

Sex dimorphism in the tumor microenvironment – From bench to bedside and back

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ARTICLE INFO

Keywords:

Sex dimorphism
Immune system
Cancer
Tumor microenvironment
Genderised cancer therapy

ABSTRACT

Summary: Cancer represents a significant cause of death and suffering in both the developed and developing countries. Key underlying issues in the mortality of cancer are delayed diagnosis and resistance to treatments. However, improvements in biomarkers represent one important step that can be taken for alleviating the suffering caused by malignancy. Precision-based medicine is promising for revolutionizing diagnostic and treatment strategies for cancer patients worldwide. Contemporary methods, including various omics and systems biology approaches, as well as advanced digital imaging and artificial intelligence, allow more accurate assessment of tumor characteristics at the patient level. As a result, treatment strategies can be specifically tailored and adapted for individual and/or groups of patients that carry certain tumor characteristics. This includes immunotherapy, which is based on characterization of the immunosuppressive tumor microenvironment (TME) and, more specifically, the presence and activity of immune cell subsets. Unfortunately, while it is increasingly clear that gender strongly affects immune regulation and response, there is a knowledge gap concerning differences in sex-specific immune responses and how these contribute to the immunosuppressive TME and the response to immunotherapy. In fact, sex dimorphism is poorly understood in cancer progression and is typically ignored in current clinical practice. In this review, we aim to survey the available literature and highlight the existing knowledge gap in order to encourage further studies that would contribute to understanding both gender-biased immunosuppression in the TME and the driver of tumor progression towards invasive and metastatic disease. The review highlights the need to include sex optimized/genderized medicine as a new concept in future medicine cancer diagnostics and treatments.

1. Introduction

It has been known for over one hundred years that the immune system has the capacity to recognize and kill tumors. However, it is only recently that immunotherapy has started to become effective and is now taking its place alongside surgery, radiotherapy and chemotherapy as a fourth option for treatment of many cancers [1]. The reason that it has taken so long is that most tumors develop evasive mechanisms that prevent immune recognition and tumor killing, as described by ourselves [2–7] and others [8]. However, recent breakthroughs have allowed some of these immuno-evasive aspects to be overcome, although much work remains to be done if immunotherapies are to reach their

maximum efficacy [9]. Differences in the distributions between men and women, including gender-biased behaviors and clinicopathological subtypes, have not been considered [10–12]. In immunotherapy clinical trials, women are significantly underrepresented compared to men [13]. This may be in part due to concerns related to cyclical hormonal changes in a woman's body and how they could influence clinical trials. However, when considering sex-based immunological differences, it is likely that the results obtained from male patients would not always apply to female patients and vice versa, and accordingly there is now a clear understanding that both sexes should be represented in trial-based research.

A shortage of evidence-based and gender-specific markers hinders

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efficient drug development. Therefore, wide omics assessments combined with mechanistic studies will reveal a marked enrichment of tissue-specific immune subsets in males and females that can be used as predictive biomarkers and therapeutic targets. Here, we provide a comprehensive review concerning immune differences related to gender in the field of tumor immunology and immunotherapy, which will be critical for both basic cancer research and translational application, as well as guiding the mechanistic studies of sex dimorphism in human cancers and the development of sex-specific precision cancer medicine.

1.1. Sex dimorphism in the immune-tumor microenvironment

Whilst sex immune dimorphism is acknowledged for its impact on multiple health-related conditions, such as autoimmune diseases, chronic infections and vaccination responses, how it affects tumor development remains ill-defined [14]. Cancer incidence is predominantly higher throughout male populations, which, in addition to genetic and behavioral factors, could be inherently dictated by the immune-cellular and molecular variations that exist between the two sexes [15]. Interestingly, breast and thyroid cancers are two exceptions with increased incidence in women compared to men [16]. The higher breast cancer incidence in female has been directly linked to estrogen receptor (ER) up-regulation. This leads to activation of downstream signaling proteins (such as the antiapoptotic protein Bcl-2) ultimately resulting in unrestrained tumor growth with genomic instability via p53/Erb-B2-dependent pathways. Contrary, in men breast cancer such estrogen-dependent pathways do not seem to trigger genomic instability

nor aggressive tumoral transformation. This has been mostly associated with the different hormonal milieu in males as well as other environmental carcinogens, namely smoking, radiation or chemical pesticides [17,18]. Additionally, thyroid cancer is 2.9-times more prevalent in women than men. Similarly, in breast neoplasms, the papillary thyroid cancer is also dependent on estrogen receptor status and hence affected by sex hormones. Lee et al., described how estrogen can dramatically induce thyroid cancer cell line proliferation, compared with male sex hormones, which was also associated with an up-regulation of the antiapoptotic protein Bcl-xL expression [19,20]. Altogether indicating that sex hormones play inherently decisive roles at multiple molecular, cellular and physiological stages which trigger malignant transformation. Hereby, we discuss how sex-biased differences can govern the anti-tumoral properties of immune cells belonging to both myeloid and lymphoid cell lineages (Fig. 1).

1.2. Myeloid-derived sex dimorphism in the TME

1.2.1. Dendritic cells

Dendritic cells (DC) are professional antigen-presenting monocytes in charge of orchestrating both innate and adaptive immune systems [21]. Immune-transcriptional profiling in males and females with chronic inflammation has unraveled key genes involved in monocytic inflammatory responses, such as the interferon (IFN) signaling pathway, immune cell activation, phagocytosis and antigen-processing machinery. However, of note are genes that include ubiquitin proteasome-mediated antigen processing; *UBA1*, or major

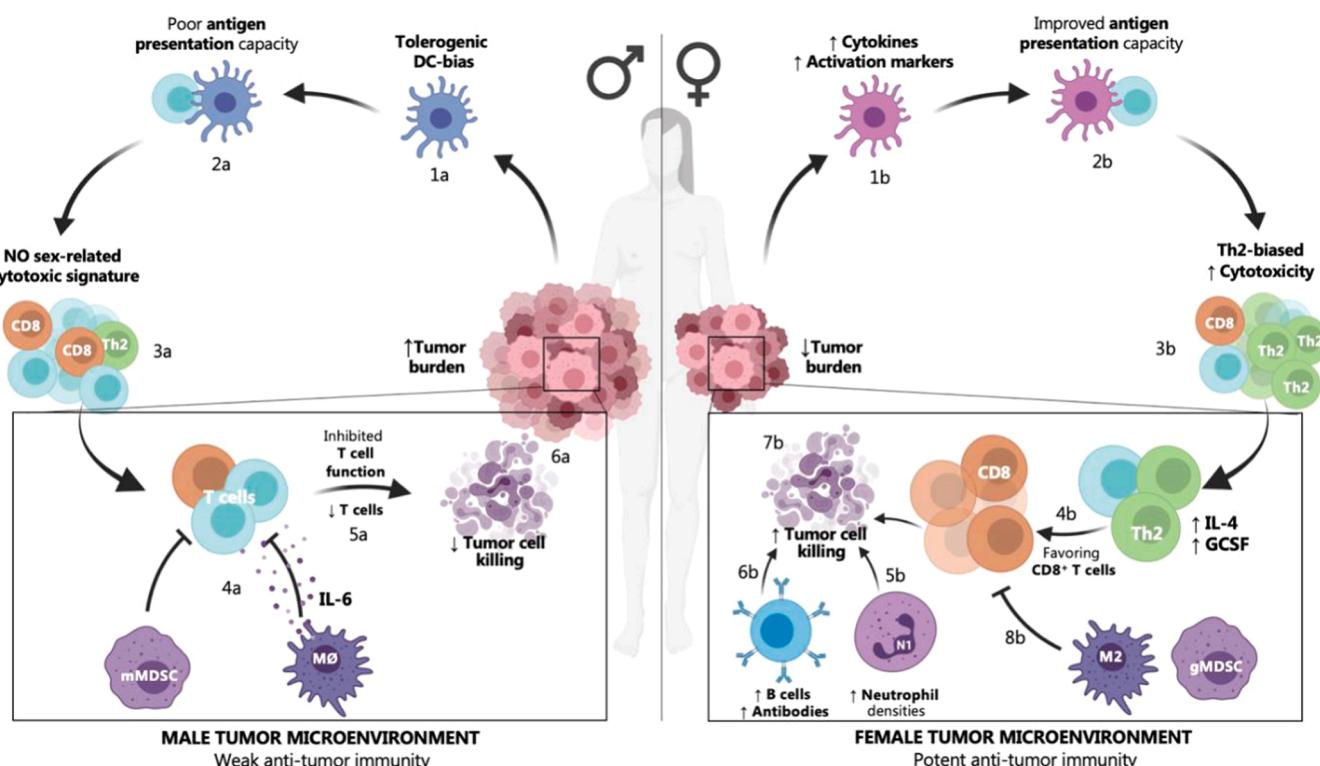


Fig. 1. Sex dimorphism in the immune-tumor microenvironment. Schematic representation of how immune sex dimorphism could affect tumor development. (Left) Higher cancer incidence in males could be due to an overall combination of less vigilant and tolerogenic dendritic cell (DC) phenotypes (1a), which poorly present tumor-associated antigens to T cells (2a). Male T cells lack many important X-linked cytotoxic genes, which deprives them of potent inflammatory responses (3a). The male tumor microenvironment (TME) is enriched with tumor-resident macrophages and monocytic MDSC (mMDSC) (4a), which secrete anti-inflammatory cytokines (e.g. IL-6) leading to an inhibited T-cell function, low numbers (5a) and, ultimately, inefficient tumor cell killing and increased tumor burden (6a). (Right) Females possess vigorous immune responses characterized by highly inflammatory monocytes (1b) with an improved antigen presentation capacity compared to males (2b). Females display a Th2-biased phenotype (3b), which has been hypothesized to support CD8⁺ T-cell function in the TME (4b). Together with the CD8⁺ T cells, the high neutrophil densities (5b) and greater humoral immunity (6b) found in female TMEs contribute to efficient tumor cell killing (7b). However, some studies have reported the presence of immunosuppressive cells in female TMEs, such as M2 macrophages or granulocytic MDSCs (8b), which could hinder anti-tumor immunity.

histocompatibility complex (MHC) antigen loading; *CD1E*, which is found upregulated in female individuals. This implies that female monocytes are more vigilant and possess an improved antigen presentation capacity [22].

Antigen presenting cells, especially DC development, both quantity and functionality, have been reported to be positively influenced by estrogens [23,24]. For instance, downstream signaling of estrogen receptor α (ER α) promotes DC-mediated interferon (IFN)- α and IL-6 production, as well as enhancing DC surface activation marker expression, such as CD40, CD86 and MHCII [25]. Moreover, plasmacytoid DC (pDCs) IFN-mediated production depends on the activation of Toll-like receptor 7 (TLR-7), whose gene expression, found on the X-chromosome, is positively regulated in vivo by the 17- β -estradiol (E2)-ER α signaling axis [26–28]. Lastly, estrogens can also indirectly impact tolerogenic DC subset functional responses. Female mice engrafted with melanoma and breast tumors have less infiltration of tolerogenic FOXO3-expressing DC with reduced functionality compared to the male counterpart. FOXO3 transcription factor, which is the key for DC tolerance and immunosuppression, could exclusively regulate male androgen receptor expression through binding to its promoter region, initiating a positive feedback loop that was shown to polarize DC towards a tolerogenic phenotype [29]. Overall, this implies that androgen favors immunoregulatory DC, while estrogens favor DC anti-tumoral properties, which can be advantageous for female cancer survival rates.

1.2.2. Macrophages

Under normal physiological conditions, female macrophages possess greater phagocytic activity and produce higher levels of anti-inflammatory prostanooids compared to the male equivalent [30,31]. On the other hand, the macrophages found in multiple female TME have been associated with immunosuppressive phenotypes, such as M2 macrophages (M2). In bladder cancer, poor female prognosis and a minor response to immunotherapy have been correlated with high anti-inflammatory CD163 $^{+}$ -M2 macrophage infiltration. The latter has been associated with the sex-related immune differences within bladder mucous membranes or the cancer cell-mediated induction of tissue-resident macrophage polarized towards the M2 phenotype [32–34]. In colorectal cancer, only female mice presented an elevated granulocyte colony-stimulating factor (GCSF) concentration in the TME that supported high intratumoral IL-10 $^{+}$ macrophage levels, which is known to be an M2-like marker [35].

Similar to dendritic cells, estrogens also affect macrophage function. At low estrogenic concentrations, the macrophage-mediated production of pro-inflammatory IL-1, IL-6 and TNF cytokines increases, whereas at higher concentrations this process is reversed [36]. In hepatocellular carcinoma, lower systemic levels of estrogen found in males have been shown to promote tumor development by endowing liver-resident macrophages with a greater capacity to secrete IL-6. On the contrary, the high systemic estrogen levels found in females inhibited IL-6 promoter activity in liver macrophages, hindering hepatocellular carcinoma development [37].

1.2.3. Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) possess potent anti-inflammatory and immunosuppressive functions, hence they are associated with poor clinical outcomes in many cancer types [38,39]. Interestingly, glioblastoma progression has been reported to be supported by distinct MDSC subsets in a sex-dependent manner. In glioblastoma TME, male tumors were shown to be enriched with monocytic MDSCs, whereas female tumors were mostly infiltrated by granulocytic MDSCs, which strongly favored antitumor immune responses [40]. Although they were not associated with the latter study, estrogens are known to display a pivotal role in cancer during pathological myelopoiesis by accelerating MDSC mobilization and enhancing their immunosuppressive activity in vivo [41]. This suggests that hormones could determine both systemic and tumor-related MDSC frequencies, as well

as the phenotype, in a sex-dependent manner.

1.2.4. Neutrophils

Females possess higher neutrophil phagocytic activity [30]. In fact, females with gastric cancer in different ethnic cohorts had higher tumor-associated neutrophil densities relative to men, which could predict overall survival. It has been hypothesized that the presence of an advantageous neutrophil phenotype in women, such as N1-tumor-associated neutrophils, is associated with a reduction of tumor burden [42]. In fact, estrogens can positively impact neutrophil inflammatory activity, motility and recruitment in tumoral areas. For instance, women with increased estrogens due to longer fertility periods or later-menopause stages have shown a lower risk of suffering from gastric cancer [43,44].

1.3. Lymphoid progenitor-derived cell sex dimorphism in the TME

1.3.1. Natural killer cells

Similar to the cells belonging to the myeloid lineage, natural killer (NK) cell cytotoxicity could also be influenced by estrogen signaling pathways. It has been demonstrated that E2-G-protein-coupled estrogen receptor 1 (GPER1) signaling promotes the downstream phosphatidylinositol 3-kinase (PI3K)-mechanistic target of rapamycin (mTOR) activation, which is needed for NK cell functionality and development [45–47]. However, further studies are needed to confirm the physiological link between estrogen signaling and NK cell performance. In comparison, NK cell frequencies are higher in healthy male populations compared to females [48]. Similar observations have pointed out that greater systematic NK cell numbers occurred in males compared to females in a lung cancer murine model, concomitantly leading to lower tumor cell retention and development of fewer lung tumor colonies [49]. Nonetheless, it was reported from a human lung cancer transcriptomic study that tumor-associated NK cells and non-tumoral NK cells did not differ between males and females [50]. Additionally, in colorectal cancer patients, NK cell-cytotoxic parameters were also similar between the two sexes [51]. Overall, this suggests that further research is needed to better understand how gender variability affects NK cell anti-tumor responses.

1.3.2. B cells

Throughout their lifetime, females possess higher B-cell frequencies, greater systemic immunoglobulin levels and demonstrate a higher capability to mount antigen-specific antibody responses upon vaccination compared to males [48,52–54]. A systems immunology study of women and men receiving inactivated influenza vaccine revealed higher antibody responses and inflammatory cytokines in the female group [53]. In the same study, it was also found that anti-vaccine responses correlated negatively with the testosterone levels in males. In a differential gene expression study between male and female individuals, important B-cell genetic signatures were significantly upregulated in females, some of which displayed a possible correlation with estrogen signaling pathways [55]. In fact, B cells exhibit high levels of ER β , which favors B-cell survival upon estrogenic exposure, by upregulating survival proteins, including CD22, SHP-1 and Bcl-2, and downregulating apoptotic mediators (e.g. PD-1) [56,57]. Moreover, the E2-ER complex has been shown to directly stimulate activation-induced deaminase (AID), hence, initiating B-cell somatic hypermutation and class switch recombination [58]. On the other hand, the male-associated hormone testosterone has been reported to suppress humoral immune responses and inhibit immunoglobulin production [59]. In addition to sex steroids, sex chromosomes also appear to control B-cell responses. Patients with inherited disorders where the X-chromosome is duplicated (e.g. Klinefelter syndrome) or deleted (e.g. Turner syndrome) present enhanced or decreased B-cell frequencies, respectively [60,61]. Patients with sex chromosome aberrations also face an increased risk of sex-biased autoimmune disorders, in particular, autoimmune thyroiditis in Turner

syndrome [62] and systemic lupus erythematosus in Klinefelter syndrome [63]. Although not correlated with B cell numbers, patients with such inherited chromosomal disorders could be at substantially elevated risks for non-Hodgkin lymphoma, breast cancer and lung cancer (Klinefelter syndrome) or melanoma, central nervous system, colon and rectal cancers (Turner syndrome) [64]. B-cell sex dysmorphic patterns have been observed in cancer studies. Female bladder tumors associated with decreased recurrence-free survival were characterized by increased CD79⁺ B-cell numbers, recruitment (increased CXCL13 gene expression) and function (increased CD40 gene expression) [32]. This altogether indicates that anti-tumoral B-cell immune responses in females could outperform those present in male individuals.

1.3.3. T cells

Under normal physiological conditions, the T-cell family shows differences between the sexes. Females are known to have an increased CD4⁺/CD8⁺ T-cell ratio, which is associated with greater Th2 cell frequencies and higher T-cell proliferation, as well as cytotoxicity. The latter could be due to the fact that multiple cytotoxic and inflammatory T-cell genes (including IFN- γ , lymphotoxin beta (LTbeta), granzyme A (GZMA), interleukin-12 receptor beta2 (IL12Rbeta2), or granulysin (GNLY)) are located on the X-chromosome and carry estrogen response elements (EREs) on their promoters [65]. Regardless of age, males display diminished T-cell immunity compared to premenopausal women, and yet this is characterized by having higher CD8⁺ and T regulatory (Treg) cell numbers, as well as IL-17 cytokine gene (*IL17A*) upregulation [65,66]. It has also been shown that the negative selection of autoreactive naïve T cells in the thymus differs between females and males. The autoimmune regulator (AIRE) gene plays a key role in the establishment of central immune tolerance by promoting a thymic display of tissue-restricted antigens [67]. This process was shown to be sex hormone-dependent and less active in females [68], and may represent one of many factors contributing to sex differences in autoimmunity, including adverse events of the checkpoint blockade. In this review, we include different studies that report T-cell family members have immune sex dimorphism in cancer.

1.3.4. CD4

1.3.4.1. T helper cells. Female Th2 dominance could be related to the influence of estrogen during CD4⁺ T-cell differentiation, since E2 stimulates Th2-mediated anti-inflammatory cytokine secretion [69]. In colorectal cancer, female changes in G-CSF and IL-4 cytokine production within the TME have been associated with a biased Th2 phenotype. Additionally, it was reported that the greater increase in Th2 cells could favor high CD8⁺ T-cell numbers, which altogether correlates with overall enhanced female survival in colorectal cancer (CRC) compared to males [35]. Interestingly, although estrogens inhibit Th1-mediated proinflammatory cytokine secretion, female melanoma patients were found to have high tumor-specific-antigen Th1 cell frequencies compared to males [70]. It has been hypothesized that female monocytes can foster Th1 differentiation, given that the Th1-biased female profile was associated with inflammatory monocyte activation marker upregulation, such as MHC-II and IFN-STAT1 [22,71]. Nonetheless, there are no studies regarding this for cancer. Lastly, Th17 cells have been shown to be an important immune biomarker for pancreatic cancer prognosis prediction, although no differences were observed between the sexes [72].

1.3.4.2. Regulatory T cells. Treg cells promote immune self-tolerance and hinder tumor immune surveillance [73]. In both healthy and chronic inflammatory conditions, females have been reported to have lower and dampened Treg cells [74,75]. In parallel, Treg cells in B16 melanoma-bearing female mice displayed high levels of the exhaustion marker B7-H1 [76]. The master regulator of the Treg cell function gene

(Forkhead box protein P3 (FOXP3)) is X-linked, and Treg cell frequencies positively correlate with systemic estradiol concentrations, altogether implying that Treg cell number and function are likely to be favored in females, contradicting what has been seen both *in vivo* and *in vitro* to date [77,78]. However, Treg functionality and FOXP3 expression are also under the control of testosterone exposure, and multiple cytokines are elevated in males, such as IL-6 and IL-1 [77,79], hence indicating that the Treg cell subset is complexly regulated and involves numerous factors biased by gender.

1.3.5. CD8

Cytotoxic CD8⁺ T-cell immune surveillance and anti-tumor properties correlate with good clinical outcomes for the majority of cancers. However, upon engagement with the checkpoint inhibitor PD-1 (programmed cell death-1) receptor their function is hampered, and immune checkpoint blockade (ICB) therapy has only proved to be successful in 20–40% of patients [80]. The impact of sex differences in cytotoxic cell exhaustion is becoming a topic of study, since the PD-L1 gene is significantly upregulated in female melanoma, colorectal or bladder cancer patients [32,81–83]. Concomitantly, this leads to increasing numbers of CD8⁺-exhausted T cells in females, making them more susceptible to ICB therapies. The reasons behind this may be due to the fact that the PD-L1 gene is partially modulated by estrogens and X-linked mRNA (including miR-221, miR-222, miR-106b, miR-20b, and miR-513) [84–87]. However, this is still a matter for debate, since a meta-analysis of multiple clinical trials in different cancers treated with ICB therapy have suggested that female individuals had objective low response rates [88]. Indeed, different checkpoint gene expressions are under the control of multiple variables, such as the gut microbiome or sex hormones. For example, several melanoma models showed that highly heterogeneous microbiomes have greater tumor-infiltrating cytotoxic cell numbers leading to an overall better response to ICB [89,90]. Thus, further research is needed to decipher better if CD8⁺ T-cell intratumoral activity is dictated in a gender-dependent manner.

1.4. Gender differences in tumor invasion and metastasis

Gender differences have also been reported when it comes to cancer invasion and metastasis. For example, males are statistically overrepresented in patients with malignant melanoma showing metastatic disease [91]. Moreover, early studies suggested sex differences in the metastatic spread of hepatocellular carcinoma (HCC) to bone [92]. Further studies have shown that men not only have a higher incidence of HCC but also a worse prognosis compared to women [93]. Similar to this, it is known that women with colorectal cancer (CRC) have a better survival outcome compared to men in the same age group [94]. In line with this, it was found that females had increased survival and infiltration of T cells in a mouse model of metastatic CRC [35].

Part of the gender-based differences in CRC may also be explained by sex hormones regulating the fate and function of various cell types in the TME, including tumor cells, cancer-associated fibroblasts (CAFs) and immune cells [95]. Estrogen has been shown to have protective effects in CRC development and progression into invasive and metastatic disease. Estrogen preserves the epithelial phenotype and inhibits epithelial-mesenchymal transition (EMT) by regulating the activity of ion channels, including voltage-gated K⁺ channels, such as KCNQ1, which stabilize the E-cadherin/β-catenin complex at adherens junctions [96]. Deregulation of the Wnt/β-catenin signaling pathway is found in a large majority of patients with CRC, and loss of the E-cadherin/β-catenin complex is a hallmark of EMT. This leads to loss of cell adhesion and nuclear translocation of β-catenin, which interacts with other transcription factors to promote EMT, in part by repressing the gene encoding KCNQ1.

EMT has also been linked to male predominance in HCC by the recently discovered oncoprotein RBMY (RNA-binding motif on the Y-chromosome), a protein frequently overexpressed in HCC [97]. RBMY

promotes phosphorylation and inactivation of glycogen synthase kinase 3 β (GSK-3 β), which is a kinase that plays a key role in controlling epithelial cell differentiation through its capacity to phosphorylate and target β -catenin and EMT-promoting transcription factors for degradation, including members of the Snail, Zeb and Twist families [98,99]. Inactivation of GSK-3 β promotes EMT and the development of cancer stem cell properties [100,101], whereas sex-biased differences in the expression of EMT markers, such as Zeb1, have also been associated with an invasive phenotype in cancer cell lines [102]. Another factor associated with EMT are tissue inhibitors of metalloproteinases 1 (TIMP1). Male-specific upregulation and secretion of TIMP1 promote liver metastasis in pancreatic cancer [103].

1.5. Gender differences in cancer immunotherapy outcomes and efficacy

Immune checkpoint blockade (ICB) therapies, including inhibition of PD-1 or PD-L1 and CTLA-4, have extended patient survival in several forms of malignancy by unleashing anti-tumor T-cell activities [9]. In randomized trials, ICB compared to standard chemotherapy has significantly improved cancer survival rates [104]. However, although tumor immunotherapy has been well developed, clinical outcomes and treatment efficacy are highly influenced by adapted immuno-evasion strategies. Nevertheless, recent breakthroughs have allowed some of these immuno-evasion aspects to be overcome, although much work remains to be carried out if immunotherapies are to reach their maximum efficacy [105]. It is clear that sex-based immunological differences have significant impacts on the immune response, and thus it is likely that they also affect responses to cancer immunotherapy. Gender-biased factors related to the pathogenesis and prognosis of tumors have been suggested, but a large knowledge gap still remains in this area. Data from meta-analyses based on subgroup hazard ratios (HR) from published clinical trials have given rise to conflicting data, and may introduce bias due to the lack of analyses for individual patients, and they have not taken into account features that differ because of their distributions between men and women, including gender-biased behaviors and clinicopathological subtypes [10,11]. In immunotherapy clinical trials, women are significantly underrepresented compared to men [13]. This may be in part due to concerns related to cyclical hormonal changes in a woman's body and how these could influence clinical trials. However, it would be inappropriate to assume that the results obtained from male patients could also apply to female patients and vice versa, and accordingly there is now a clear understanding that both sexes should be represented in trial-based research.

In the next sections, we will discuss the importance of gender differences in clinical practice.

1.6. Checkpoint inhibitors for cancer

At present, there is no clear conclusion as to whether there is a gender-biased benefit from ICB treatments. In melanoma patients, it was confirmed that men have higher HR in clinical outcomes relative to women on anti-PD1 treatment [106,107]. For melanoma, men had higher overall survival rates in six out of seven clinical trials for ICB treatment (alone or in combination with anti-CTLA-4) compared to women [106,108–112]. Compared to men, anti-PD-1 or anti-PD-L1 treatment can improve the overall survival rate and remission rate of female patients with NSCLC [113]. In addition, the survival time of female individuals in CRC was significantly longer than that of males under 45 [114]. In contrast, among 65–99 year-old patients, the survival time of male individuals was significantly longer than that of females [115].

It has been suggested that microbiota diversity in different genders may affect patient responses to ICB. In the case where increased fecal bacterial diversity was found in both mouse tumor models and melanoma patients treated with ICBs, the survival rates were correlative better [116]. However, importantly, these bacterial communities were

observed to be higher in healthy women, suggesting that women in the non-responding group might have been heavily treated with antibiotics at higher doses compared to men, thus compromising the microbiota diversity [14].

Although ICB treatments are intended to potentiate anti-tumoral responses, they result in a non-specific upregulation of immune responses that may also release detrimental autoimmune reactions [117]. Such immune-related adverse events of ICB treatments are a major clinical challenge that limit the use of these very potent therapies. The endocrine system, gastrointestinal tract, skin and lungs are major targets for immune-related adverse events of ICB treatments [118]. There is growing understanding of sex differences in these adverse events, since the risk of endocrinopathies, such as autoimmune thyroiditis, is higher in women, whereas neuromuscular immune complications appear to be more common in men [118].

1.7. Adoptive cell therapy

There is a lack of advance in current reports concerning the clinical responses to chimeric antigen receptor T-cell treatments in different genders. Studies have shown that T cells given as adoptive transfer therapy can continue to be regulated by the superior physiological levels of estrogen in the TME [119]. Thus, concerns about gender benefits in cellular therapies should be addressed. Although there are few studies on allogeneic adoptive cell therapy addressing sex-biased factors, data in mouse models show that the function of transferred female donor leukocytes is not immunosuppressed in male recipients. In contrast, male donor leukocytes transferred into female recipients were highly dysfunctional [120]. It has been shown that female TRAMP-C2-primed or naïve T cells effectively reject TRAMP-C2 prostate tumors, where no pathological autoimmune responses were observed in the treated tumor-bearing male mice [121]. Hence, female T-cell donors should be considered for cellular therapies. Female cells can be transferred to male recipients, where no Y-chromosome related rejection will occur, whereas on the contrary, male cells will be rejected by female recipients due to the presence of the Y-chromosome presenting the foreign male antigens.

In an experiment using expanded tumor-infiltrating lymphocytes (TIL) for adoptive T-cell therapy (ACT), the effects of the clinical and pathological characteristics of patients on the success rate of initial TIL growth were compared. Female patients compared to males (71% vs. 57% for males; $P = 0.04$) had the highest rate of TIL expansion success in 226 consecutive patients undergoing tumor resection [122]. These results suggest a link between gender-biased factors in TME and TIL expansion success.

1.8. Sex differences in cancer immunotherapy predictive biomarkers

Most patients with solid tumors do not respond well to ICB, so effective biomarkers are obviously necessary as the selection criteria for treatment options. At present, the response rate of most solid tumors to PD-1 inhibition is less than 30%. According to various reports, the objective remission rate of tumors is affected by many factors in the TME, including tumor mutation burden, immune checkpoint protein expression, DNA mismatch repair, immune infiltrating subtype, T-cell subpopulation ratio, antigen presentation defect, and the microbial community.

1.8.1. Sex-related differences in tumor immunogenicity

Tumor mutational burden (TMB) is consistent with the increased immunogenicity of tumors, where enhanced neoantigen production is observed. At present, there have been many reports confirming that TMB has good predictive value in ICB therapies, and it may be used as a classification index [123]. Comparing the two sexes, the predictive value of tumor burden on clinical prognosis is not consistent, which may be due to differences in protein levels in healthy individuals of both

sexes. Wang et al. found that using TMB as a predictive biomarker for ICB responses had more power in female than male lung cancer patients [124]. In addition, Karantanos et al. believed that male sex was an independent prediction factor for adverse outcomes in myeloproliferative neoplasms (MPN) [125]. This seems to be due to the increased risk of non-MPN-specific somatic mutations, especially high-risk mutations, rather than MPN-specific mutation allele frequencies. On the contrary, the disease progression of female subjects was more dependent on JAK2 mutant allele load rather than the acquisition of other somatic mutations [125]. Gupta et al. analyzed a metastatic melanoma patient cohort from the Cancer Genome Atlas (TCGA) and found that the burden of missense mutations in men was significantly higher and correlated with a higher survival rate [126]. In summary, different tumor types present completely different sex-dependent tumor mutational burdens (Table 1).

Tumor antigens induce immune responses at different intensities in different genders. This may be related to differences in hormone levels, XY chromosomes, and genomics. On the other hand, tumor antigens themselves also have a certain degree of gender differences that serve as potential diagnostic or therapeutic targets. Cancer-testis antigens (CTA) are named based on their expression patterns in many normal and abnormal tissues, which are usually expressed in normal male germ cells, also types of cancers, but not normal somatic cells [127]. To date, 228 CTAs have been distinguished: 120 CTAs (52%) are located on the X-chromosome, while the rest are located on the autosomes and Y chromosomes [128]. Due to the specificity of sex-linked expression of tumor testis antigens, it is often reported that there is a sex-specific bias in some types of tumors [129,130]. Mirandola et al. reported new data showing that the expression of CTA Ropporin-1 was significantly increased in male patients with multiple myeloma compared with female patients [129]. Kim et al. showed evaluated expression of 13 CTAs in lung cancer patients by PCR and immunohistochemistry. The data confirmed that the positive rate of CTA expression was associated with the male gender ($p = 0.001$) [130]. CTAs have strong immunogenicity, as well as cancer-restricted expression patterns. These characteristics make them fairly ideal tumor-specific therapeutic targets in male cancer patients [131]. Currently, a certain number of pre-clinical and clinical trials have been carried out to target CTAs [132,133]. Due to the specific expression of these XY chromosome-linked genes, some potential

gender-related adverse effects may appear associated with these treatments.

Although gender-related factors, such as androgenic or estrogenic hormone levels amongst sex-specific tumors, cannot be compared, they can provide profound clinical insights into specific tumors. For instance, estrogen and progesterone are of great significance in tumors, especially breast cancer, endometrial cancer and ovarian cancer [134–137]. Several studies even claim that long-term oral contraceptives represent a crucial risk factor for breast cancer [138,139]. Lokich et al. found that 17β -estradiol can induce the up-regulation of HE4 antigen expression and mediate importin-dependent nuclear translocation in ovarian cancer cell lines [140].

1.9. Cancer vaccines

These emerging treatment methods, although their history is not long, have achieved remarkable success in the field of tumor treatment, such as in human papilloma virus (HPV) related cancers. Nevertheless, HPV infection is still the most commonly diagnosed sexually transmitted infection worldwide [141]. A significant proportion of oropharyngeal, anal, penile, vaginal and vulvar cancers, as well as almost all cervical cancers, are related to HPV infection [142,143]. A succession of evidence confirms that men and women have different immune responses to foreign antigens and autoantigens. The research results of Aldakak et al. showed that women's titers after being vaccinated with the HPV vaccine were higher than men's [144]. On the other hand, gender perception may strongly influence HPV vaccination preference. In most regions of the world, there is no policy explicitly supporting HPV vaccination in men, which can cause controversy in a small number of countries [145,146]. In fact, in addition to oropharyngeal cancer, which itself is more common in males, male patients who are diagnosed with anal/rectal squamous cell carcinoma (SCC) have a higher risk of death than SCC female patients [147]. Thus, medical preference and social attitudes may also become an important part of gender differences in immunotherapy.

In addition, it is still controversial whether bacillus Calmette-Guérin (BCG) perfusion therapy has gender-biased efficacy in bladder cancer. A multicenter study covering 2635 patients with T1 urinary bladder cancer found that female factors were related to disease progression after

Table 1
Tumor mutational burden in male vs. female patients.

Antigen	Position	Gender	Sample# (M/F)	Conclusion	Reference
BRAF	Colorectal	Female	662/635	Higher Mutation rate	[199]
	Colorectal	Female	990/515	Higher Mutation rate	[200]
BRAF V600E	Papillary Thyroid Cancer	Male	623/2015	Longer distant and higher rate of metastasis (BRAF V600E CPTC)	[201]
Ropporin-1	Multiple myeloma	Female	37/22	5x higher Ropporin-1 expression	[202]
BCR-ABL1	CML	Female	240/183	Independent predictor of stable, undetectable BCR-ABL1 during first-line imatinib therapy	[203]
DDX3X (MYC derived)	Burkitt lymphoma	Female	11/1	Lower mutation rate	[204]
EGFR mutation	Non-small Cell Lung Cancer	Female	18/17	Female gender predicts EGFR mutation burden	[205]
EGFR mutation	lung adenocarcinomas	Female	691/687	Incidence of EGFR mutation positively associated with age	[206]
FLT3-ITD	acute myeloid leukemia	Female	276/222	Mutation overrepresented in females	[207]
Gastrin-releasing peptide receptor (GRPR)	Lung	Female	40/38	The presence of two expressed copies of the GRPR gene in females may be a factor in the increased susceptibility of women to tobacco-induced lung cancer	[208]
Her2/neu	Non-Small-Cell Lung Cancer	Female	68/22	Predicts survival only in females	[209]
JAK2 V617F mut	Chronic myeloproliferative neoplasms	Female	346/469	Disease progression in females depends on JAK2 mutation	[210]
KDM6A	Bladder	Male	56/27	Lower mutation rate in non-invasive disease	[211]
KRAS mut	Lung	Female	1898/1128	KRAS G12C mut high in women	[212]
MAGE-1, MAGE-4, CT-7, etc.	Lung	Male	49/19	CT antigen expression associated with male gender	[213]
PIK3CA	Colorectal	Male	88/87	Lower mutation rate	[214]
p53	Lung	Male	607/404	Higher mutation rate among poor survivals	[215]
	Pan-cancer	Male	3271/1913	Poor survival in males is contributed by high frequencies of TP53 mutations	[216]
UTX mut	T-cell leukemia	Male	25/10	UTX mutations exclusively present in male T-ALL patients	[217]

BCG treatment [148]. Similarly, in a cohort of 1062 patients treated only with BCG, female gender (HR=1.71) compared to male gender was associated with increased risk of recurrence [149]. Nevertheless, there are also other studies that believe there was no significant difference

between men and women after BCG treatment [150].

Table 2
Registered clinical trials of combined endocrine and immunotherapies.

NCT number	Title	Status	Conditions	Population description	Collaborators	Phase
NCT00170157	Hormone Therapy and Ipilimumab in Treating Patients With Advanced Prostate Cancer	Completed	Advanced Prostate Cancer	n = 112 ; Drug: Bicalutamide/Flutamide/ Goserelin Acetate/ Ipilimumab/ Leuprolide Acetate Other: Pharmacological Study	Mayo Clinic	Phase II
NCT02221999	Weekly Paclitaxel and Cisplatin to Treat Hormone Receptor Positive and Triple Negative Breast Cancer Patients (SHPD002)	Active, not recruiting	Tubular Breast Cancer/ Mucinous Breast Cancer/ Invasive Ductal Breast Cancer/ Inflammatory Breast Cancer	n = 250; Drug: Paclitaxel Cisplatin Gonadotropin-releasing hormone agonist Letrozole	Renji Hospital	Phase II
NCT02990845	Pembrolizumab and Exemestane/ Leuprolide in Premenopausal HR+ / HER2- Locally Advanced or Metastatic Breast Cancer (PEER)	Recruiting	Premenopausal Breast Cancer	n = 25; Drug: Pembrolizumab/ Exemestane/ Leuprolide	National Taiwan University Hospital	Phase II& III
NCT04934722	Efficacy and Safety of Pembrolizumab (MK-3475) Plus Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (MK-3475-991/KEYNOTE-991)-China Extension	Recruiting	Metastatic Hormone-Sensitive Prostate Cancer	n = 186; Biological: Pembrolizumab Drug: Enzalutamide Procedure: Androgen Deprivation Therapy (ADT) Other: Placebo	Merck Sharp & Dohme Corp.	Phase III
NCT04191096	Efficacy and Safety of Pembrolizumab (MK-3475) Plus Enzalutamide Plus Androgen Deprivation Therapy (ADT) Versus Placebo Plus Enzalutamide Plus ADT in Participants With Metastatic Hormone-Sensitive Prostate Cancer (mHSPC) (MK-3475-991/KEYNOTE-991)	Active, not recruiting	Metastatic Hormone-Sensitive Prostate Cancer	n = 1232; Biological: Pembrolizumab Drug: Enzalutamide Procedure: Androgen Deprivation Therapy (ADT) Other: Placebo	Merck Sharp & Dohme Corp.	Phase III
NCT04046185	Programmed Death-1(PD-1) Inhibitor Combined With Progesterone Treatment in Endometrial Cancer (ECCT)	Not yet recruiting	Endometrial Cancer Stage I	n = 60 ; Drug: PD-1 inhibitor combined progesterone Drug: progesterone	Shanghai First Maternity and Infant Hospital	Early Phase I
NCT03753243	Neoadjuvant Pembrolizumab Plus Androgen Axis Blockade Prior to Prostatectomy for High Risk Localized Prostate Cancer	Recruiting	Prostate Cancer	n = 32; Drug: Pembrolizumab Drug: Enzalutamide	VA Portland Healthcare System Portland, Oregon, United States	Phase II
NCT04946370	Maximizing Responses to Anti-PD1 Immunotherapy With PSMA-targeted Alpha Therapy in mCRPC	Recruiting	Prostate Cancer	n = 76; Drug: 225Ac-J591 Drug: Pembrolizumab Drug: Androgen receptor pathway inhibitor Diagnostic Test: 68Ga-PSMA-11	Dana-Farber Cancer Institute New York Presbyterian/ Brooklyn Methodist Hospital New York Presbyterian/Weill Cornell Medical Center	Phase I & II
NCT02312557	Pembrolizumab in Treating Patients With Metastatic Castration Resistant Prostate Cancer Previously Treated With Enzalutamide	Active, not recruiting	Castration-Resistant Prostate Carcinoma Hormone-Resistant Prostate Cancer PSA Progression Recurrent Prostate Carcinoma Stage IV Prostate Adenocarcinoma AJCC v7	n = 58; Drug: Enzalutamide Other: Laboratory Biomarker Analysis Biological: Pembrolizumab	OHSU Knight Cancer Institute	Phase II
NCT04631601	Safety and Efficacy of Therapies for Metastatic Castration-resistant Prostate Cancer (mCRPC)	Recruiting	Metastatic Castration-resistant Prostate Cancer	n = 159; Drug: Acapatumab Drug: Enzalutamide Drug: Abiraterone Drug: AMG 404	University of Alabama at Birmingham University of California San Francisco Mission Bay Campus University of Chicago	Phase I & II

1.10. Endocrine therapy

Sex hormones play an essential role in anti-tumor immunity, and the differential regulation of the immune-tumor microenvironment both by sex hormones and other gender-related factors may pave the way for different therapeutic targets. Estrogen and androgens have been shown to have opposite effects on B cells and T cells, macrophages, neutrophils and NK cells, where they are often suspected to be the driving forces for gender differences in the immune system [151–155]. However, most of these differences have been studied in *in vitro* experiments and mouse models, thus it remains uncertain whether they are applicable to human pathology.

Menopausal hormone therapy using a combination of estrogen and progesterone (synthetic analogs of progesterone) is associated with an increased risk of cancer in hormone-responsive tissues, such as the breast [156], endometrium [157] and the ovaries [158]. Similarly, various forms of hormonal contraception, mainly oral estrogen-progesterone combinations, are associated with a small increase in breast cancer risk depending on the length of time they are used for [159]. Nevertheless, although an increase in estrogen and progesterone also increases the number of B cells and T cells, this risk still occurs. This may be due to the effect of estrogen on epithelial cells that exceed the enhancement of the immune cell responses, thus resulting in immunoevasion.

Whether testosterone replacement therapy increases the risk of prostate cancer is still inconclusive. However, the available meta-data analysis of clinical trials of testosterone treatment has indicated no significant increase in the incidence of prostate cancer and prostate-specific antigen (PSA) levels [160,161].

Sex hormone deprivation therapy can be used as an adjunct to immunotherapy. Tamoxifen (estrogen receptor target) stimulates neutrophil activity *in vitro* and *in vivo* by regulating sphingolipid biosynthesis. It has also been shown to reduce the number of immunosuppressive MDSCs and increases the number of effector T cells and cytotoxic T-cell infiltration in ER α -negative ovarian tumors [162]. In addition, enzalutamide (androgen receptor antagonist) has been found to promote the differentiation and proliferation of MDSCs [163], which may partly explain the mechanism of enzalutamide resistance in prostate cancer. Androgen deprivation therapy (ADT) is the standard treatment for prostate cancer, which induces initial T-cell expansion and increases the T-cell response. This effect is observed within 1–24 months [164]. Several studies have shown that ADT enhances the susceptibility of androgen receptor (AR)-overexpressing prostate cancer cells to immune-mediated T-cell killing by improving immune recognition [165, 166]. In addition, there is evidence showing that the combination of ADT and immunotherapy for prostate cancer patients can increase the treatment efficacy [164,165]. (Table 2).

1.11. Gender differences and immune response in other cancer treatment approaches

1.11.1. Surgery

The perioperative period of any major surgery is accompanied by immunosuppression, which is caused by the interaction of many factors, including the use of prophylactic drugs for postoperative pain [167]. Impairment of the immune system during the perioperative period results in an increased risk for postoperative infection and sepsis [168]. Crucially, cell-mediated immunity is important in reducing the spread of metastasis during cancer surgery. Therefore, surgeons are very concerned about the changes in immunological indicators before and after surgery [169]. On the other hand, pain can also induce immunosuppression [170].

Postoperatively, male sex hormones have immunosuppressive properties after trauma and bleeding compared to women [171,172]. Castration of mice before traumatic bleeding can prevent immunosuppression in males, while treatment of females with physiological levels

of testosterone suppresses the immune response [173]. In contrast, female sex steroids have immunoprotective effects under these conditions [174,175]. Therefore, the immunomodulatory properties of sex hormones may represent a new strategy for the treatment of immunosuppressed patients after trauma and blood loss, in possible combination with cancer immunotherapy.

1.12. Chemotherapy

Almost all patients receiving extensive chemotherapy experience immunosuppression [176]. In principle, chemotherapy targets rapidly dividing cells and does not distinguish cancer cells from other rapidly dividing cells [177]. Since cells of the immune system divide rapidly, especially during the immune response, they represent one of the off-target effects of chemotherapy. The degree of treatment benefit between men and women may be different due to inherent biological characteristics. Bins et al. took paclitaxel chemotherapy as an example to discuss the correction of factors, such as gender and the body surface area (BSA), in the measurement of drug concentration [178]. In a previous calculation method, only the effect of height and weight on drug dosage was considered. Gender, as a simple and obtainable variable, is often ignored in many cases. The sex dimorphism of immunity has been recognized, and gender differences have become accepted as one of the underlying reasons for differences in immunity [179].

Systemic immune suppression of chemotherapy, such as a decline in white blood cells and neutrophil counts, is widely recognized and has been associated with poor prognosis in most reports [180,181]. Systemic and local immunosuppression has been shown to be closely related. Primary and secondary located tumors may affect many immunosuppressed sites, including peripheral veins [182], hepatic portal veins [183], lymph nodes [184], spleen [185], and bone marrow [186]. The most reported is the increase of IL-10, TGF- β plasma levels in cancer patients receiving chemotherapies [187,188]. Zhang et al. observed higher proportion of male patients with increased IL-10 plasma levels that correlated with worse clinical response to chemotherapy in T cell lymphoma compared to female patients. This effect was believed to be regulated by hormonal discrepancies, where lower estradiol levels in elderly female patients correlates with higher IL-10 and MDSC frequency [187].

In recent years, it has been an increased focus on the role of immune checkpoints in tumor prognosis, and the combination with traditional therapies such as chemotherapy and surgery has received special attention. Neoadjuvant therapy and chemotherapy both can induce changes in gene expression of immune checkpoint modulating the anti-tumor immune responses [189]. There is indeed evidence that gender is to some extent an adjunct factor in neoadjuvant chemotherapy, where combination of ICB and chemotherapy benefits female cancer patients [190–192]. Gender mediated differences in medical treatment habits, economic conditions, living habits, and immune responses, which we are most concerned about, contribute to the differential benefits in different cancer treatments at different levels.

1.13. Radiotherapy

The purpose of radiotherapy is usually to induce DNA double-strand breaks (DSBs) in cancer cells, leading to senescence or apoptosis. For every 1 Gy dose of sparse ionizing radiation absorbed, approximately 40 DSBs are generated. DNA damage to surrounding tissues is limited by careful planning of the delivery speed and route, but many side effects, such as hair loss, hyperpigmentation, dermatitis, intestinal malabsorption, mucositis, sexual dysfunction, and even tumor transformation, may occur in the acute phase or appear a few years after treatment [193].

There is evidence that radiation may cause damage in gender-specific ways. After the Chernobyl disaster, the male and female birth rates increased slightly in the short term, however, long-term data showed that the number of girls born, compared to males exposed to

radiation, decreased [194]. Another study in the Marshall Islands following nuclear testing, showed that infants of women explosively exposed may have had an increased risk of specific birth defects [195]. In addition, studies on occupational and accidental radiation have found that women's long-term radiation sensitivity was higher than that of men receiving the same dose [196]. There are strong reasons to suspect that the effects of radiation are significantly different between the two sexes. Indeed, it has been found in clinical trials that gender differences are reflected in the sensitivity of radiotherapy. Gasinska et al. studied the treatment efficacy in rectal cancer patients who received short-course radiotherapy before surgery, and subsequent overall survival (OS), progression-free survival (PFS), metastasis-free survival (MFS) and tumor proliferation were evaluated. Only OS was significantly lower in male patients receiving radiotherapy of longer than 15 days prior to surgery ($p = 0.018$), while no difference was observed in female patients [197]. Another study, although not significant, indicated there was a trend showing differences in males vs females in mean time to recurrence (23.5 vs. 15.2 months, $p = 0.234$) and metastasis (14.0 vs. 23.2 months, $p = 0.092$). Interestingly, only male patients treated with fractionated radiotherapy had improved survival when

stratified to age and tumor differentiation ($P = 0.013$, $P = 0.040$), while these parameters were not significant in female patients. It has also been proposed that estrogen levels may contribute to treatment response and improved radiosensitivity of female tumor cells but not those in males [198].

1.14. Concluding remarks

In aggressive cancers, such as pancreatic cancer and lung cancer, five-year survival has improved only marginally since the 1970's from 3% to 12% to 7–18.6%, and this highlights the need for more effective treatments. Thus, the exciting possibility of targeting sex immune dimorphism in the TME may have a large impact on health care that also goes beyond these cancers. In this review, we have highlighted the importance of sex-related factors (Fig. 2) in regulating cancer progression and treatments. Nevertheless, there are many discrepancies and difficulties that hinder the possibility of reaching a conclusion at this point concerning the mechanisms driving tumor progression and metastasis, and the response to different therapies. However, there is a clear consensus based on sex-based immunological differences and it is

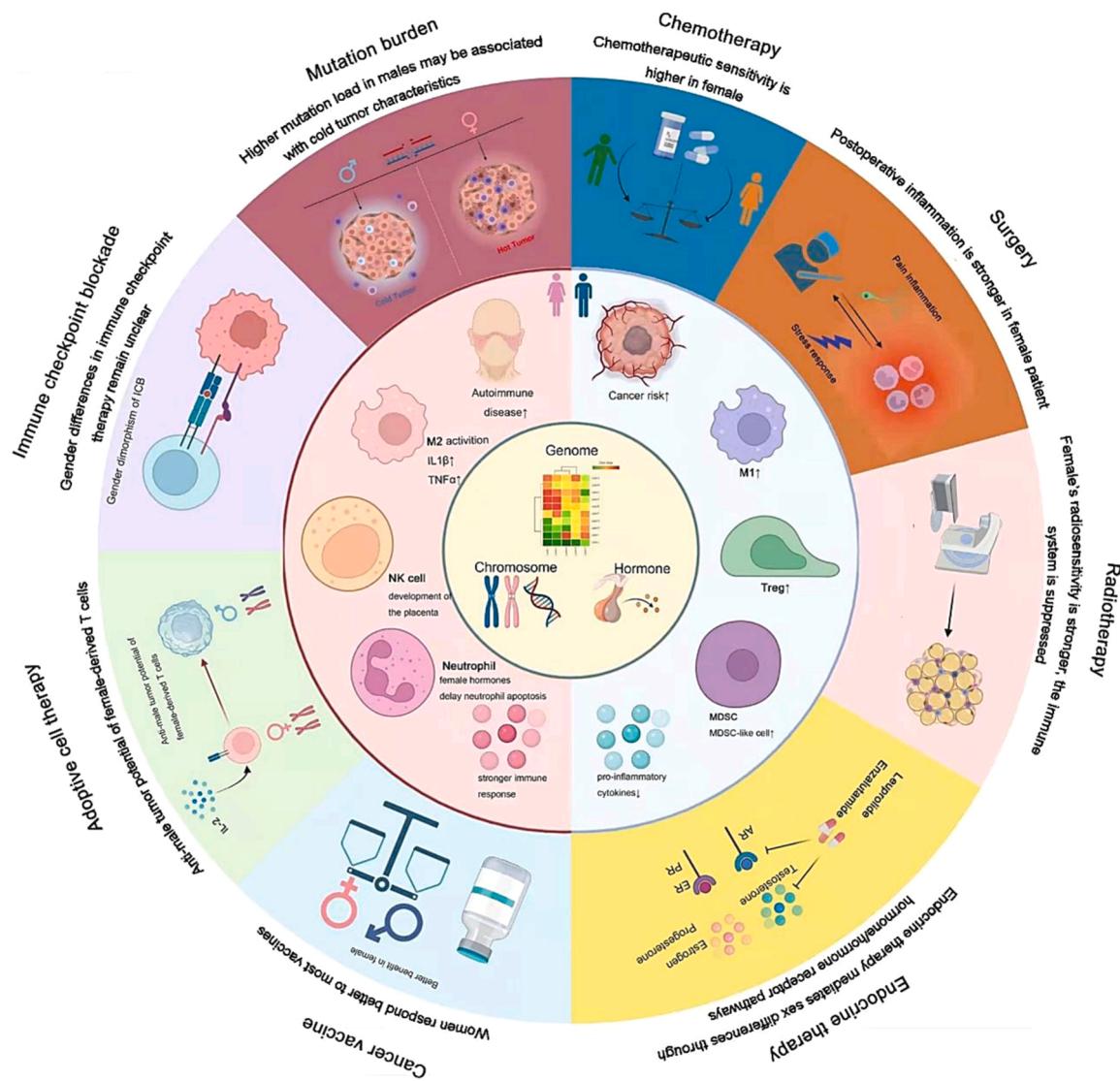


Fig. 2. The hallmarks of Cancer immune responses biased by sex. Schematic representation of how sex dimorphism can affect incident risk for different diseases and how it plays role in the various cancer treatments. The inner circle represents the internal factors of the three gender-biased differences (Genome, Chromosome, and Hormones). The middle circle shows differences in the immune system caused by gender differences. The outer circle represents the gender-specific immune response differences in the eight tumor treatment approaches.

unlikely that the results obtained from male patients would always apply to female patients and vice versa, thus both sexes should be represented in trial-based research. Gender optimized/genderized cancer medicine has the potential to revolutionize precision medicine aimed at customizing the healthcare of patients and leading towards more effective cancer therapies.

Acknowledgements

Karolinska Institutet Funding, Sweden, 2020-01829.

References

- [1] P. Sharma, J.P. Allison, The future of immune checkpoint therapy, *Science* 348 (6230) (2015) 56–61.
- [2] D. Sarhan, J. Wang, U. Sunil Arvindam, C. Hallstrom, M.R. Verneris, B. Grzywacz, E. Warlick, B.R. Blazar, J.S. Miller, Mesenchymal stromal cells shape the MDS microenvironment by inducing suppressive monocytes that dampen NK cell function, *JCI Insight* 5 (5) (2020).
- [3] S. Eisinger, D. Sarhan, V.F. Boura, I. Ibarlucea-Benitez, S. Tyystjarvi, G. Oliynyk, M. Arsenian-Henriksson, D. Lane, S.L. Wikstrom, R. Kiessling, T. Virgilio, S. F. Gonzalez, D. Kaczynska, S. Kanatani, E. Daskalaki, C.E. Wheelock, S. Sedimbi, B.J. Chambers, J.V. Ravetch, M.C.I. Karlsson, Targeting a scavenger receptor on tumor-associated macrophages activates tumor cell killing by natural killer cells, *Proc. Natl. Acad. Sci. U.S.A.* 117 (50) (2020) 32005–32016.
- [4] L. La Fleur, J. Botling, F. He, C. Pelicano, C. Zhou, C. He, G. Palano, A. Mezheyeuski, P. Micke, J.V. Ravetch, M.C.I. Karlsson, D. Sarhan, Targeting MARCO and IL37R on immunosuppressive macrophages in lung cancer blocks regulatory T cells and supports cytotoxic lymphocyte function, *Cancer Res.* 81 (4) (2021) 956–967.
- [5] A. Rao, O. Strauss, E. Kokkinou, M. Bruchard, K.P. Tripathi, H. Schlums, A. Carrasco, L. Mazzurana, V. Konya, E.J. Villablanca, N.K. Bjorkstrom, U. Lindforss, H. Spits, J. Mjosberg, Cytokines regulate the antigen-presenting characteristics of human circulating and tissue-resident intestinal ILCs, *Nat. Commun.* 11 (1) (2020) 2049.
- [6] J. Johansson, V. Tabor, A. Wikell, S. Jalkanen, J. Fuxé, TGF-beta1-induced epithelial-mesenchymal transition promotes monocyte/macrophage properties in breast cancer cells, *Front. Oncol.* 5 (2015) 3.
- [7] A. Palazon, P.A. Tyrakis, D. Macias, P. Velica, H. Rundqvist, S. Fitzpatrick, N. Vojnovic, A.T. Phan, N. Loman, I. Hedenfalk, T. Hatschek, J. Lovrot, T. Foukakis, A.W. Goldrath, J. Berg, R.S. Johnson, An HIF-1alpha/VEGF-A axis in cytotoxic T cells regulates tumor progression, *Cancer Cell* 32 (5) (2017) 669–683, e5.
- [8] D.S. Chen, I. Mellman, Oncology meets immunology: the cancer-immunity cycle, *Immunity* 39 (1) (2013) 1–10.
- [9] S.C. Wei, C.R. Duffy, J.P. Allison, Fundamental mechanisms of immune checkpoint blockade therapy, *Cancer Discov.* 8 (9) (2018) 1069–1086.
- [10] C.J.D. Wallis, M. Butaney, R. Satkunasivam, S.J. Freedland, S.P. Patel, O. Hamid, S.K. Pal, Z. Klaassen, Association of patient sex with efficacy of immune checkpoint inhibitors and overall survival in advanced cancers: a systematic review and meta-analysis, *JAMA Oncol.* 5 (4) (2019) 529–536.
- [11] F. Conforti, L. Pala, V. Bagnardi, T. De Pas, M. Martinetti, G. Viale, R.D. Gelber, A. Goldhirsch, Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis, *Lancet Oncol.* 19 (6) (2018) 737–746.
- [12] Z. Huang, B. Chen, X. Liu, H. Li, L. Xie, Y. Gao, R. Duan, Z. Li, J. Zhang, Y. Zheng, W. Su, Effects of sex and aging on the immune cell landscape as assessed by single-cell transcriptomic analysis, *Proc. Natl. Acad. Sci. U.S.A.* 118 (33) (2021).
- [13] Y. Zhu, X. Shao, X. Wang, L. Liu, H. Liang, Sex disparities in cancer, *Cancer Lett.* 466 (2019) 35–38.
- [14] E.J. Marquez, C.H. Chung, R. Marches, R.J. Rossi, D. Nehar-Belaid, A. Eroglu, D. J. Mellert, G.A. Kuchel, J. Banchereau, D. Ucar, Sexual-dimorphism in human immune system aging, *Nat. Commun.* 11 (1) (2020) 751.
- [15] D. Zheng, J. Trynda, C. Williams, J.A. Vold, J.H. Nguyen, D.M. Harnois, S. P. Bagaria, S.A. McLaughlin, Z. Li, Sexual dimorphism in the incidence of human cancers, *BMC Cancer* 19 (1) (2019) 684.
- [16] E.L. Bolf, B.L. Sprague, F.E. Carr, A linkage between thyroid and breast cancer: a common etiology? *Cancer Epidemiol. Biomark. Prev.* 28 (4) (2019) 643–649.
- [17] D. Muir, R. Kanthan, S.C. Kanthan, Male versus female breast cancers: a population-based comparative immunohistochemical analysis, *Arch. Pathol. Lab. Med.* 127 (1) (2003) 36–41.
- [18] T.D. Hill, H.J. Khamis, J.E. Tyczynski, H.J. Berk, Comparison of male and female breast cancer incidence trends, tumor characteristics, and survival, *Ann. Epidemiol.* 15 (10) (2005) 773–780.
- [19] R. Rahbari, L. Zhang, E. Kebebew, Thyroid cancer gender disparity, *Future Oncol.* 6 (11) (2010) 1771–1779.
- [20] M.L. Lee, G.G. Chen, A.C. Vlantis, G.M. Tse, B.C. Leung, C.A. van Hasselt, Induction of thyroid papillary carcinoma cell proliferation by estrogen is associated with an altered expression of Bcl-xL, *Cancer J.* 11 (2) (2005) 113–121.
- [21] M.R. Buckwalter, M.L. Albert, Orchestration of the immune response by dendritic cells, *Curr. Biol.* 19 (9) (2009) R355–R361.
- [22] J. So, A.K. Tai, A.H. Lichtenstein, D. Wu, S. Lamon-Fava, Sexual dimorphism of monocyte transcriptome in individuals with chronic low-grade inflammation, *Biol. Sex Differ.* 12 (1) (2021) 43.
- [23] V. Paharkova-Vatchkova, R. Maldonado, S. Kovats, Estrogen preferentially promotes the differentiation of CD11c+ CD11b(intermediate) dendritic cells from bone marrow precursors, *J. Immunol.* 172 (3) (2004) 1426–1436.
- [24] Y. Weinstein, S. Ran, S. Segal, Sex-associated differences in the regulation of immune responses controlled by the MHC of the mouse, *J. Immunol.* 132 (2) (1984) 656–661.
- [25] J.P. Mackern-Oberli, E.L. Jara, C.A. Riedel, A.M. Kalergis, Hormonal modulation of dendritic cells differentiation, maturation and function: implications for the initiation and progress of systemic autoimmunity, *Arch. Immunol. Ther. Exp.* 65 (2) (2017) 123–136.
- [26] C. Seillet, S. Laffont, F. Tremolieres, N. Rouquie, C. Ribot, J.F. Arnal, V. Douine-Echinard, P. Gourdy, J.C. Guery, The TLR-mediated response of plasmacytoid dendritic cells is positively regulated by estradiol in vivo through cell-intrinsic estrogen receptor alpha signaling, *Blood* 119 (2) (2012) 454–464.
- [27] S. Laffont, N. Rouquie, P. Azar, C. Seillet, J. Plumas, C. Aspord, J.C. Guery, X-Chromosome complement and estrogen receptor signaling independently contribute to the enhanced TLR7-mediated IFN-alpha production of plasmacytoid dendritic cells from women, *J. Immunol.* 193 (11) (2014) 5444–5452.
- [28] M. Griesbeck, S. Ziegler, S. Laffont, N. Smith, L. Chauveau, P. Tomezsko, A. Sharei, G. Kourjian, F. Porichis, M. Hart, C.D. Palmer, M. Sirignano, C. Beisel, H. Hildebrandt, C. Cenac, A.C. Villani, T.J. Dieffenbach, S. Le Gall, O. Schwartz, J. P. Herbeau, B. Autran, J.C. Guery, J.J. Chang, M. Altfeld, Sex differences in plasmacytoid dendritic cell levels of IRF5 drive higher IFN-alpha production in women, *J. Immunol.* 195 (11) (2015) 5327–5336.
- [29] M.G. Thompson, D.S. Peiffer, M. Larson, F. Navarro, S.K. Watkins, 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 (5) (2017) 615–625.
- [30] J.A. Spitzer, Gender differences in some host defense mechanisms, *Lupus* 8 (5) (1999) 380–383.
- [31] I. Marriott, K.L. Bost, Y.M. Huet-Hudson, Sexual dimorphism in expression of receptors for bacterial lipopolysaccharides in murine macrophages: a possible mechanism for gender-based differences in endotoxic shock susceptibility, *J. Reprod. Immunol.* 71 (1) (2006) 12–27.
- [32] S. Chenard, C. Jackson, T. Vidotto, L. Chen, C. Hardy, T. Jamaspishvili, D. Berman, D.R. Siemens, M. Koti, Sexual dimorphism in outcomes of non-muscle-invasive bladder cancer: a role of CD163+ macrophages, B cells, and PD-L1 immune checkpoint, *Eur. Urol. Open Sci.* 29 (2021) 50–58.
- [33] A. Zychlinsky Schaffarz, M. Rousseau, L. Lacerda Mariano, T. Canton, C. R. Consiglio, M.L. Albert, M. Fontes, D. Duffy, M.A. Ingersoll, Sex differences in IL-17 contribute to chronicity in male versus female urinary tract infection, *JCI Insight* 5 (2019).
- [34] V.G. Martinez, C. Rubio, M. Martinez-Fernandez, C. Segovia, F. Lopez-Calderon, M.I. Garin, A. Teijeira, E. Munera-Maravilla, A. Varas, R. Sacedon, F. Guerrero, F. Villacampa, F. de la Rosa, D. Castellano, E. Lopez-Collazo, J.M. Paramio, A. Vicente, M. Duñas, BMP4 induces M2 macrophage polarization and favors tumor progression in bladder cancer, *Clin. Cancer Res.* 23 (23) (2017) 7388–7399.
- [35] A.L. Ray, R.A. Nofchissey, M.A. Khan, M.A. Reidy, M.R. Lerner, X. Wu, S. Guo, S. L. Hill, N. Weygant, S.F. Adams, E.F. Castillo, W.L. Berry, M.B. Stout, K.T. Morris, The role of sex in the innate and adaptive immune environment of metastatic colorectal cancer, *Br. J. Cancer* 123 (4) (2020) 624–632.
- [36] S.L. Klein, K.L. Flanagan, Sex differences in immune responses, *Nat. Rev. Immunol.* 16 (10) (2016) 626–638.
- [37] W.E. Naugler, T. Sakurai, S. Kim, S. Maeda, K. Kim, A.M. Elsharkawy, M. Karin, Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production, *Science* 317 (5834) (2007) 121–124.
- [38] D.I. Gabrilovich, S. Nagaraj, Myeloid-derived suppressor cells as regulators of the immune system, *Nat. Rev. Immunol.* 9 (3) (2009) 162–174.
- [39] A. Pastaki Khoshbin, M. Eskian, M. Keshavarz-Fathi, N. Rezaei, Roles of myeloid-derived suppressor cells in cancer metastasis: immunosuppression and beyond, *Arch. Immunol. Ther. Exp.* 67 (2) (2019) 89–102.
- [40] D. Bayik, Y. Zhou, C. Park, C. Hong, D. Vail, D.J. Silver, A. Lauko, G. Roversi, D. C. Watson, A. Lo, T.J. Alban, M. McGraw, M. Sorensen, M.M. Grabowski, B. Otvos, M.A. Vogelbaum, C. Horbinski, B.W. Kristensen, A.M. Khalil, T. H. Hwang, M.S. Ahluwalia, F. Cheng, J.D. Lathia, Myeloid-derived suppressor cell subsets drive glioblastoma growth in a sex-specific manner, *Cancer Discov.* 10 (8) (2020) 1210–1225.
- [41] N. Svoronos, A. Perales-Puchalt, M.J. Allegrezza, M.R. Rutkowski, K.K. Payne, A. J. Tesone, J.M. Nguyen, T.J. Curiel, M.G. Cadungog, S. Singhal, E.B. Eruslanov, P. Zhang, J. Tchou, R. Zhang, J.R. Conejo-Garcia, Tumor cell-independent estrogen signaling drives disease progression through mobilization of myeloid-derived suppressor cells, *Cancer Discov.* 7 (1) (2017) 72–85.
- [42] F. Clausen, H.M. Behrens, S. Kruger, C. Rocken, Sexual dimorphism in gastric cancer: tumor-associated neutrophils predict patient outcome only for women, *J. Cancer Res. Clin. Oncol.* 146 (1) (2020) 53–66.
- [43] D. Palli, M. Galli, N.E. Caporaso, F. Cipriani, A. Decarli, C. Saieva, J. F. Fraumeni Jr., E. Buiatti, Family history and risk of stomach cancer in Italy, *Cancer Epidemiol. Biomark. Prev.* 3 (1) (1994) 15–18.
- [44] S. Laffont, E. Blanquart, M. Savignac, C. Cenac, G. Laverny, D. Metzger, J. P. Girard, G.T. Belz, L. Pelletier, C. Seillet, J.C. Guery, Androgen signaling negatively controls group 2 innate lymphoid cells, *J. Exp. Med.* 214 (6) (2017) 1581–1592.

- [45] A. Alayev, R.S. Salamon, S.M. Berger, N.S. Schwartz, R. Cuesta, R.B. Snyder, M. K. Holz, mTORC1 directly phosphorylates and activates eRalpha upon estrogen stimulation, *Oncogene* 35 (27) (2016) 3535–3543.
- [46] C. Yang, S.W. Tsaih, A. Lemke, M.J. Flister, M.S. Thakar, S. Malarkannan, mTORC1 and mTORC2 differentially promote natural killer cell development, *Elife* 7 (2018).
- [47] C. Yang, S. Malarkannan, Transcriptional regulation of NK cell development by mTOR complexes, *Front. Cell. Dev. Biol.* 8 (2020), 566090.
- [48] M. Abdullah, P.S. Chai, M.Y. Chong, E.R. Tohit, R. Ramasamy, C.P. Pei, S. Vidyadarshan, Gender effect on *in vitro* lymphocyte subset levels of healthy individuals, *Cell Immunol.* 272 (2) (2012) 214–219.
- [49] G.G. Page, S. Ben-Eliyahu, A.N. Taylor, The development of sexual dimorphism in natural killer cell activity and resistance to tumor metastasis in the Fischer 344 rat, *J. Neuroimmunol.* 63 (1) (1995) 69–77.
- [50] J. Russick, P.E. Joubert, M. Gillard-Bocquet, C. Torset, M. Meylan, F. Petitprez, M. A. Dragon-Durey, S. Marmier, A. Varthaman, N. Josseaume, C. Germain, J. Goc, M.C. Dieu-Nosjean, P. Validire, L. Fournel, L. Zitvogel, G. Bindea, A. Lupo, D. Damotte, M. Alifano, I. Cremer, Natural killer cells in the human lung tumor microenvironment display immune inhibitory functions, *J. Immunother. Cancer* 8 (2) (2020).
- [51] Y.P. Tang, M.Z. Xie, K.Z. Li, J.L. Li, Z.M. Cai, B.L. Hu, Prognostic value of peripheral blood natural killer cells in colorectal cancer, *BMC Gastroenterol.* 20 (1) (2020) 31.
- [52] D. Teixeira, I.M. Longo-Maugeri, J.L. Santos, Y.A. Duarte, M.L. Lebrao, V. Bueno, Evaluation of lymphocyte levels in a random sample of 218 elderly individuals from Sao Paulo city, *Rev. Bras. Hematol. Hemoter.* 33 (5) (2011) 367–371.
- [53] D. Furman, B.P. Hejblum, N. Simon, V. Jovic, C.L. Dekker, R. Thiebaut, R. J. Tibshirani, M.M. Davis, Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination, *Proc. Natl. Acad. Sci. U.S.A.* 111 (2) (2014) 869–874.
- [54] F.X. Lu, K. Abel, Z. Ma, T. Rourke, D. Lu, J. Torten, M. McChesney, C.J. Miller, The strength of B cell immunity in female rhesus macaques is controlled by CD8+ T cells under the influence of ovarian steroid hormones, *Clin. Exp. Immunol.* 128 (1) (2002) 10–20.
- [55] H. Fan, G. Dong, G. Zhao, F. Liu, G. Yao, Y. Zhu, Y. Hou, Gender differences of B cell signature in healthy subjects underlie disparities in incidence and course of SLE related to estrogen, *J. Immunol. Res.* 2014 (2014), 814598.
- [56] K.L. Phiel, R.A. Henderson, S.J. Adelman, M.M. Elliso, Differential estrogen receptor gene expression in human peripheral blood mononuclear cell populations, *Immunol. Lett.* 97 (1) (2005) 107–113.
- [57] C.M. Grimaldi, J. Cleary, A.S. Dagtas, D. Moussai, B. Diamond, Estrogen alters thresholds for B cell apoptosis and activation, *J. Clin. Investig.* 109 (12) (2002) 1625–1633.
- [58] S. Pauklin, I.V. Sernandez, G. Bachmann, A.R. Ramiro, S.K. Petersen-Mahrt, Estrogen directly activates AID transcription and function, *J. Exp. Med.* 206 (1) (2009) 99–111.
- [59] N. Kanda, T. Tsuchida, K. Tamaki, Testosterone inhibits immunoglobulin production by human peripheral blood mononuclear cells, *Clin. Exp. Immunol.* 106 (2) (1996) 410–415.
- [60] I.H. Kocar, Z. Yesilova, M. Ozata, M. Turan, A. Sengul, I. Ozdemir, The effect of testosterone replacement treatment on immunological features of patients with Klinefelter's syndrome, *Clin. Exp. Immunol.* 121 (3) (2000) 448–452.
- [61] E. Cacciari, M. Masi, M.P. Fantini, F. Licastro, A. Cicognani, P. Pirazzoli, M. P. Villa, F. Specchia, A. Forabosco, C. Franceschi, L. Martoni, Serum immunoglobulins and lymphocyte subpopulations derangement in Turner's syndrome, *J. Immunogenet.* 8 (5) (1981) 337–344.
- [62] M.J. Goldacre, O.O. Seminog, Turner syndrome and autoimmune diseases: record-linkage study, *Arch. Dis. Child* 99 (1) (2014) 71–73.
- [63] O.O. Seminog, A.B. Seminog, D. Yeates, M.J. Goldacre, Associations between Klinefelter's syndrome and autoimmune diseases: English national record linkage studies, *Autoimmunity* 48 (2) (2015) 125–128.
- [64] M.H. Viuff, K. Stochholm, A. Lin, A. Berglund, S. Juul, C.H. Gravholt, Cancer occurrence in Turner syndrome and the effect of sex hormone substitution therapy, *Eur. J. Endocrinol.* 184 (1) (2021) 79–88.
- [65] A. Hewagama, D. Patel, S. Yarlagadda, F.M. Strickland, B.C. Richardson, Stronger inflammatory/cytotoxic T-cell response in women identified by microarray analysis, *Genes Immun.* 10 (5) (2009) 509–516.
- [66] L.M. Pennell, C.L. Galligan, E.N. Fish, Sex affects immunity, *J. Autoimmun.* (2–3) (2012) J282–J291.
- [67] M.S. Anderson, E.S. Venanzi, L. Klein, Z. Chen, S.P. Berzins, S.J. Turley, H. von Boehmer, R. Bronson, A. Dierich, C. Benoit, D. Mathis, Projection of an immunological self shadow within the thymus by the aire protein, *Science* 298 (5597) (2002) 1395–1401.
- [68] N. Dragan, J. Bismuth, G. Cizeron-Clairac, M.G. Biferi, C. Berthault, A. Serraf, R. Nottin, D. Klatzmann, A. Cumano, M. Barkats, R. Le Panse, S. Berrih-Aknin, Estrogen-mediated downregulation of AIRE influences sexual dimorphism in autoimmune diseases, *J. Clin. Investig.* 126 (4) (2016) 1525–1537.
- [69] M.L. Salem, 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 (1) (2004) 97–104.
- [70] A.K. Wesa, M. Mandic, J.L. Taylor, S. Moschos, J.M. Kirkwood, W.W. Kwok, J. H. Finke, W.J. Storkus, Circulating type-1 anti-tumor CD4(+) T cells are preferentially pro-apoptotic in cancer patients, *Front. Oncol.* 4 (2014) 266.
- [71] J. Zhu, H. Yamane, W.E. Paul, Differentiation of effector CD4 T cell populations (*), *Annu. Rev. Immunol.* 28 (2010) 445–489.
- [72] S. He, M. Fei, Y. Wu, D. Zheng, D. Wan, L. Wang, D. Li, Distribution and clinical significance of Th17 cells in the tumor microenvironment and peripheral blood of pancreatic cancer patients, *Int. J. Mol. Sci.* 12 (11) (2011) 7424–7437.
- [73] H. von Boehmer, C. Daniel, Therapeutic opportunities for manipulating T(Reg) cells in autoimmunity and cancer, *Nat. Rev. Drug Discov.* 12 (1) (2013) 51–63.
- [74] G. Afshan, N. Afzal, S. Qureshi, CD4+CD25(hi) regulatory T cells in healthy males and females mediate gender difference in the prevalence of autoimmune diseases, *Clin. Lab.* 58 (5–6) (2012) 567–571.
- [75] C.C. Whitacre, Sex differences in autoimmune disease, *Nat. Immunol.* 2 (9) (2001) 777–780.
- [76] P.Y. Lin, L. Sun, S.R. Thibodeaux, S.M. Ludwig, R.K. Vadlamudi, V.J. Hurez, R. Bahar, M.J. Kious, C.B. Livi, S.R. Wall, L. Chen, B. Zhang, T. Shin, T.J. Curiel, B7-H1-dependent sex-related differences in tumor immunity and immunotherapy responses, *J. Immunol.* 185 (5) (2010) 2747–2753.
- [77] J. Nie, Y.Y. Li, S.G. Zheng, A. Tsun, B. Li, FOXP3(+) treg cells and gender bias in autoimmune diseases, *Front. Immunol.* 6 (2015) 493.
- [78] M.J. Polanczyk, B.D. Carson, S. Subramanian, M. Afentoulis, A.A. Vandenbark, S. F. Ziegler, H. Offner, Cutting edge: estrogen drives expansion of the CD4+CD25+ regulatory T cell compartment, *J. Immunol.* 173 (4) (2004) 2227–2230.
- [79] M. Walecki, F. Eisel, J. Klug, N. Baal, A. Paradowska-Dogan, E. Wahle, H. Hackstein, A. Meinhardt, M. Fijak, Androgen receptor modulates Foxp3 expression in CD4+CD25+Foxp3+ regulatory T-cells, *Mol. Biol. Cell* 26 (15) (2015) 2845–2857.
- [80] H. Raskov, A. Orhan, J.P. Christensen, I. Gogenur, Cytotoxic CD8(+) T cells in cancer and cancer immunotherapy, *Br. J. Cancer* 124 (2) (2021) 359–367.
- [81] K. Loo, K.K. Tsai, K. Mahuron, J. Liu, M.L. Pauli, P.M. Sandoval, A. Nosrati, J. Lee, L. Chen, J. Hwang, L.S. Levine, M.F. Krummel, A.P. Algazi, M. Pampaloni, M. D. Alvarado, M.D. Rosenblum, A.I. Daud, Partially exhausted tumor-infiltrating lymphocytes predict response to combination immunotherapy, *JCI Insight* 2 (14) (2017).
- [82] X. Wu, H. Zhang, Q. Xing, J. Cui, J. Li, Y. Li, Y. Tan, S. Wang, PD-1(+) CD8(+) T cells are exhausted in tumours and functional in draining lymph nodes of colorectal cancer patients, *Br. J. Cancer* 111 (7) (2014) 1391–1399.
- [83] A.E. Prizment, R.A. Vierkant, T.C. Smyrk, L.S. Tillmans, H.H. Nelson, C.F. Lynch, T. Pengo, S.N. Thibodeau, T.R. Church, J.R. Cerhan, K.E. Anderson, P.J. Limburg, Cytotoxic T cells and granzyme B associated with improved colorectal cancer survival in a prospective cohort of older women, *Cancer Epidemiol. Biomark. Prev.* 26 (4) (2017) 622–631.
- [84] Z. Shen, M. Rodriguez-Garcia, M.V. Patel, F.D. Barr, C.R. Wira, Menopausal status influences the expression of programmed death (PD)-1 and its ligand PD-L1 on immune cells from the human female reproductive tract, *Am. J. Reprod. Immunol.* 76 (2) (2016) 118–125.
- [85] A. Care, M. Bellenghi, P. Matarrese, L. Gabriele, S. Salvioli, W. Malorni, Sex disparity in cancer: roles of microRNAs and related functional players, *Cell Death Differ.* 25 (3) (2018) 477–485.
- [86] R. Dai, S.A. Ahmed, Sexual dimorphism of miRNA expression: a new perspective in understanding the sex bias of autoimmune diseases, *Ther. Clin Risk Manag.* 10 (2014) 151–163.
- [87] M.A. Smolle, H.N. Calin, M. Pichler, G.A. Calin, Noncoding RNAs and immune checkpoints-clinical implications as cancer therapeutics, *FEBS J.* 284 (13) (2017) 1952–1966.
- [88] A. Castro, R.M. Pyke, X. Zhang, W.K. Thompson, C.P. Day, L.B. Alexandrov, M. Zanetti, H. Carter, Strength of immune selection in tumors varies with sex and age, *Nat. Commun.* 11 (1) (2020) 4128.
- [89] M. Vetizou, J.M. Pitt, R. Daillere, P. Lepage, N. Waldschmitt, C. Flament, S. Rusakiewicz, B. Routy, M.P. Roberti, C.P. Duong, V. Poirier-Colame, A. Roux, S. Becharef, S. Formenti, E. Golden, S. Cording, G. Eberl, A. Schlitzer, F. Ginhoux, S. Mani, T. Yamazaki, N. Jacquelin, D.P. Enot, M. Berard, J. Nigou, P. Opolon, A. Eggmont, P.L. Woerther, E. Chatachay, N. Chaput, C. Robert, C. Mateus, G. Kroemer, D. Raoult, I.G. Boneca, F. Carbonnel, M. Chamaillard, L. Zitvogel, Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota, *Science* 350 (6264) (2015) 1079–1084.
- [90] A. Sivan, L. Corrales, N. Hubert, J.B. Williams, K. Aquino-Michaels, Z.M. Earley, F.W. Benyamin, Y.M. Lei, B. Jabri, M.L. Alegre, E.B. Chang, T.F. Gajewski, Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy, *Science* 360 (6264) (2015) 1084–1089.
- [91] S. Voinea, A. Blidaru, E. Panaitescu, A. Sandru, Impact of gender and primary tumor location on outcome of patients with cutaneous melanoma, *J. Med. Life* 9 (4) (2016) 444–448.
- [92] T. Fukusato, H. Aoyama, W. Mori, Age and sex differences in bone metastasis of hepatocellular carcinoma in Japanese autopsy cases, *Gastroenterol. Jpn.* 24 (2) (1989) 127–134.
- [93] Y. Li, H. Li, J.M. Spitsbergen, Z. Gong, Males develop faster and more severe hepatocellular carcinoma than females in kras(V12) transgenic zebrafish, *Sci. Rep.* 7 (2017) 4128.
- [94] M. Abancens, V. Bustos, H. Harvey, J. McBryan, B.J. Harvey, Sexual dimorphism in colon cancer, *Front. Oncol.* 10 (2020), 607909.
- [95] A. Clocchiatti, E. Cora, Y. Zhang, G.P. Dotto, Sexual dimorphism in cancer, *Nat. Rev. Cancer* 16 (5) (2016) 330–339.
- [96] C. Serrano-Novillo, J. Capera, M. Colomer-Molera, E. Condom, J.C. Ferreres, A. Felipe, Implication of voltage-gated potassium channels in neoplastic cell proliferation, *Cancers* 11 (3) (2019).
- [97] H.H. Chua, D.J. Tsuei, P.H. Lee, Y.M. Jeng, J. Lu, J.F. Wu, D.S. Su, Y.H. Chen, C. S. Chien, P.C. Kao, C.N. Lee, R.H. Hu, Y.H. Ni, M.H. Chang, RBMY, a novel inhibitor of glycogen synthase kinase 3beta, increases tumor stemness and

- predicts poor prognosis of hepatocellular carcinoma, *Hepatology* 62 (5) (2015) 1480–1496.
- [98] T. Vincent, E.P. Neve, J.R. Johnson, A. Kukalev, F. Rojo, J. Albanell, K. Pietras, I. Virtanen, L. Phillipson, P.L. Leopold, R.G. Crystal, A.G. de Herreros, A. Moustakas, R.F. Pettersson, J. Fuxé, A. SNAIL1-SMAD3/4, transcriptional repressor complex promotes TGF-beta mediated epithelial-mesenchymal transition, *Nat. Cell Biol.* 11 (8) (2009) 943–950.
- [99] J. Fuxé, T. Vincent, A. García, de Herreros, Transcriptional crosstalk between TGF-beta and stem cell pathways in tumor cell invasion: role of EMT promoting Smad complexes, *Cell Cycle* 9 (12) (2010) 2363–2374.
- [100] B.P. Zhou, J. Deng, W. Xia, J. Xu, Y.M. Li, M. Gunduz, M.C. Hung, Dual regulation of Snail by GSK-3beta-mediated phosphorylation in control of epithelial-mesenchymal transition, *Nat. Cell Biol.* 6 (10) (2004) 931–940.
- [101] G.V. Vijay, N. Zhao, P. Den Hollander, M.J. Toneff, R. Joseph, M. Pietila, J. H. Taube, T.R. Sarkar, E. Ramirez-Pena, S.J. Werden, M. Shariati, R. Gao, M. Sobieski, C.C. Stephan, N. Sphyris, N. Miura, P. Davies, J.T. Chang, R. Soundararajan, J.M. Rosen, S.A. Mani, GSK3beta regulates epithelial-mesenchymal transition and cancer stem cell properties in triple-negative breast cancer, *Breast Cancer Res.* 21 (1) (2019) 37.
- [102] S.Y. Kim, S. Lee, E. Lee, H. Lim, J.Y. Shin, J. Jung, S.G. Kim, A. Moon, Sex-biased differences in the correlation between epithelial-to-mesenchymal transition-associated genes in cancer cell lines, *Oncol. Lett.* 18 (6) (2019) 6852–6868.
- [103] C.D. Hermann, B. Schoeps, C. Eckfeld, E. Munkhbaatar, L. Kniep, O. Prokophchuk, N. Wirges, K. Steiger, D. Haussler, P. Knolle, E. Poulton, R. Khokha, B. T. Grunwald, I.E. Demir, A. Kruger, TIMP1 expression underlies sex disparity in liver metastasis and survival in pancreatic cancer, *J. Exp. Med.* 218 (11) (2021).
- [104] X. Liu, H. Xing, H. Zhang, H. Liu, J. Chen, Immunotherapy versus standard chemotherapy for treatment of extensive-stage small-cell lung cancer: a systematic review, *Immunotherapy* 13 (12) (2021) 989–1000.
- [105] P.S. Hegde, D.S. Chen, Top 10 challenges in cancer immunotherapy, *Immunity* 52 (1) (2020) 17–35.
- [106] F.S. Hodin, J. Chesney, A.C. Pavlick, C. Robert, K.F. Grossmann, D.F. McDermott, G.P. Linette, N. Meyer, J.K. Giguere, S.S. Agarwala, M. Shaheen, M.S. Ernstoff, D. R. Minor, A.K. Salama, M.H. Taylor, P.A. Ott, C. Horak, P. Gagnier, J. Jiang, J. D. Wolchok, M.A. Postow, Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial, *Lancet Oncol.* 17 (11) (2016) 1558–1568.
- [107] C. Robert, A. Ribas, J. Schachter, A. Arance, J.J. Grob, L. Mortier, A. Daud, M. S. Carlino, C.M. McNeil, M. Lotem, J.M.G. Larkin, P. Lorigan, B. Neyns, C. U. Blank, T.M. Petrella, O. Hamid, S.C. Su, C. Krepler, N. Ibrahim, G.V. Long, Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study, *Lancet Oncol.* 20 (9) (2019) 1239–1251.
- [108] C. Robert, J. Schachter, G.V. Long, A. Arance, J.J. Grob, L. Mortier, A. Daud, M. S. Carlino, C. McNeil, M. Lotem, J. Larkin, P. Lorigan, B. Neyns, C.U. Blank, O. Hamid, C. Mateus, R. Shapira-Frommer, M. Kosh, H. Zhou, N. Ibrahim, S. Ebbinghaus, A. Ribas, Pembrolizumab versus Ipilimumab in advanced Melanoma, *New Engl. J. Med.* 372 (26) (2015) 2521–2532.
- [109] M.A. Postow, J. Chesney, A.C. Pavlick, C. Robert, K. Grossmann, D. McDermott, G.P. Linette, N. Meyer, J.K. Giguere, S.S. Agarwala, M. Shaheen, M.S. Ernstoff, D. Minor, A.K. Salama, M. Taylor, P.A. Ott, L.M. Rollin, C. Horak, P. Gagnier, J. D. Wolchok, F.S. Hodin, Nivolumab and ipilimumab versus ipilimumab in untreated melanoma, *New Engl. J. Med.* 372 (21) (2015) 2006–2017.
- [110] F.S. Hodin, S.J. O'Day, D.F. McDermott, R.W. Weber, J.A. Sosman, J.B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J.C. Hassel, W. Akerley, A.J. van den Eertwegh, J. Lutzky, P. Lorigan, J.M. Vaubel, G.P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbe, C. Peschel, I. Quirt, J.I. Clark, J.D. Wolchok, J.S. Weber, J. Tian, M.J. Yellin, G.M. Nichol, A. Hoos, W.J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma, *New Engl. J. Med.* 363 (8) (2010) 711–723.
- [111] A. Ribas, R. Kefford, M.A. Marshall, C.J. Punt, J.B. Haanen, M. Marmol, C. Garbe, H. Gogas, J. Schachter, G. Linette, P. Lorigan, K.L. Kendra, M. Mai, U. Trefzer, M. Smylie, G.A. McArthur, B. Dreno, P.D. Nathan, J. Mackiewicz, J.M. Kirkwood, J. Gomez-Navarro, B. Huang, D. Pavlov, A. Hauschild, Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma, *J. Clin. Oncol.* 31 (5) (2013) 616–622.
- [112] J. Schachter, A. Ribas, G.V. Long, A. Arance, J.J. Grob, L. Mortier, A. Daud, M. S. Carlino, C. McNeil, M. Lotem, J. Larkin, P. Lorigan, B. Neyns, C. Blank, T. M. Petrella, O. Hamid, H. Zhou, S. Ebbinghaus, N. Ibrahim, C. Robert, Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006), *Lancet* 390 (10105) (2017) 1853–1862.
- [113] F. Conforti, L. Pala, E. Pagan, C. Corti, V. Bagnardi, P. Queirolo, C. Catania, T. De Pas, G. Giaccone, Sex-based differences in response to anti-PD-1 or PD-L1 treatment in patients with non-small-cell lung cancer expressing high PD-L1 levels. A systematic review and meta-analysis of randomized clinical trials, *ESMO Open* 6 (5) (2021), 100251.
- [114] O. Majek, A. Gondos, L. Jansen, K. Emrich, B. Holleczek, A. Katalinic, A. Nennecke, A. Eberle, H. Brenner, G.C.S.W. Group, Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany, *PLoS One* 8 (7) (2013), e68077.
- [115] A. White, L. Ironmonger, R.J.C. Steele, N. Ormiston-Smith, C. Crawford, A. Seims, A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK, *BMC Cancer* 18 (1) (2018) 906.
- [116] V. Gopalakrishnan, C.N. Spencer, L. Nezi, A. Reuben, M.C. Andrews, T. V. Karpinetis, P.A. Prieto, D. Vicente, K. Hoffman, S.C. Wei, A.P. Cogdill, L. Zhao, C.W. Hudgens, D.S. Hutchinson, T. Manzo, M. Petaccia de Macedo, T. Cotechini, T. Kumar, W.S. Chen, S.M. Reddy, R. Szczepanik Sloane, J. Galloway-Pena, H. Jiang, P.L. Chen, E.J. Shpall, K. Rezvani, A.M. Alousi, R.F. Chemaly, S. Shelburne, L.M. Vence, P.C. Okhuyse, B.W. Jensen, A.G. Swennes, F. McAllister, E. Marcelo Riquelme Sanchez, Y. Zhang, E. Le Chatelier, L. Zitzvogel, N. Pons, J.L. Austin-Breneman, L.E. Haydu, E.M. Burton, J.M. Gardner, E. Sirmans, J. Hu, A.J. Lazar, T. Tsujikawa, A. Diab, H. Tawbi, I.C. Glitzka, W. J. Hwu, S.P. Patel, S.E. Woodman, R.N. Amaria, M.A. Davies, J.E. Gershewald, P. Hwu, J.E. Lee, J. Zhang, L.M. Coussens, Z.A. Cooper, P.A. Futreal, C.R. Daniel, N.J. Ajami, J.F. Petrosino, M.T. Tetzlaff, P. Sharma, J.P. Allison, R.R. Jenq, J. A. Wargo, Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients, *Science* 359 (6371) (2018) 97–103.
- [117] M. Ramos-Casals, J.R. Brahmer, M.K. Callahan, A. Flores-Chavez, N. Keegan, M. A. Khamashita, O. Lambotte, X. Mariette, A. Prat, M.E. Suarez-Almazor, Immune-related adverse events of checkpoint inhibitors, *Nat. Rev. Dis. Primers* 6 (1) (2020) 38.
- [118] P. Triggiani, L. Novelli, M.R. Gallardo, M.S. Chimenti, P. Conigliaro, R. Perricone, C. Perricone, R. Gerli, Immune checkpoint inhibitors-induced autoimmunity: the impact of gender, *Autoimmun. Rev.* 19 (8) (2020), 102590.
- [119] B. Yuan, C.A. Clark, B. Wu, J. Yang, J.M. Drerup, T. Li, V.X. Jin, Y. Hu, T.J. Curiel, R. Li, Estrogen receptor beta signaling in CD8(+) T cells boosts T cell receptor activation and antitumor immunity through a phosphotyrosine switch, *J. Immunother. Cancer* 9 (1) (2021).
- [120] J.R. Stehle Jr., M.J. Blanks, G. Riedlinger, J.W. Kim-Shapiro, A.M. Sanders, J. M. Adams, M.C. Willingham, Z. Cui, Impact of sex, MHC, and age of recipients on the therapeutic effect of transferred leukocytes from cancer-resistant SR/CR mice, *BMC Cancer* 9 (2009) 328.
- [121] H. Yi, X. Yu, C. Guo, M.H. Manjili, E.A. Repasky, X.Y. Wang, Adoptive cell therapy of prostate cancer using female mice-derived T cells that react with prostate antigens, *Cancer Immunol. Immunother.* 60 (3) (2011) 349–360.
- [122] R.W. Joseph, V.R. Peddarreddigari, P. Liu, P.W. Miller, W.W. Overwijk, N. B. Bekele, M.I. Ross, J.E. Lee, J.E. Gershewald, A. Lucci, V.G. Prieto, J. D. McMannis, N. Papadopoulos, K. Kim, J. Homsi, A. Bedikian, W.J. Hwu, P. Hwu, L.G. Radvanyi, Impact of clinical and pathologic features on tumor-infiltrating lymphocyte expansion from surgically excised melanoma metastases for adoptive T-cell therapy, *Clin. Cancer Res.* 17 (14) (2011) 4882–4891.
- [123] J. Wei, J. Feng, Y. Weng, Z. Xu, Y. Jin, P. Wang, X. Cui, P. Ruan, R. Luo, N. Li, M. Peng, The prognostic value of ctDNA and btMB on immune checkpoint inhibitors in human cancer, *Front. Oncol.* 11 (2021), 706910.
- [124] S. Wang, J. Zhang, Z. He, K. Wu, X.S. Liu, The predictive power of tumor mutational burden in lung cancer immunotherapy response is influenced by patients' sex, *Int. J. Cancer* 145 (10) (2019) 2840–2849.
- [125] T. Karantanos, S. Chaturvedi, E.M. Braunstein, J. Spivak, L. Resar, S. Karanika, D. M. Williams, O. Rogers, C.D. Gocke, A.R. Moliterno, Sex determines the presentation and outcomes in MPN and is related to sex-specific differences in the mutational burden, *Blood Adv.* 4 (12) (2020) 2567–2576.
- [126] S. Gupta, M. Artomov, W. Goggins, M. Daly, H. Tsao, Gender disparity and mutation burden in metastatic melanoma, *J. Natl. Cancer Inst.* 107 (11) (2015).
- [127] S.N. Akers, K. Odunsi, A.R. Karpf, Regulation of cancer germline antigen gene expression: implications for cancer immunotherapy, *Future Oncol.* 6 (5) (2010) 717–732.
- [128] A. Grigoriadis, O.L. Caballero, K.S. Hoek, L. da Silva, Y.T. Chen, S.J. Shin, A. A. Jungbluth, L.D. Miller, D. Clouston, J. Cebon, L.J. Old, S.R. Lakhani, A. J. Simpson, A.M. Neville, CT-X antigen expression in human breast cancer, *Proc. Natl. Acad. Sci. U.S.A.* 106 (32) (2009) 13493–13498.
- [129] L. Mirandola, R. Wade, R. Verma, C. Pena, N. Hosiriluck, J.A. Figueroa, E. Cobos, M.R. Jenkins, M. Chiriva-Internati, Sex-driven differences in immunological responses: challenges and opportunities for the immunotherapies of the third millennium, *Int. Rev. Immunol.* 34 (2) (2015) 134–142.
- [130] Y.D. Kim, H.R. Park, M.H. Song, D.H. Shin, C.H. Lee, M.K. Lee, S.Y. Lee, Pattern of cancer/testis antigen expression in lung cancer patients, *Int. J. Mol. Med.* 29 (4) (2012) 656–662.
- [131] M.F. Gjerstorff, M.H. Andersen, H.J. Ditzel, Oncogenic cancer/testis antigens: prime candidates for immunotherapy, *Oncotarget* 6 (18) (2015) 15772–15787.
- [132] P.F. Robbins, R.A. Morgan, S.A. Feldman, J.C. Yang, R.M. Sherry, M.E. Dudley, J. R. Wunderlich, A.V. Nahvi, L.J. Helman, C.L. Mackall, U.S. Kammula, M. S. Hughes, N.P. Restifo, M. Raffeld, C.C. Lee, C.L. Levy, Y.F. Li, M. El-Gamil, S. L. Schwarz, C. Laurencot, S.A. Rosenberg, Tumor regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1, *J. Clin. Oncol.* 29 (7) (2011) 917–924.
- [133] N. Peled, A.B. Oton, F.R. Hirsch, P. Bunn, MAGE A3 antigen-specific cancer immunotherapeutic, *Immunotherapy* 1 (1) (2009) 19–25.
- [134] D. Germain, Estrogen carcinogenesis in breast cancer, *Endocrinol. Metab. Clin. North Am.* 40 (3) (2011) 473–484.
- [135] J.J. Kim, T. Kurita, S.E. Bulun, Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer, *Endocr. Rev.* 34 (1) (2013) 130–162.
- [136] T.L. Rizner, Estrogen biosynthesis, phase I and phase II metabolism, and action in endometrial cancer, *Mol. Cell. Endocrinol.* 381 (1–2) (2013) 124–139.
- [137] J.R. Ribeiro, R.N. Freiman, Estrogen signaling crosstalk: Implications for endocrine resistance in ovarian cancer, *J. Steroid Biochem. Mol. Biol.* 143 (2014) 160–173.
- [138] E.C. Grant, Oral contraceptives and the risk of breast cancer, *New Engl. J. Med.* 347 (18) (2002) 1448–1449.

- [139] M. Ewertz, Oral contraceptives and breast cancer risk in Denmark, *Eur. J. Cancer* (6–7) (1992) 1176–1181.
- [140] E. Lokich, R.K. Singh, A. Han, N. Romano, N. Yano, K. Kim, R.G. Moore, HE4 expression is associated with hormonal elements and mediated by importin-dependent nuclear translocation, *Sci. Rep.* 4 (2014) 5500.
- [141] R.A. Watson, Human papillomavirus: confronting the epidemic-a urologist's perspective, *Rev. Urol.* 7 (3) (2005) 135–144.
- [142] J.M. Palefsky, Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women, *J. Natl. Cancer Inst. Monogr.* 23 (1998) 15–20.
- [143] C. de Martel, M. Plummer, J. Vignat, S. Franceschi, Worldwide burden of cancer attributable to HPV by site, country and HPV type, *Int. J. Cancer* 141 (4) (2017) 664–670.
- [144] L. Aldakak, V.M. Huber, F. Ruhli, N. Bender, Sex difference in the immunogenicity of the quadrivalent Human Papilloma Virus vaccine: systematic review and meta-analysis, *Vaccine* 39 (12) (2021) 1680–1686.
- [145] K. Reszka, L. Moskal, A. Remiorz, A. Walas, K. Szewczyk, U. Staszek-Szewczyk, Should men be exempted from vaccination against human papillomavirus? Health disparities regarding HPV: the example of sexual minorities in Poland, *J. Prev. Med. Hyg.* 62 (2) (2021) E386–E391.
- [146] A.D. Spinu, R.F. Anghel, D.R. Marcu, D.L. Iorga, A. Cherciu, D.L.D. Mischianu, HPV vaccine for men: Where to? (Review), *Exp. Ther. Med.* 22 (5) (2021) 1266.
- [147] N. Osazuwa-Peters, M.C. Simpson, R.L. Rohde, S.D. Challapalli, S.T. Massa, E. Adjei Boakye, Differences in sociodemographic correlates of human papillomavirus-associated cancer survival in the United States, *Cancer Control* 28 (2021), 10732748211041894.
- [148] D. D'Andrea, F. Soria, A.J. Grotenhuis, E.K. Cha, N. Malats, S. Di Stasi, S. Joniau, T. Cai, B.W.G. van Rhijn, J. Irani, J. Karnes, J. Varkarakis, J. Baniel, J. Palou, M. Babjuk, M. Spahn, P. Ardel, R. Colombo, V. Serretta, G. Dalbagni, P. Gontero, R. Bartoletti, S. Larre, P.U. Malmstrom, R. Sylvester, S.F. Shariat, Association of patients' sex with treatment outcomes after intravesical bacillus Calmette-Guerin immunotherapy for T1G3/HG bladder cancer, *World J. Urol.* 39 (9) (2021) 3337–3344.
- [149] J. Fernandez-Gomez, E. Solsona, M. Unda, L. Martinez-Pineiro, M. Gonzalez, R. Hernandez, R. Madero, A. Ojea, C. Pertusa, J. Rodriguez-Molina, J.E. Camacho, S. Isorna, M. Rabadian, A. Astobiza, M. Montesinos, P. Muntanola, A. Gimeno, M. Blas, J.A. Martinez-Pineiro, O. Club, Urologico Espanol de Tratamiento, Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: multivariate analysis of data from four randomized CUETO trials, *Eur. Urol.* 53 (5) (2008) 992–1001.
- [150] S.A. Boorjian, F. Zhu, H.W. Herr, The effect of gender on response to bacillus Calmette-Guerin therapy for patients with non-muscle-invasive urothelial carcinoma of the bladder, *BJU Int.* 106 (3) (2010) 357–361.
- [151] F. Xiu, Z. Sabz Ali, N. Palaniyar, N. Sweezy, A dual neutrophil-T cell purification procedure and methodological considerations in studying the effects of estrogen on human Th17 cell differentiation, *J. Immunol. Methods* 467 (2019) 1–11.
- [152] W.A. Goodman, S.M. Bedoyan, H.L. Havran, B. Richardson, M.J. Cameron, T. T. Pizarro, Impaired estrogen signaling underlies regulatory T cell loss-of-function in the chronically inflamed intestine, *Proc. Natl. Acad. Sci. U.S.A.* 117 (29) (2020) 17166–17176.
- [153] D.A. Gibson, E. Greaves, H.O. Critchley, P.T. Saunders, Estrogen-dependent regulation of human uterine natural killer cells promotes vascular remodelling via secretion of CCL2, *Hum. Reprod.* 30 (6) (2015) 1290–1301.
- [154] A.C. Roden, M.T. Moser, S.D. Tri, M. Mercader, S.M. Kuntz, H. Dong, A. A. Hurwitz, D.J. McKeon, E. Celis, B.C. Leibovich, J.P. Allison, E.D. Kwon, Augmentation of T cell levels and responses induced by androgen deprivation, *J. Immunol.* 173 (10) (2004) 6098–6108.
- [155] H.T. Kissick, M.G. Sanda, L.K. Dunn, K.L. Pellegrini, S.T. On, J.K. Noel, M. S. Arredouani, Androgens alter T-cell immunity by inhibiting T-helper 1 differentiation, *Proc. Natl. Acad. Sci. U.S.A.* 111 (27) (2014) 9887–9892.
- [156] R.T. Chlebowski, G.L. Anderson, Changing concepts: Menopausal hormone therapy and breast cancer, *J. Natl. Cancer Inst.* 104 (7) (2012) 517–527.
- [157] L.A. Brinton, A.S. Felix, Menopausal hormone therapy and risk of endometrial cancer, *J. Steroid Biochem. Mol. Biol.* 142 (2014) 83–89.
- [158] J.V. Lacey Jr., P.J. Mink, J.H. Lubin, M.E. Sherman, R. Troisi, P. Hartge, A. Schatzkin, C. Schairer, Menopausal hormone replacement therapy and risk of ovarian cancer, *JAMA* 288 (3) (2002) 334–341.
- [159] L. Nachtigall, F. Naftolin, D.L. Keefe, Contemporary hormonal contraception and the risk of breast cancer, *New Engl. J. Med.* 378 (13) (2018) 1265.
- [160] P. Boyle, A. Koechlin, M. Bota, A. d'Onofrio, D.G. Zaridze, P. Perrin, J. Fitzpatrick, A.L. Burnett, M. Boniol, Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis, *BJU Int.* 118 (5) (2016) 731–741.
- [161] Y. Cui, H. Zong, H. Yan, Y. Zhang, The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis, *Prostate Cancer Prostatic Dis.* 17 (2) (2014) 132–143.
- [162] S. Milette, M. Hashimoto, S. Perrino, S. Qi, M. Chen, B. Ham, N. Wang, R. Istomine, A.M. Lowy, C.A. Piccirillo, P. Brodt, Sexual dimorphism and the role of estrogen in the immune microenvironment of liver metastases, *Nat. Commun.* 10 (1) (2019) 5745.
- [163] C.R. Consiglio, O. Udartseva, K.D. Ramsey, C. Bush, S.O. Gollnick, Enzalutamide, an androgen receptor antagonist, enhances myeloid cell-mediated immune suppression and tumor progression, *Cancer Immunol. Res.* 8 (9) (2020) 1215–1227.
- [164] M. Gamat, D.G. McNeil, Androgen deprivation and immunotherapy for the treatment of prostate cancer, *Endocr. Relat. Cancer* 24 (12) (2017) T297–T310.
- [165] X. Lu, J.W. Horner, E. Paul, X. Shang, P. Troncoso, P. Deng, S. Jiang, Q. Chang, D. J. Spring, P. Sharma, J.A. Zebala, D.Y. Maeda, Y.A. Wang, R.A. DePinho, Effective combinatorial immunotherapy for castration-resistant prostate cancer, *Nature* 543 (7647) (2017) 728–732.
- [166] A.Z. Obradovic, M.C. Dallos, M.L. Zahurak, A.W. Partin, E.M. Schaeffer, A.E. Ross, M.E. Allaf, T.R. Nirschl, D. Liu, C.G. Chapman, T. O'Neal, H. Cao, J.N. Durham, G. Guner, J.A. Baena-Del Valle, O. Ertunc, A.M. De Marzo, E.S. Antonarakis, C. G. Drake, T-cell infiltration and adaptive treg resistance in response to androgen deprivation with or without vaccination in localized prostate cancer, *Clin. Cancer Res.* 26 (13) (2020) 3182–3192.
- [167] T.A. Colacchio, M.P. Yeager, L.W. Hildebrandt, Perioperative immunomodulation in cancer surgery, *Am. J. Surg.* 167 (1) (1994) 174–179.
- [168] A.M. Dabrowska, R. Slotwinski, The immune response to surgery and infection, *Cent. Eur. J. Immunol.* 39 (4) (2014) 532–537.
- [169] E. Lin, S.E. Calvano, S.F. Lowry, Inflammatory cytokines and cell response in surgery, *Surgery* 127 (2) (2000) 117–126.
- [170] G.G. Page, The immune-suppressive effects of pain, *Adv. Exp. Med. Biol.* 521 (2003) 117–125.
- [171] A. Kher, M. Wang, B.M. Tsai, J.M. Pitcher, E.S. Greenbaum, R.D. Nagy, K.M. Patel, G.M. Wairiuko, T.A. Markel, D.R. Meldrum, Sex differences in the myocardial inflammatory response to acute injury, *Shock* 23 (1) (2005) 1–10.
- [172] P.J. Offner, E.E. Moore, W.L. Biffle, Male gender is a risk factor for major infections after surgery, *Arch. Surg.* 134 (9) (1999) 935–938, discussion 938–40.
- [173] M.W. Wichmann, R. Zellweger, C.M. DeMaso, A. Ayala, I.H. Chaudry, Mechanism of immunosuppression in males following trauma-hemorrhage critical role of testosterone, *Arch. Surg.* 131 (11) (1996) 1186–1191, discussion 1191–2.
- [174] M.K. Angele, M.G. Schwacha, A. Ayala, I.H. Chaudry, Effect of gender and sex hormones on immune responses following shock, *Shock* 14 (2) (2000) 81–90.
- [175] M.K. Angele, M.C. Frantz, I.H. Chaudry, Gender and sex hormones influence the response to trauma and sepsis: potential therapeutic approaches, *Clinics* 61 (5) (2006) 479–488.
- [176] I. Penn, T.E. Starzl, Proceedings: the effect of immunosuppression on cancer, *Proc. Natl. Cancer Conf.* 7 (1972) 425–436.
- [177] V. Malhotra, M.C. Perry, Classical chemotherapy: mechanisms, toxicities and the therapeutic window, *Cancer Biol. Ther.* 2 (1) (2003) S2–S4.
- [178] S. Bins, M.J. Ratain, R.H. Mathijssen, Conventional dosing of anticancer agents: precisely wrong or just inaccurate? *Clin. Pharmacol. Ther.* 95 (4) (2014) 361–364.
- [179] M.J. Legato, P.A. Johnson, J.E. Manson, Consideration of sex differences in medicine to improve health care and patient outcomes, *JAMA* 316 (18) (2016) 1865–1866.
- [180] B. Shang, L. Guo, R. Shen, C. Cao, R. Xie, W. Jiang, L. Wen, X. Bi, H. Shi, S. Zheng, C. Li, J. Ma, K. Zhang, L. Feng, J. Shou, Prognostic significance of NLR About NETosis and lymphocytes perturbations in localized renal cell carcinoma with tumor thrombus, *Front. Oncol.* 11 (2021), 771545.
- [181] K.G. Paulson, J.G. Iyer, A. Blom, E.M. Warton, M. Sokil, L. Yelistratova, L. Schuman, K. Nagase, S. Bhatia, M.M. Asgari, P. Nghiem, Systemic immune suppression predicts diminished Merkel cell carcinoma-specific survival independent of stage, *J. Investig. Dermatol.* 133 (3) (2013) 642–646.
- [182] N. Palazon-Carrion, C. Jimenez-Cortegana, M.L. Sanchez-Leon, F. Henao-Carrasco, E. Nogales-Fernandez, M. Chiesa, R. Caballero, F. Rojo, M.A. Nieto-Garcia, V. Sanchez-Margalef, L. de la Cruz-Merino, G. Spanish, Breast Cancer, C. the Spanish Group for Immunotherapy of, Circulating immune biomarkers in peripheral blood correlate with clinical outcomes in advanced breast cancer, *Sci. Rep.* 11 (1) (2021) 14426.
- [183] J.P. Arnoletti, X. Zhu, A.J. Almodovar, P.P. Veldhuis, R. Sause, E. Griffith, G. Corpus, J.C. Chang, N. Fanaian, S.A. Litherland, Portal venous blood circulation supports immunosuppressive environment and pancreatic cancer circulating tumor cell activation, *Pancreas* 46 (1) (2017) 116–123.
- [184] E.R. Pereira, D. Jones, K. Jung, T.P. Padera, The lymph node microenvironment and its role in the progression of metastatic cancer, *Semin. Cell Dev. Biol.* 38 (2015) 98–105.
- [185] K.R. Jordan, P. Kapoor, E. Spongberg, R.P. Tobin, D. Gao, V.F. Borges, M. D. McCarter, Immunosuppressive myeloid-derived suppressor cells are increased in splenocytes from cancer patients, *Cancer Immunol. Immunother.* 66 (4) (2017) 503–513.
- [186] J.D. Roder, S. Thorban, K. Pantel, J.R. Siewert, Micrometastases in bone marrow: prognostic indicators for pancreatic cancer, *World J. Surg.* 23 (9) (1999) 888–891.
- [187] Y. Zhang, Y. Zheng, L. Shou, Y. Shi, H. Shen, M. Zhu, X. Ye, J. Jin, W. Xie, Increased serum level of interleukin-10 predicts poor survival and early recurrence in patients with peripheral T-cell lymphomas, *Front. Oncol.* 10 (2020), 584261.
- [188] J. Luo, X.Q. Chen, P. Li, The role of TGF-beta and its receptors in gastrointestinal cancers, *Transl. Oncol.* 12 (3) (2019) 475–484.
- [189] N. Jabbari, H.L. Kenerson, C. Lausted, X. Yan, C. Meng, K.M. Sullivan, P. Baloni, D. Bergey, V.G. Pillarisetty, L.E. Hood, R.S. Yeung, Q. Tian, Modulation of immune checkpoints by chemotherapy in human colorectal liver metastases, *Cell Rep. Med.* 1 (9) (2020), 100160.
- [190] D. D'Andrea, P.C. Black, H. Zargar, K. Zargar-Shoshtari, S. Zehetmayer, A. S. Fairey, L.S. Mertens, C.P. Dinney, M.C. Mir, L.M. Krabbe, M.S. Cookson, N. E. Jacobsen, J.S. Montgomery, N. Vasdev, E.Y. Yu, E. Xylinas, N.J. Campain, W. Kassouf, M.A. Dall'Era, J.A. Seah, C.E. Ercole, S. Horenblas, S.S. Sridhar, J. S. McGrath, J. Aning, J.L. Wright, A.C. Thorpe, T.M. Morgan, J.M. Holzbeierlein, T.J. Bivalacqua, S. North, D.A. Barocas, Y. Lotan, P. Grivas, A.J. Stephenson, J. B. Shah, B.W. van Rhijn, S. Daneshmand, P.E. Spiess, S.F. Shariat, Impact of sex

- on response to neoadjuvant chemotherapy in patients with bladder cancer, *Urol. Oncol.* 38 (7) (2020) 639 e1–639 e9.
- [191] I. Baiu, A.L. Titan, L.W. Martin, A. Wolf, L. Backhus, The role of gender in non-small cell lung cancer: a narrative review, *J. Thorac. Dis.* 13 (6) (2021) 3816–3826.
- [192] W.M. Brueckl, J.H. Ficker, G. Zeitler, Clinically relevant prognostic and predictive markers for immune-checkpoint-inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC), *BMC Cancer* 20 (1) (2020) 1185.
- [193] J. Thoms, R.G. Bristow, DNA repair targeting and radiotherapy: a focus on the therapeutic ratio, *Semin. Radiat. Oncol.* 20 (4) (2010) 217–222.
- [194] A. Petrova, T. Gnedko, I. Maistrova, M. Zafranskaya, N. Dainiak, Morbidity in a large cohort study of children born to mothers exposed to radiation from Chernobyl, *Stem Cells* 15 (2) (1997) 141–150.
- [195] W.N. Nemphard, P.A. McElfish, B. Ayers, R.T. Collins, X. Shan, N.Z. Rabie, Y. A. Zarate, S. Maity, R. Cen, J.A. Robbins, Nuclear radiation and prevalence of structural birth defects among infants born to women from the Marshall Islands, *Birth Defects Res.* 111 (16) (2019) 1192–1204.
- [196] N. Narendran, L. Luzhna, O. Kovalchuk, Sex difference of radiation response in occupational and accidental exposure, *Front. Genet.* 10 (2019) 260.
- [197] A. Gasinska, Z. Darasz, A. Adamczyk, J. Skolyszewski, Gender-related significance of time interval between radiotherapy and surgery in hypofractionated preoperative radiotherapy for rectal cancer patients' survival, *Rep. Pract. Oncol. Radiother.* 21 (3) (2016) 174–180.
- [198] A. Gasinska, Z. Darasz, A. Adamczyk, B. Biesaga, J. Niemiec, M. Reinfuss, Gender-related prognostic significance of clinical and biological tumor features in rectal cancer patients receiving short-course preoperative radiotherapy, *Rep. Pract. Oncol. Radiother.* 22 (5) (2017) 368–377.
- [199] L.S. Rozek, C.M. Herron, J.K. Greenson, V. Moreno, G. Capella, G. Rennert, S. B. Gruber, Smoking, gender, and ethnicity predict somatic BRAF mutations in colorectal cancer, *Cancer Epidemiol. Biomark. Prev.* 19 (3) (2010) 838–843.
- [200] Y.J. Tsai, S.C. Huang, H.H. Lin, C.C. Lin, Y.T. Lan, H.S. Wang, S.H. Yang, J. K. Jiang, W.S. Chen, T.C. Lin, J.K. Lin, S.C. Chang, Differences in gene mutations according to gender among patients with colorectal cancer, *World J. Surg. Oncol.* 16 (1) (2018) 128.
- [201] F. Wang, S. Zhao, X. Shen, G. Zhu, R. Liu, D. Viola, R. Elisei, E. Puxeddu, L. Fugazzola, C. Colombo, B. Jarzab, A. Czarniecka, A.K. Lam, C. Mian, F. Vianello, L. Yip, G. Riesco-Eizaguirre, P. Santisteban, C.J. O'Neill, M.S. Sywak, R. Clifton-Bligh, B. Bendlova, V. Sykorova, Y. Wang, M. Xing, B.R.A.F. V600E, Confers male sex disease-specific mortality risk in patients with papillary thyroid cancer, *J. Clin. Oncol.* 36 (27) (2018) 2787–2795.
- [202] L. Mirandola, R. Wade, R. Verma, C. Pena, N. Hosiriluck, J.A. Figueroa, E. Cobos, M.R. Jenkins, M. Chiriva-Internati, Sex-driven differences in immunological responses: challenges and opportunities for the immunotherapies of the third millennium, *Int. Rev. Immunol.* 34 (2) (2015) 134–142.
- [203] S. Branford, D.T. Yeung, D.M. Ross, J.A. Prime, C.R. Field, H.K. Altamura, A. L. Yeoman, J. Georgievski, B.A. Jamison, S. Phillis, B. Sullivan, N.E. Briggs, M. Hertzberg, J.F. Seymour, J. Reynolds, T.P. Hughes, Early molecular response and female sex strongly predict stable undetectable BCR-ABL1, the criteria for imatinib discontinuation in patients with CML, *Blood* 121 (19) (2013) 3818–3824.
- [204] C. Gong, J.A. Krupka, J. Gao, N.F. Grigoropoulos, G. Giotopoulos, R. Asby, M. Screen, Z. Usheva, F. Cucco, S. Barrans, D. Painter, N.B.M. Zaini, B. Haupl, S. Bornelov, I. Ruiz De Los Mozos, W. Meng, P. Zhou, A.E. Blain, S. Forde, J. Matthews, M.G. Khim Tan, G.A.A. Burke, S.K. Sze, P. Beer, C. Burton, P. Campbell, V. Rand, S.D. Turner, J. Ule, E. Roman, R. Tooze, T. Oellerich, B.
- [205] J. Huntly, M. Turner, M.Q. Du, S.A. Samarajiwa, D.J. Hodson, Sequential inverse dysregulation of the RNA helicases DDX3X and DDX3Y facilitates MYC-driven lymphomagenesis, *Mol. Cell* 81 (19) (2021) 4059–4075, e11.
- [206] R.K. Hsieh, K.H. Lim, H.T. Kuo, C.Y. Tzen, M.J. Huang, Female sex and bronchioloalveolar pathologic subtype predict EGFR mutations in non-small cell lung cancer, *Chest* 128 (1) (2005) 317–321.
- [207] H.R. Kim, S.Y. Kim, C.H. Kim, S.H. Yang, J.C. Lee, C.M. Choi, I.I. Na, Sex-specific incidence of EGFR mutation and its association with age and obesity in lung adenocarcinomas: a retrospective analysis, *J. Cancer Res. Clin. Oncol.* 143 (11) (2017) 2283–2290.
- [208] S.P. Shriner, H.A. Bourdeau, C.T. Gubish, D.L. Tirpak, A.L. Davis, J.D. Luketich, J. M. Siegfried, Sex-specific expression of gastrin-releasing peptide receptor: relationship to smoking history and risk of lung cancer, *J. Natl. Cancer Inst.* 92 (1) (2000) 24–33.
- [209] D. Vallbohmer, J. Brabender, D.Y. Yang, K. Danenberg, P.M. Schneider, R. Metzger, A.H. Holscher, P.V. Danenberg, Sex differences in the predictive power of the molecular prognostic factor HER2/neu in patients with non-small-cell lung cancer, *Clin. Lung Cancer* 7 (5) (2006) 332–337.
- [210] T. Karantanos, S. Chaturvedi, E.M. Braunstein, J. Spivak, L. Resar, S. Karanika, D. M. Williams, O. Rogers, C.D. Gocke, A.R. Moliterno, Sex determines the presentation and outcomes in MPN and is related to sex-specific differences in the mutational burden, *Blood Adv.* 4 (12) (2020) 2567–2576.
- [211] C.D. Hurst, O. Alder, F.M. Platt, A. Droop, L.F. Stead, J.E. Burns, G.J. Burghel, S. Jain, L.J. Klimczak, H. Lindsay, J.A. Roulson, C.F. Taylor, H. Thygesen, A. J. Cameron, A.J. Ridley, H.R. Mott, D.A. Gordenin, M.A. Knowles, Genomic subtypes of non-invasive bladder cancer with distinct metabolic profile and female gender bias in KDM6A mutation frequency, *Cancer Cell* 32 (5) (2017) 701–715, e7.
- [212] S. Dogan, R. Shen, D.C. Ang, M.L. Johnson, S.P. D'Angelo, P.K. Paik, E. B. Brzostowski, G.J. Riely, M.G. Kris, M.F. Zakowski, M. Ladanyi, Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers, *Clin. Cancer Res.* 18 (22) (2012) 6169–6177.
- [213] Y.D. Kim, H.R. Park, M.H. Song, D.H. Shin, C.H. Lee, M.K. Lee, S.Y. Lee, Pattern of cancer/testis antigen expression in lung cancer patients, *Int. J. Mol. Med.* 29 (4) (2012) 656–662.
- [214] S. Benvenuti, M. Frattini, S. Arena, C. Zanon, V. Cappelletti, D. Coradini, M. G. Daidone, S. Pilotti, M.A. Pierotti, A. Bardelli, PIK3CA cancer mutations display gender and tissue specificity patterns, *Hum. Mutat.* 29 (2) (2008) 284–288.
- [215] D. Freudenstein, C. Litchfield, F. Caramia, G. Wright, B.J. Solomon, D. Ball, S. P. Keam, P. Neeson, Y. Haupt, S. Haupt, TP53 status, patient sex, and the immune response as determinants of lung cancer patient survival, *Cancers* 12 (6) (2020).
- [216] S. Haupt, F. Caramia, A. Herschthal, T. Soussi, G. Lozano, H. Chen, H. Liang, T. P. Speed, Y. Haupt, Identification of cancer sex-disparity in the functional integrity of p53 and its X chromosome network, *Nat. Commun.* 10 (1) (2019) 5385.
- [217] J. Van der Meulen, V. Sanghvi, K. Mavrakis, K. Durinck, F. Fang, F. Matthijssens, P. Rondou, M. Rosen, T. Pieters, P. Vandenberghe, E. Delabesse, T. Lammens, B. De Moerloose, B. Menten, N. Van Roy, B. Verhasselt, B. Poppe, Y. Benoit, T. Taghon, A.M. Melnick, F. Speleman, H.G. Wendel, P. Van, Vlierberghe, The H3K27me3 demethylase UTX is a gender-specific tumor suppressor in T-cell acute lymphoblastic leukemia, *Blood* 125 (1) (2015) 13–21.