J 14: 403-406. https://doi.org/10.1515/med-2019-0042

87. De Martinis M, Sirufo MM, Viscido A, Ginaldi L (2019) Food allergies and ageing. Int J Mol Sci. 20: 5580. https://doi.org/10.3390/ijms20225580

88. De Martinis M, Sirufo MM, Viscido A, Ginaldi L (2019) Food allergies and ageing. Int J Mol Sci 20: 5580. https://doi.org/10.3390/ijms20225580

89. De Martinis M, Sirufo MM, Viscido A, Ginaldi L. (2020) Food allergy insights: A changing landscape. Arch Immunol Ther Archivum Immunologiae et Therapiae Experimentalis. 68: 1-5. https://doi.org/10.1007/s00005-020-00574-6

90. Sirufo MM, De Pietro F, Bassino EM, Ginaldi L, De Martinis M (2020) Osteoporosis in skin diseases. Int J Mol Sci. 21: 4749. https://doi.org/10.3390/ijms21134749

91. Jendoubi F, Gaudenzio N, Gallini A, Negretto M, Paul C, et al. (2020) Omalizumab in the treatment of adult patients with mastocytosis: a systematic review. Clin Exp Allergy. 50: 654-661. https://doi.org/10.1111/cea.13592

92. Gouder C, Asciak R, Montefort S (2017) Sex differences in the efficacy, safety, and tolerability of omalizumab after 1 year in Maltese patients with asthma. Ann Allergy Asthma Immnol 118: 513-514. https://doi.org/10.1016/j.anai.2017.01.019

93. Sirufo MM, De Pietro F, Bassino EM, Ginaldi L, De Martinis M (2021) Translational allergy and omalizumab: The pioneer. Indian J Pharma Educ Res. 55: 259-264. https://doi.org/10.5530/ijper.55.1s.58

94. Iwai K, Soejima K, Kudoh S, Umezato Y, Kaneko T, et al. (2012) Extended survival observed in adoptive activated T lymphocyte immunotherapy for advanced lung cancer: results of a multicenter historical cohort study. Cancer Immunol Immunother. 61: 1781-1790. https://doi.org/10.1007/s00262-012-1226-4

95. Kim SW, Asakura Y, Tajima K, Iwai T, Taji H, et al. (2020) RETRACTED ARTICLE: High-dose therapy and autologous stem cell transplantation for relapsed or high-risk diffuse large B-cell lymphoma: a nationwide survey. Int J Hematol. 111: 256-266. https://doi.org/10.1007/s12185-019-02772-1

96. Kim HI, Lim H, Moon A (2018) Sex differences in cancer: epidemiology, genetics and therapy. Biomol therapeutics. 26: 335. https://doi.org/10.4062/biomolther.2018.103

97. Gratwohl A, de Elvira CR, Gratwohl M, Greinix HT, Duarte R (2016) Gender and graft-versus-host disease after hematopoietic stem cell transplantation. Biol Blood Marrow Tran. 22: 1145-1146. https://doi.org/10.1016/j.bbmt.2016.03.020

98. Nakasone H, Kawamura K, Yakushijin K, Shinohara A, Tanaka M, et al. (2019) BM is preferred over PBSCs in transplantation from an HLA-matched related female donor to a male recipient. Blood Adv. 3: 1750-1760. https://doi.org/10.1182/bloodadvances.2019000077

99. Ciurea SO, Cao K, Fernandez-Vina M, Kongtim P, Malki MA, et al. (2018) The European Society for Blood and Marrow Transplantation (EBMT) consensus guidelines for the detection and treatment of donor-specific anti-HLA antibodies (DSA) in haploidentical hematopoietic cell transplantation. Bone Marrow Transplant. 53: 521-534. https://doi.org/10.1038/s41409-017-0062-8

100. Takekiyo T, Dozono K, Nara S, Murayama Y, Minamihama N, et al. (2017) Gender differences in physical function and muscle mass change in patients undergoing allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 52: 1460-1462. https://doi.org/10.1038/bmt.2017.156

101. Bhatt NS, Brazauskas R, Tecca HR, Vogel J, Mattila D, et al. (2019) Female sex is associated with poor health-related quality of life in children at 12 months post-hematopoietic cell transplantation. Pediatr Hematol Oncol J. 41: 233-237. https://doi.org/10.1097/MPH.0000000000001239

102. Volk V, Schneider A, Spineli LM, Grosshennig A, Stripecke R (2016) The gender gap: discrepant human T-cell reconstitution after cord blood stem cell transplantation in humanized female and male mice. Bone marrow transplant. 51: 596-597. https://doi.org/10.1038/bmt.2015.290

103. Lafta IJ, Bryant HE, Goldman AS (2014) 'Sex'in the cancer cell. Oncotarget. 5: 7984. https://doi.org/10.18632/oncotarget.2355

104. Shin JY, Jung HJ, Moon A (2019) Molecular markers in sex differences in cancer. Toxicol Res. 35: 331-341. https://doi.org/10.5487/TR.2019.35.4.331

105. Colli LM, Morton LM, Chanock SJ (2019) Sex-related effect on immunotherapy response: implications and opportunities. J Natl Cancer Inst. 111: 749-750. https://doi.org/10.1093/jnci/djz096

106. Díaz A, Beleña Á, Zueco J (2020) The role of age and gender in perceived vulnerability to infectious diseases. Int J Environ Res Public Health. 17: 485. https://doi.org/10.3390/ijerph17020485

107. Shin H, Bartlett R, De Gagne JC (2019) Health-related quality of life among survivors of cancer in adolescence: an integrative literature review. J Pediatr Nurs. 44: 97-106. https://doi.org/10.1016/j.pedn.2018.11.009

108. Westby RP, Berg CJ, Leach C. (2016) Gender, race, BMI, and social support in relation to the health-related quality of life of cancer survivors: a report from the American Cancer Society's Study of Cancer Survivors II (SCS-II). Qual Life Res. 25: 409-421. https://doi.org/10.1007/s11136-015-1084-6

109. Inderberg EM, Wälchli S (2020) Sympathetic improvement of cancer vaccine efficacy. Hum Vaccin Immunother. 16: 1888-1890. https://doi.org/10.1080/21645515.2019.1703456

110. McFarland DC (2019) New lung cancer treatments (immunotherapy and targeted therapies) and their associations with depression and other psychological side effects as compared to chemotherapy. Gen Hosp Psychiatry. 60: 148-155. https://doi.org/10.1016/j.genhosppsych.2019.04.001

111. Lim H, Kim SY, Lee E, Lee S, Oh S, et al. (2019) Sex-dependent adverse drug reactions to 5-fluorouracil in colorectal cancer. Biol Pharm Bull. 42: 594-600. https://doi.org/10.1248/bpb.b18-00707

112. Duma N, Abdel-Ghani A, Yadav S, Hoversten KP, Reed CT, et al. (2019) Sex differences in tolerability to anti-programmed cell death protein 1 therapy in patients with metastatic melanoma and non-small cell lung cancer: are we all equal?. The oncologist. 24: 1148-1155. https://doi.org/10.1634/theoncologist.2019-0094

113. Carrera C, Potrony M, Puig S. (2018) Sex as a predictor of response to cancer immunotherapy. Lancet Oncol. 19: 375. https://doi.org/10.1016/S1470-2045(18)30443-1

114. He M, Roussak K, Ma F, Borcherding N, Garin V, White M, et al. (2023) CD5 expression by dendritic cells directs T cell immunity and sustains immunotherapy responses. *Science*. 379: 2752. https://doi.org/10.1016/S1470-2045(18)30443-1

115. de Vries NL, van de Haar J, Veninga V, Chalabi M, Ijsselsteijn ME, et al. (2023) γδ T cells are effectors of immunotherapy in cancers with HLA class I defects. *Nature.* 613: 743-750. https://doi.org/10.1038/s41586-022-05593-1

116. Ng KW, Boumelha J, Enfield KS, Almagro J, Cha H, et al. (2023) Antibodies against endogenous retroviruses promote lung cancer immunotherapy. Nature. 12: 1-1. https://doi.org/10.1038/s41586-023-05771-9

117. Rahim MK, Okholm TL, Jones KB, McCarthy EE, Liu CC, et al. (2023) Dynamic CD8+ T cell responses to cancer immunotherapy in human regional lymph nodes are disrupted in metastatic lymph nodes. Cell. 186: 1127-1143. https://doi.org/10.1016/j.cell.2023.02.021

118. Bender MJ, McPherson AC, Phelps CM, Pandey SP, Laughlin CR, et al. (2023) Dietary tryptophan metabolite released by intratumoral Lactobacillus reuteri facilitates immune checkpoint inhibitor treatment. Cell. 186: 1846-1862. https://doi.org/10.1016/j.cell.2023.03.011

119. Wang C, Barnoud C, Cenerenti M, Sun M, Caffa I, et al. (2023) Dendritic cells direct circadian anti-tumour immune responses. Nature. 614: 136-143. https://doi.org/10.1038/s41586-022-05605-0

120. Yu J, Zhuang A, Gu X, Hua Y, Yang L, et al. (2023) Nuclear PD-L1 promotes EGR1-mediated angiogenesis and accelerates tumorigenesis. Cell Discovery. 9:33. https://doi.org/10.1038/s41421-023-00521-7

121. Sun Y, Revach OY, Anderson S, Kessler EA, Wolfe CH, et al. (2023) Targeting TBK1 to overcome resistance to cancer immunotherapy. Nature. 615: 158-167. https://doi.org/10.1038/s41586-023-05704-6

122. Li G, Choi JE, Kryczek I, Sun Y, Liao P, et al. (2023) Intersection of immune and oncometabolic pathways drives cancer hyperprogression during immunotherapy. *Cancer Cell*. 41: 304-322. https://doi.org/10.1016/j.ccell.2022.12.008

123. Guy C, Mitrea DM, Chou PC, Temirov J, Vignali KM, et al. (2022) LAG3 associates with TCR–CD3 complexes and suppresses signaling by driving co-receptor–Lck dissociation. *Nature Immunol*. 23 :757-767. https://doi.org/10.1038/s41590-022-01176-4

124. Nyberg WA, Ark J, To A, Clouden S, Reeder G, et al. (2023) An evolved AAV variant enables efficient genetic engineering of murine T cells. Cell. 186(2):446-460. https://doi.org/10.1016/j.cell.2022.12.022

125. Jain N, Zhao Z, Feucht J, Koche R, Iyer A, et al. (2023) TET2 guards against unchecked BATF3-induced CAR T cell expansion. Nature. 615: 315-322. https://doi.org/10.1038/s41586-022-05692-z

126. Ma L, Hostetler A, Morgan DM, Maiorino L, Sulkaj I, et al. (2023) Vaccine-boosted CAR T crosstalk with host immunity to reject tumors with antigen heterogeneity. Cell. 186: 3148-3165. https://doi.org/10.1016/j.cell.2023.06.002

127. Tousley AM, Rotiroti MC, Labanieh L, Rysavy LW, Kim WJ, et al. (2023) Co-opting signalling molecules enables logic-gated control of CAR T cells. Nature. 615: 507-516. https://doi.org/10.1038/s41586-023-05778-2

128. Foy SP, Jacoby K, Bota DA, Hunter T, Pan Z, et al. (2023) Non-viral precision T cell receptor replacement for personalized cell therapy. Nature. 615: 687-696. https://doi.org/10.1038/s41586-022-05531-1

129. Puig-Saus C, Sennino B, Peng S, Wang CL, Pan Z, et al. 2023. Neoantigen-targeted CD8+ T cell responses with PD-1 blockade therapy. *Nature*. 615(7953):697-704. https://doi.org/10.1038/s41586-023-05787-1