Seminars in Immunopathology (2019) 41:203–211
https://doi.org/10.1007/s00281-018-0727-4

REVIEW

Sexual dimorphism in hepatitis B and C and hepatocellular carcinoma

Nico Buettner[1] · Robert Thimme[1]

Received: 11 October 2018 / Accepted: 4 November 2018 / Published online: 29 November 2018

Abstract

The incidence of viral hepatitis B or C (HBV/HCV) infection and hepatocellular carcinoma is higher in male compared to female populations, showing a faster disease progression and results in a worse overall survival. Indeed, women are in general better protected from viral infections and show a lower risk of death from malignant cancer in comparison to men. Females mount stronger innate and adaptive immune responses than males, and therefore, most of the autoimmune diseases occur predominantly in females. Next to occupational and/or behavioral factors, cellular and molecular differences between the two sexes contribute to this observation. In this review, we will discuss underlying mechanisms that are important for the observed sex-related differences in liver diseases. A better appreciation of these differences between the two sexes might be of value for better and gender-specific treatment options.

Keywords Sexual dimorphism · Hepatitis B virus · Hepatitis C virus · Hepatocellular carcinoma · Liver disease

Introduction

The liver is a good example for a sexually dimorphic organ. Transcriptome and proteome studies have indicated that up to 70% of the genes in the liver may have characteristics of sex specificity. Therefore, the liver appears to be, together with the brain, the organ most sexually differentiated in mammals [1]. Hepatocellular carcinoma (HCC) and, to a lesser degree, intrahepatic cholangiocarcinoma [2] are more common in males, whereas autoimmune liver diseases are more common in females [3]. Furthermore, it has been reported that females in general have a more robust immune response compared to their male counterparts. This has also been argued as the reason for the significantly longer life spans of women compared to men [4]. This suggests that differences in immunity may be responsible for some part of the sexual dichotomy [5]. Innate immune cell frequencies such as monocytes, macrophages, and dendritic cells are higher in females. In addition, immune cells of females exhibit a 10-fold higher expression of Toll-like receptors (TLRs) compared to males [6]. With regard to the adaptive immune system, the T cell composition differs between sexes and age groups [4, 7]. Indeed, females have higher CD4+ T cell counts, whereas males have higher CD8+ T cell frequencies [8]. But also, cytokine production and antibody responses differ between sexes [9–11].

A new aspect of sex disparity has been recognized with the emergence of immunotherapy in oncology. For example, sex differences in malignant melanoma are well established as there is a higher incidence in men [12] and survival is better in females [13]. Tumors from men may harbor statistically more genetic alterations than female tumors after adjustment for age, stage, and smoking status [14, 15]. In this context, it is also interesting to note that sex hormones regulate the expression of PD1 and PD-1L [16–18]. Therefore, the authors from a recent meta-analysis posed the question whether the efficacy of checkpoint inhibitor blockade might be different between sexes. Interestingly, men seemed to respond better to checkpoint blockade than women [19]. The authors have discussed three main mechanisms that could be responsible for this difference. First, the pronounced anti-tumor immunity in women may lead to an increased tumor immune escape that may lead to immunotherapy resistance. Second, the higher mutational burden in males may lead to a better tumor recognition from the immune system, and finally, sex-related behavior (e.g.,

This article is a contribution to the special issue on Sexual Dimorphism in Immunity - Guest Editors: Hanna Lotter and Marcus Altfed

✉ Robert Thimme
robert.thimme@uniklinik-freiburg.de

[1] Department of Medicine II (Gastroenterology, Hepatology, Endocrinology and Infectious Diseases), Medical Center University of Freiburg, Faculty of Medicine, University of Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany

tobacco smoking, sunlight exposure) may contribute to this difference. However, the meta-analysis was criticized for several biases (heterogeneous study populations, selection bias, publication bias, etc.) so that in conclusion, the results of this study should be interpreted with caution and are still of limited value for clinical practice until confirmed in future studies.

Overall, two major mechanisms seem to be responsible for the sex disparity: First, the effects of genes encoded on sex chromosomes; and second, the modifying effects of sex hormones.

The most obvious difference between the two sexes resides in the X and Y chromosomes. The X chromosome is known to contain the largest number of immune-regulating genes of the whole human genome [20]. Copy number variations or structural abnormalities of the X chromosome lead to genetic disorders like the Turner syndrome (X0) and the Klinefelter syndrome (XXY) and both are often associated with autoimmune diseases [20–22]. Examples for X-linked genes are summarized in Fig. 1. X-linked genes are, for example, interleukin 2-/-3-/-9-/-13-receptors, X-inactive–specific transcript (XIST), Toll-like receptors (TLR) 7/8, and Forkhead box P3 (FOXP3). An example for a Y-linked gene is sex-determining region Y (SRY). Different gene expression in XX and XY cells is regulated with mechanisms like X chromosome inactivation, epigenetic modifications, or Y-chromosome polymorphisms [23].

Sex hormones are responsible to some extent for the observed sex disparity [24]. The liver is especially responsive to sex hormones that regulate gene expression, immune responses, and metabolism. The androgen receptor (AR), progesterone receptors (PR), and estrogen receptors (ER) all belong to the family of nuclear receptors. Therefore, sex hormones, the androgen testosterone in males, and estrogens (estrone, 17ß-estradiol, estriol) and progesterone in females mediate gene expression including promoter activation or epigenetic modifications. Estrogens bind to the nuclear ER α and ß, which are expressed in varying degrees by different cell types and play a vital role in several signaling pathways. ER can mediate anti-inflammatory signaling as well as pro-inflammatory signaling and are expressed in various lymphoid tissue cells, lymphocytes, macrophages, and DCs with ERα preferentially expressed on T cells and ERβ mainly upregulated in B cells [25]. Similar mechanisms apply for progesterone signaling with transcriptional regulation through the PR α and ß isoforms. Progesterone also mediates stimulatory and suppressive roles in immune responses. PR are primarily expressed by T and NK cells, but also by dendritic and mesenchymal stem cells, where they suppress Th1 cytokine secretion and increase Th2 cytokine secretion [26, 27]. Suppression of T cell cytotoxicity, as well as regulatory T cell (Treg) proliferation, is also mediated by progesterone [28]. During pregnancy, progesterone enhances immunomodulatory functions of mesenchymal stem cells through upregulation of PGE-2 and IL-6, which is essential to maintain the fetal-maternal interface [27]. Cancer formation is supported by progesterone through induction of cell proliferation by cell-intrinsic, cyclin D1–dependent mechanism or a paracrine, RANKL-dependent mechanism [29–31]. The androgen receptor is stimulated by dihydrotestosterone, the active metabolite of testosterone, and has effects on the immune system by regulating neutrophil, T and B cell function, and development [32]. In general, androgens occur in higher concentrations in men and suppress immune cell activation.

Sexual dimorphism in:

Hepatitis B virus infection

The sex disparity of HBV-related liver diseases has been noticed for a long time [33]. Some of the differences have been attributed to effects of the sex hormones, e.g., by directly regulating HBV transcription, HBV entry, viral integration, and by modulating the immune response to HBV infection. The estrogen axis exerts protective effects in HBV infection and this is reflected by the fact that exposure to estrogen in female HBV carriers, such as exposure to oral contraceptives or postmenopausal hormone replacement therapy, is associated with a lower risk of HCC development [34]. Estrogen can suppress hepatic fibrosis [35], can act as an endogenous antioxidant by reducing reactive oxidant species [36], and can modulate cytokine production to protect females from inflammation-induced liver injury [37].

One of the best studied molecular explanations for the difference in the outcome of HBV infection in men and women is direct binding of the estrogen receptor and androgen receptor to binding sites within HBV enhancer I. For example, the estrogen receptor prevents binding of hepatocyte nuclear factor 4 α transcription factor to bind to HBV enhancer I, thus inhibiting HBV transcription [38]. Vice versa, the androgen receptor can bind directly to a specific response element within HBV enhancer I and can increase overall HBV transcription [39] (see Fig. 1). On the other hand, HBx was shown to enhance hepatic AR activity which creates a positive feedback loop between AR and HBx leading to more active viral replication and higher oncogenic potential in male HBV patients [40, 41]. Estrogen additionally affects viral entry. Indeed, estradiol represses expression of the major HBV entry receptor sodium taurocholate cotransporting polypeptide (NTCP) in liver cells through ERα and thus inhibits viral entry, restricts infection, and spreads in the liver [42, 43].

The overall HBV integration frequency is much higher in tumor genomes of males compared to females, with a significant enrichment of integration into chromosome 2 and 17 [44]. Many genes in chromosome 17p are known to play important roles in hepatocarcinogenesis including TP53. The influence of sex hormones on HBV chromosomal integration

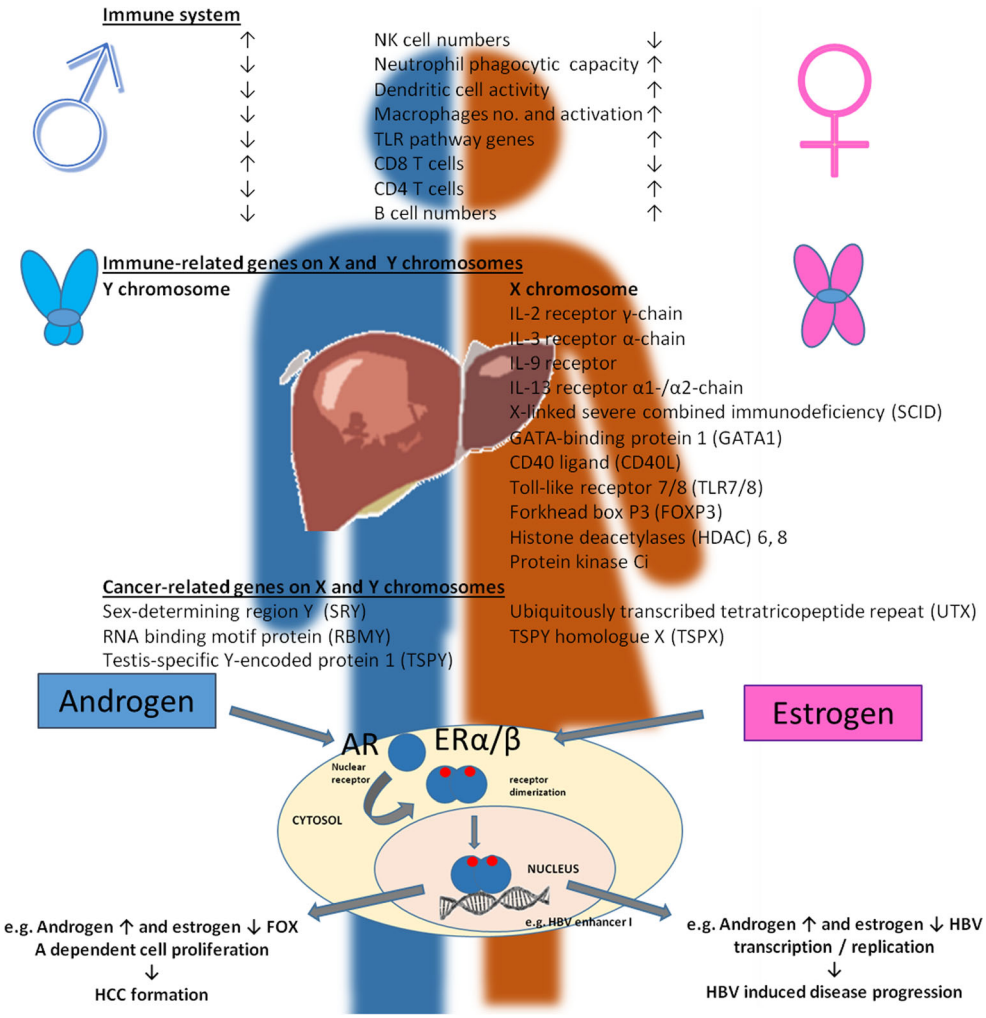

Fig. 1 Examples for sex-related differences in immunity, gene expression, and hormone actions important for liver disease like hepatitis B and C and hepatocellular carcinoma

though is still poorly understood and warrants further investigation.

Sex hormones also play a crucial role in the regulation of the immune system and immune responses to HBV. This is reflected by the fact that, for example, viral vaccines against HAV and HBV exhibit higher antibody titers but also stronger side effects in young females following immunization [45]. Furthermore, seroconversion from HBeAg to anti-HBe and HBsAg to anti-HBs is more often observed in females [46]. Also pointing toward a sex-dependent role of the immune system, the baseline serum HBV titer was reported to be significantly associated with male sex in chronic HBV patients [47]. One example that demonstrates the influence of sex hormones on the HBV-specific immune response is a single nucleotide polymorphism in the gene for ERα that was associated with persistent HBV infection [48]. In addition, androgen was reported to exert immunosuppressive effects on the development and activation of T cells [32]. However, overall, the impact of sex hormones on HBV-specific immunity is not well characterized except from general mechanisms known to alter the immune system [49, 50].

Hepatitis C virus infection

Similar to HBV infection, HCV infection affects men more often than women. HCV is more commonly reported among men than women, with a male-to-female ratio of nearly 2 to 1 [51]. HCV infection is cleared spontaneously more often in females than in males. Next to IL28b and HCV genotype [52], female sex has also been reported as an independent predictor of clearance in acute HCV [53, 54], although the effect is less pronounced. Chronic infection will develop in about 70–80% of men and ~ 60% of women [55, 56] depending on genotype but independent of age or mode of acquisition.

But, not only clearance of infection but also disease progression is dependent on sex [57–60]. As in hepatitis B virus infection, differences in disease progression are postulated to be linked to the protective effects of estrogen. For example, the rate of disease progression changes over time in women. Postmenopausal women have increased rates of fibrosis compared with women of reproductive age due to the loss of protective effects of estrogen. Additionally, age-matched men have more severe fibrosis than women of reproductive

age, premenopause, and in early menopause, and this difference is lost in late menopause [61]. With a slower disease progression, it is obvious that the complications from HCV infection as liver cirrhosis and HCC mainly affect men and, in a lower proportion, women [62]. Clearly, alcohol consumption may also contribute to disease progression as men are more likely to engage in heavy drinking than women [63, 64].

Sex differences have also been reported for treatment-induced clearance of the virus. An increased and sustained clearance of the virus from the blood stream (sustained virological response, SVR) has been reported for women after treatment with pegylated interferon and ribavirin in a randomized study [62]. Women may also have a higher SVR with higher doses of peginterferon [65]. In a subgroup of young women in reproductive age with normal transaminases and easy to treat genotype, a regimen with ribavirin and peginterferon achieved a nearly 100% chance to reach SVR [66]. In contrast to that, early menopause was associated with a lack of response to antiviral therapy, again indicating a role of estrogen in that setting [67]. In a subsequent study, the addition of raloxifene, an oral selective estrogen receptor modulator, to pegylated interferon and ribavirin improved SVR rates in the treatment of postmenopausal women but this treatment approach was not followed up due to the development and licensing of direct-acting antiviral agents (DAAs) [68]. Indeed, with the introduction of DAAs, demographic factors have lost its importance on overall rates of cure, as response rates for HCV therapy have increased tremendously.

Hepatocellular adenoma

Hepatocellular adenoma (HCA) is a rare benign tumor of the liver with an estimated incidence of 3–4 per 100,000 women [69]. It is rarer in men, children, and women over 65 years. The female:male ratio was reported to be 10:1, so precisely the reverse to malignant HCC. Many studies have documented the role of sex hormones in HCA through exogenous factors such as oral contraceptive pills in women or androgen intake in men. Recently, the HCA prevalence was reported to increase mainly because of rising prevalence of obesity and the metabolic syndrome [70] which is associated with higher estrogen levels.

HCAs encompass mainly three molecular subtypes. First, HCA inactivated for HNF-1α, second inflammatory adenomas which are heterogeneous regarding the variety of gene mutations, and finally ß-catenin–activated HCA. Molecular subtyping has not yet had an impact on clinical practice; however, ß-catenin–activated HCAs have been found to be more common in men and so display a higher risk of malignant transformation. The potential for malignant transformation of HCAs is minor for women, but men have a very high risk of progression to HCC [71]. This is also reflected by the different treatment strategies of HCA in males and females. Indeed, because of the significantly higher incidence of malignant transformation in men [72], resection or curative treatment is recommended for all HCA diagnosed in men irrespective of size. In women, risk for rupture, bleeding, or malignant transformation is rare in HCAs smaller than 5 cm on baseline scan. Here, resection is only recommended in lesions bigger than 5 cm or if there is a significant increase in size [73].

Hepatocellular carcinoma

The male to female ratio averages between 2:1 and 4:1 in patients with HCC, and this discrepancy is also observed in mice models [74]. Interestingly, the sex disparity is also existent in childhood malignancy hepatoblastoma [75]. Male sex is considered to be an independent risk factor for poor outcome of hepatocellular carcinoma (HCC) and females are more likely to be treated with curative intention, e.g., surgical resection or transplantation [76]. HBV-related HCC prevalence is much higher in men than in women, and male-to-female ratio for patients with HBV-related HCC has been reported to be even higher than that of patients with HCV-related HCC [77]. This effect might be explained by the mechanisms mentioned above but also by regional particularities like, e.g., a higher prevalence of HBV and HCV infection among men.

A large part of women's resistance to HCC can be explained by the action of hormones, as evidenced by the major increase in HCC incidence in postmenopausal women. Noteworthy, all sex-related protein hormones, androgen, progesterone, estrogen, prolactin (PRL), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and growth hormone (GH) play a role in HCC development. Both androgens (i.e., anabolic steroids) and estrogens (e.g., oral contraceptives) are able to induce benign liver tumors (i.e., adenomas) and ultimately lead to HCC formation in individuals without underlying liver disease. The effect on cancer development is mainly thought to occur on the DNA level, as lipid-soluble sex steroid hormones enter the plasma membrane and directly interact with intracellular receptors. AR and ERα act in an antagonistic manner through differential regulation of gene expression. A central role for the transcription factors Foxa1/Foxa2 in controlling estrogen and androgen signaling was proposed [78] (see Fig. 1). Indeed, certain single nucleotide polymorphisms at FOXA2 binding sites reduce its affinity with ERα and sexually dimorphic HCC is completely reversed in Foxa1- and Foxa2-deficient mice. Interestingly, it was suggested that estrogens act as a general suppressor of HCC by reducing the production of the inflammatory mediator IL-6 [74]. Indeed, ablation of IL-6 abolishes the sex differences in hepatocarcinogenesis in mice and IL-6 has been reported to be a target of the FOXA transcription factor [79]. Overall, estrogens can exert most diverse tumorigenic and anti-tumorigenic properties in different cancer models. It is

required for organ morphogenesis [80–82] but ERß-activation has been shown to be beneficial in multiple cancer models. For example, sustained ERß expression is a favorable prognostic marker in renal cell cancer [83] and certain polymorphisms in the promoter of the ERß gene or within the EGFR gene, which interacts with sex steroid hormone receptors, are associated with increased patient survival in colorectal cancer [84, 85]. Molecular data indicate that androgens contribute to HCC development by acting as a tumor promoter by upregulation of beta-catenin/TCF signaling and via induction of DNA damage and oxidative stress [74, 86, 87]. Several other effects of sex steroid hormones relate to regeneration or homeostasis of organs, e.g., through increased stem cell self-renewal induced by estrogens [88, 89], cancer-associated fibroblasts [90], angiogenesis [91–93], inflammation, the immune system [94], and metabolism.

In general, an intact pituitary gland is necessary for the action of androgens and estrogens that can be seen by the fact that hypophysectomy abolishes sex-dependent differences in HCC. For example, mouse studies revealed that PRL protects females from liver tumorigenesis by constraining tumor-promoting liver inflammation by inhibition of c-Myc activation and proliferation [50]. When stimulating hepatocytes with anterior pituitary hormones, the effect of PRL is much bigger than for GH, but GH has also been implicated in liver cancer. GH was identified as a "feminizing factor" in the 1980s, and the pattern of secretion and concentrations of the hormone are a prerequisite for hepatic steroid metabolism and gene regulation [95].

A large body of evidence has shown a direct involvement of X chromosome–encoded genes on cancer formation. The X chromosome is highly enriched in immune-related genes and there are several X-linked microRNAs (miRNAs) located within an estrogen response element. For example, the X-inactivation process is regulated by XIST (X-inactive–specific transcript) and counteracts differences in X chromosome gene dosage. Loss or upregulation of XIST has been reported for several cancer entities [96]. But several other oncogenes [97] and tumor suppressors like ubiquitously transcribed tetratricopeptide repeat X chromosome (UTX) [98] are located on the X chromosome and have implications for cancer development.

Alterations on the Y chromosome are also common in malignancies. Loss of Y chromosome has been reported for several malignancies but it is not clear if this is a cause or a consequence of malignant transformation. Especially, sex-determining region Y (SRY) expression confers malignant properties in HCC [99]. SRY upregulates Sgf29 gene expression, which suppresses c-Myc–mediated malignant transformation. Furthermore, SRY expression increases multiple stem cell factors and ablation of SRY can impair the development of HCC [100]. Testis-specific Y-encoded protein 1 (TSPY) is another Y-linked gene reported to have an impact on HCC formation [101]. TSPY is encoded by the Y chromosome and is co-expressed with AR in HCC cell lines. Therefore, a cross-talk between AR and TSPY was suggested [102]. TSPY is an oncogene with known functions in germ-cell differentiation, mitosis, and meiosis [103], and promotes cell proliferation and oncogenesis, whereas its X-located homolog, TSPY homolog X (TSPX), retards cell cycle and oncogenic progression. TSPX promotes proteasomal degradation of hepatitis B virus–encoded X oncoprotein and has been suggested to be a tumor suppressor in virus-associated HCC [104]. Finally, RNA binding motif protein (RBMY) has been suggested to be a candidate oncogene specific for male liver cancer [105], and similar to TSPY, seems to be involved in the regulation of androgen receptor activity and contributes to male predominance of HCC [106].

Several studies have tried to evaluate the role of anti-estrogen therapy (e.g., tamoxifen) in patients with HCC. Since ERs are present in approximately one third of HCCs and since experimental data has shown estrogen-dependent HCC growth, it has been suggested that these tumors could potentially benefit from ER blockade. Several small, prospective randomized trials and a meta-analysis of tamoxifen in patients with advanced HCC have failed to show a survival benefit or improved functional status [107–109]. As tamoxifen also acts as an inhibitor of p-glycoprotein, the multidrug resistance gene product, the addition of tamoxifen to chemotherapy has also failed to show any benefit in several small studies [37, 108]. Megestrol, a progestin with progestogenic and weak partial androgenic activity, has even shown a trend toward worse overall survival in the treated group [37]. Although androgens contribute to HCC development, all antiandrogen clinical trials have failed in advanced HCC [74].

Conclusion

An important question is whether we need to treat males and females differently, in order to achieve the long-term goal of personalized medicine for more effective prevention and treatment of liver diseases. The answer is: not yet. Future studies must identify the precise interactions among hormones, genes, and environmental factors mediating sex differences. The liver is a good example for a sexually dimorphic organ and the best treatment for liver disease might be different in the two sexes. At the moment, except from HCA, most of the data and knowledge about the molecular basis of sex-related differences in liver disease are not sufficient enough to give us substantial proof for clinical application. A starting point for such efforts could be to acknowledge that sex disparity has to be taken into account when mice models of chronic viral infection or liver cancer are studied. For example, researchers use mainly male animals in mouse models of liver cancer, because incidence is higher and it is thus cheaper to use male mice. Similarly for HBV mouse models, depletion of serum androgen or estrogen could compensate for observed sex

differences [1, 33, 38, 39, 41, 110–116]. Additionally, many studies have shown that women respond differently to several drugs compared to men [117]. Sex-based differences in pharmacokinetics, e.g., variations in gastric acid secretion, blood flow, and drug/plasma protein binding profiles, might additionally be responsible for these differences [118]. Therefore, designing sex-balanced clinical trials is becoming increasingly important. In summary, much more work has to be done in the future in order to focus on a more gender-specific approach so that the understanding of sex differences can have an impact on personalized treatment strategies.

References

1. Yang X, Schadt EE, Wang S, Wang H, Arnold AP, Ingram-Drake L, Drake TA, Lusis AJ (2006) Tissue-specific expression and regulation of sexually dimorphic genes in mice. Genome Res 16(8): 995–1004
2. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, Pawlik TM, Gores GJ (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 60(6):1268–1289
3. European Association for the Study of the, L (2015) EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol 63(4):971–1004
4. Michaels RM, Rogers KD (1971) A sex difference in immunologic responsiveness. Pediatrics 47(1):120–123
5. Li Z, Gadue P, Chen K, Jiao Y, Tuteja G, Schug J, Li W, Kaestner KH (2012) Foxa2 and H2A.Z mediate nucleosome depletion during embryonic stem cell differentiation. Cell 151(7):1608–1616
6. Scotland RS, Stables MJ, Madalli S, Watson P, Gilroy DW (2011) Sex differences in resident immune cell phenotype underlie more efficient acute inflammatory responses in female mice. Blood 118(22):5918–5927
7. Wikby A, Månsson IA, Johansson B, Strindhall J, Nilsson SE (2008) The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age. Biogerontology 9(5):299–308
8. Abdullah M, Chai PS, Chong MY, Tohit ERM, Ramasamy R, Pei CP, Vidyadaran S (2012) Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell Immunol 272(2):214–219
9. Hewagama A, Patel D, Yarlagadda S, Strickland FM, Richardson BC (2009) Stronger inflammatory/cytotoxic T-cell response in women identified by microarray analysis. Genes Immun 10(5): 509–516
10. Sankaran-Walters S, Macal M, Grishina I, Nagy L, Goulart L, Coolidge K, Li J, Fenton A, Williams T, Miller MK, Flamm J, Prindiville T, George M, Dandekar S (2013) Sex differences matter in the gut: effect on mucosal immune activation and inflammation. Biol Sex Differ 4(1):10
11. Furman D, Hejblum BP, Simon N, Jojic V, Dekker CL, Thiebaut R, Tibshirani RJ, Davis MM (2014) 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):869–874
12. Lee JH, Wang C, Kim CH (2009) FoxP3+ regulatory T cells restrain splenic extramedullary myelopoiesis via suppression of hemopoietic cytokine-producing T cells. J Immunol 183(10):6377–6386
13. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, McCullough M, Patel AV, Ma J, Soerjomataram I, Flanders WD, Brawley OW, Gapstur SM, Jemal A (2018) Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 68(1):31–54
14. Xiao D, Pan H, Li F, Wu K, Zhang X, He J (2016) Analysis of ultra-deep targeted sequencing reveals mutation burden is associated with gender and clinical outcome in lung adenocarcinoma. Oncotarget 7(16):22857–22864
15. Podolskiy DI, Lobanov AV, Kryukov GV, Gladyshev VN (2016) Analysis of cancer genomes reveals basic features of human aging and its role in cancer development. Nat Commun 7:12157
16. Wang C, Dehghani B, Li Y, Kaler LJ, Proctor T, Vandenbark AA, Offner H (2009) Membrane estrogen receptor regulates experimental autoimmune encephalomyelitis through up-regulation of programmed death 1. J Immunol 182(5):3294–3303
17. Gupta SK, Kizilbash SH, Carlson BL, Mladek AC, Boakye-Agyeman F, Bakken KK, Pokorny JL, Schroeder MA, Decker PA, Cen L, Eckel-Passow JE, Sarkar G, Ballman KV, Reid JM, Jenkins RB, Verhaak RG, Sulman EP, Kitange GJ, Sarkaria JN (2016) Delineation of MGMT hypermethylation as a biomarker for veliparib-mediated temozolomide-sensitizing therapy of glioblastoma. J Natl Cancer Inst 108(5). https://doi.org/10.1093/jnci/djv369
18. Gupta S, Artomov M, Goggins W, Daly M, Tsao H (2015) Gender disparity and mutation burden in metastatic melanoma. J Natl Cancer Inst 107(11):djv221
19. Huang MT, Dai YS, Chou YB, Juan YH, Wang CC, Chiang BL (2009) Regulatory T cells negatively regulate neovasculature of airway remodeling via DLL4-Notch signaling. J Immunol 183(7): 4745–4754
20. Bianchi I, Lleo A, Gershwin ME, Invernizzi P (2012) The X chromosome and immune associated genes. J Autoimmun 38(2–3):J187–J192
21. Cacciari E, Masi M, Fantini MP, Licastro F, Cicognani A, Pirazzoli P, Villa MP, Specchia F, Forabosco A, Franceschi C, Martoni L (1981) Serum immunoglobulins and lymphocyte subpopulations derangement in Turner's syndrome. J Immunogenet 8(5):337–344
22. Kocar IH et al (2000) The effect of testosterone replacement treatment on immunological features of patients with Klinefelter's syndrome. Clin Exp Immunol 121(3):448–452
23. Ahn JH, Lee JT (2008) X chromosome: X inactivation. Nat Educ 1(1):24
24. Waxman DJ, Holloway MG (2009) Sex differences in the expression of hepatic drug metabolizing enzymes. Mol Pharmacol 76(2): 215–228
25. Phiel KL, Henderson RA, Adelman SJ, Elloso MM (2005) Differential estrogen receptor gene expression in human peripheral blood mononuclear cell populations. Immunol Lett 97(1):107–113
26. Butts CL, Shukair SA, Duncan KM, Bowers E, Horn C, Belyavskaya E, Tonelli L, Sternberg EM (2007) Progesterone inhibits mature rat dendritic cells in a receptor-mediated fashion. Int Immunol 19(3):287–296
27. Zhao X, Liu L, Liu D, Fan H, Wang Y, Hu Y, Hou Y (2012) Progesterone enhances immunoregulatory activity of human mesenchymal stem cells via PGE2 and IL-6. Am J Reprod Immunol 68(4):290–300
28. Enninga EA et al (2014) Immunomodulatory effects of sex hormones: requirements for pregnancy and relevance in melanoma. Mayo Clin Proc 89(4):520–535
29. Brisken C (2013) Progesterone signalling in breast cancer: a neglected hormone coming into the limelight. Nat Rev Cancer 13(6):385–396

30. Simon MS, Chlebowski RT, Wactawski-Wende J, Johnson KC, Muskovitz A, Kato I, Young A, Hubbell FA, Prentice RL (2012) Estrogen plus progestin and colorectal cancer incidence and mortality. J Clin Oncol 30(32):3983–3990
31. Skjefstad K, Richardsen E, Donnem T, Andersen S, Kiselev Y, Grindstad T, Hald SM, al-Shibli K, Bremnes RM, Busund LT, al-Saad S (2015) The prognostic role of progesterone receptor expression in non-small cell lung cancer patients: gender-related impacts and correlation with disease-specific survival. Steroids 98:29–36
32. Lai JJ, Lai KP, Zeng W, Chuang KH, Altuwaijri S, Chang C (2012) Androgen receptor influences on body defense system via modulation of innate and adaptive immune systems: lessons from conditional AR knockout mice. Am J Pathol 181(5):1504–1512
33. Wang SH, Chen PJ, Yeh SH (2015) Gender disparity in chronic hepatitis B: mechanisms of sex hormones. J Gastroenterol Hepatol 30(8):1237–1245
34. Yu MW, Chang HC, Chang SC, Liaw YF, Lin SM, Liu CJ, Lee SD, Lin CL, Chen PJ, Lin SC, Chen CJ (2003) Role of reproductive factors in hepatocellular carcinoma: impact on hepatitis B- and C-related risk. Hepatology 38(6):1393–1400
35. Yasuda M, Shimizu I, Shiba M, Ito S (1999) Suppressive effects of estradiol on dimethylnitrosamine-induced fibrosis of the liver in rats. Hepatology 29(3):719–727
36. Sumi D, Hayashi T, Matsui-Hirai H, Jacobs AT, Ignarro LJ, Iguchi A (2003) 17beta-estradiol inhibits NADPH oxidase activity through the regulation of p47phox mRNA and protein expression in THP-1 cells. Biochim Biophys Acta 1640(2–3):113–118
37. Dorak MT, Karpuzoglu E (2012) Gender differences in cancer susceptibility: an inadequately addressed issue. Front Genet 3:268
38. Wang SH et al (2012) Estrogen receptor alpha represses transcription of HBV genes via interaction with hepatocyte nuclear factor 4alpha. Gastroenterology 142(4):989–998 e4
39. Wang SH, Yeh SH, Lin WH, Wang HY, Chen DS, Chen PJ (2009) Identification of androgen response elements in the enhancer I of hepatitis B virus: a mechanism for sex disparity in chronic hepatitis B. Hepatology 50(5):1392–1402
40. Chiu CM, Yeh SH, Chen PJ, Kuo TJ, Chang CJ, Chen PJ, Yang WJ, Chen DS (2007) Hepatitis B virus X protein enhances androgen receptor-responsive gene expression depending on androgen level. Proc Natl Acad Sci U S A 104(8):2571–2578
41. Yang WJ, Chang CJ, Yeh SH, Lin WH, Wang SH, Tsai TF, Chen DS, Chen PJ (2009) Hepatitis B virus X protein enhances the transcriptional activity of the androgen receptor through c-Src and glycogen synthase kinase-3beta kinase pathways. Hepatology 49(5):1515–1524
42. Ni Y, Lempp FA, Mehrle S, Nkongolo S, Kaufman C, Fälth M, Stindt J, Königer C, Nassal M, Kubitz R, Sültmann H, Urban S (2014) Hepatitis B and D viruses exploit sodium taurocholate cotransporting polypeptide for species-specific entry into hepatocytes. Gastroenterology 146(4):1070–1083
43. Cao J, Wood M, Liu Y, Hoffman T, Hyde J, Park-Sarge OK, Vore M (2004) Estradiol represses prolactin-induced expression of Na+/taurocholate cotransporting polypeptide in liver cells through estrogen receptor-alpha and signal transducers and activators of transcription 5a. Endocrinology 145(4):1739–1749
44. Zhao LH, Liu X, Yan HX, Li WY, Zeng X, Yang Y, Zhao J, Liu SP, Zhuang XH, Lin C, Qin CJ, Zhao Y, Pan ZY, Huang G, Liu H, Zhang J, Wang RY, Yang Y, Wen W, Lv GS, Zhang HL, Wu H, Huang S, Wang MD, Tang L, Cao HZ, Wang L, Lee TP, Jiang H, Tan YX, Yuan SX, Hou GJ, Tao QF, Xu QG, Zhang XQ, Wu MC, Xu X, Wang J, Yang HM, Zhou WP, Wang HY (2016) Genomic and oncogenic preference of HBV integration in hepatocellular carcinoma. Nat Commun 7:12992
45. Klein SL, Pekosz A (2014) Sex-based biology and the rational design of influenza vaccination strategies. J Infect Dis 209(Suppl 3):S114–S119
46. Zacharakis GH, Koskinas J, Kotsiou S, Papoutselis M, Tzara F, Vafeiadis N, Archimandritis AJ, Papoutselis K (2005) Natural history of chronic HBV infection: a cohort study with up to 12 years follow-up in North Greece (part of the Interreg I-II/EC-project). J Med Virol 77(2):173–179
47. Chen CJ, Yang HI, Iloeje UH, The REVEAL-HBV Study Group (2009) Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. Hepatology 49(5 Suppl):S72–S84
48. Deng G, Zhou G, Zhai Y, Li S, Li X, Li Y, Zhang R, Yao Z, Shen Y, Qiang B, Wang Y, He F (2004) Association of estrogen receptor alpha polymorphisms with susceptibility to chronic hepatitis B virus infection. Hepatology 40(2):318–326
49. Ghosh S, Klein RS (2017) Sex drives dimorphic immune responses to viral infections. J Immunol 198(5):1782–1790
50. Klein SL, Flanagan KL (2016) Sex differences in immune responses. Nat Rev Immunol 16(10):626–638
51. ECDC (2016) Hepatitis C - annual epidemiological report for 2016. [cited 2018; In 2016, 33 860 cases of hepatitis C were reported in 29 EU/EEA Member States, corresponding to a crude rate of 7.4 cases per 100 000 population.]. Available from: https://ecdc.europa.eu/en/publications-data/hepatitis-c-annual-epidemiological-report-2016
52. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'hUigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, Goedert JJ, Kirk GD, Donfield SM, Rosen HR, Tobler LH, Busch MP, McHutchison JG, Goldstein DB, Carrington M (2009) Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 461(7265):798–801
53. Wang CC, Krantz E, Klarquist J, Krows M, McBride L, Scott EP, Shaw-Stiffel T, Weston SJ, Thiede H, Wald A, Rosen HR (2007) Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. J Infect Dis 196(10):1474–1482
54. Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, Morris MD, Hajarizadeh B, Amin J, Cox AL, Kim AY, McGovern BH, Schinkel J, George J, Shoukry NH, Lauer GM, Maher L, Lloyd AR, Hellard M, Dore GJ, Prins M, the InC3 Study Group (2014) The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology 59(1):109–120
55. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ (2006) The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 144(10):705–714
56. Bakr I, Rekacewicz C, el Hosseiny M, Ismail S, el Daly M, el-Kafrawy S, Esmat G, Hamid MA, Mohamed MK, Fontanet A (2006) Higher clearance of hepatitis C virus infection in females compared with males. Gut 55(8):1183–1187
57. Poynard T, Bedossa P, Opolon P (1997) Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 349(9055):825–832
58. Kenny-Walsh E (1999) Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 340(16):1228–1233
59. Wiese M, Grüngreiff K, Güthoff W, Lafrenz M, Oesen U, Porst H, East German Hepatitis C Study Group (2005) Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany–a 25-year multicenter study. J Hepatol 43(4):590–598
60. Wiese M, Fischer J, Löbermann M, Göbel U, Grüngreiff K, Güthoff W, Kullig U, Richter F, Schiefke I, Tenckhoff H, Zipprich A, Berg T, Müller T, for the East German HCV Study Group (2014) Evaluation of liver disease progression in the

German hepatitis C virus (1b)-contaminated anti-D cohort at 35 years after infection. Hepatology 59(1):49–57
61. Villa E, Vukotic R, Cammà C, Petta S, di Leo A, Gitto S, Turola E, Karampatou A, Losi L, Bernabucci V, Cenci A, Tagliavini S, Baraldi E, de Maria N, Gelmini R, Bertolini E, Rendina M, Francavilla A (2012) Reproductive status is associated with the severity of fibrosis in women with hepatitis C. PLoS One 7(9): e44624
62. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling MH, Albrecht JK (2001) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 358(9286):958–965
63. Wilsnack RW, Wilsnack SC, Kristjanson AF, Vogeltanz-Holm ND, Gmel G (2009) Gender and alcohol consumption: patterns from the multinational GENACIS project. Addiction 104(9): 1487–1500
64. Hezode C et al (2003) Impact of moderate alcohol consumption on histological activity and fibrosis in patients with chronic hepatitis C, and specific influence of steatosis: a prospective study. Aliment Pharmacol Ther 17(8):1031–1037
65. McHutchison JG et al (2009) Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 361(6):580–593
66. Floreani A, Cazzagon N, Boemo DG, Baldovin T, Baldo V, Egoue J, Antoniazzi S, Minola E (2011) Female patients in fertile age with chronic hepatitis C, easy genotype, and persistently normal transaminases have a 100% chance to reach a sustained virological response. Eur J Gastroenterol Hepatol 23(11):997–1003
67. Ogawa E, Furusyo N, Kajiwara E, Takahashi K, Nomura H, Maruyama T, Tanabe Y, Satoh T, Nakamuta M, Kotoh K, Azuma K, Dohmen K, Shimoda S, Hayashi J, Kyushu University Liver Disease Study (KULDS) Group (2013) Efficacy of pegylated interferon alpha-2b and ribavirin treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis C: a prospective, multicenter study. J Hepatol 58(3):495–501
68. Furusyo N, Ogawa E, Sudoh M, Murata M, Ihara T, Hayashi T, Ikezaki H, Hiramine S, Mukae H, Toyoda K, Taniai H, Okada K, Kainuma M, Kajiwara E, Hayashi J (2012) Raloxifene hydrochloride is an adjuvant antiviral treatment of postmenopausal women with chronic hepatitis C: a randomized trial. J Hepatol 57(6): 1186–1192
69. Bioulac-Sage P et al (2013) Pathological diagnosis of hepatocellular cellular adenoma according to the clinical context. Int J Hepatol 2013:253261
70. Chang CY et al (2013) Changing epidemiology of hepatocellular adenoma in the United States: review of the literature. Int J Hepatol 2013:604860
71. Bossen L, Grønbaek H, Lykke Eriksen P, Jepsen P (2017) Men with biopsy-confirmed hepatocellular adenoma have a high risk of progression to hepatocellular carcinoma: a nationwide population-based study. Liver Int 37(7):1042–1046
72. Farges O, Ferreira N, Dokmak S, Belghiti J, Bedossa P, Paradis V (2011) Changing trends in malignant transformation of hepatocellular adenoma. Gut 60(1):85–89
73. European Association for the Study of the, L. (2016) EASL clinical practice guidelines on the management of benign liver tumours. J Hepatol 65(2):386–398
74. Naugler WE, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, Karin M (2007) Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. Science 317(5834):121–124
75. Spector LG, Johnson KJ, Soler JT, Puumala SE (2008) Perinatal risk factors for hepatoblastoma. Br J Cancer 98(9):1570–1573
76. Farinati F, Sergio A, Giacomin A, di Nolfo MA, del Poggio P, Benvegnù L, Rapaccini G, Zoli M, Borzio F, Giannini EG, Caturelli E, Trevisani F, Italian Liver Cancer group (2009) Is female sex a significant favorable prognostic factor in hepatocellular carcinoma? Eur J Gastroenterol Hepatol 21(10):1212–1218
77. Lee CM, Lu SN, Changchien CS, Yeh CT, Hsu TT, Tang JH, Wang JH, Lin DY, Chen CL, Chen WJ (1999) Age, gender, and local geographic variations of viral etiology of hepatocellular carcinoma in a hyperendemic area for hepatitis B virus infection. Cancer 86(7):1143–1150
78. Xu X, Hou Y, Yin X, Bao L, Tang A, Song L, Li F, Tsang S, Wu K, Wu H, He W, Zeng L, Xing M, Wu R, Jiang H, Liu X, Cao D, Guo G, Hu X, Gui Y, Li Z, Xie W, Sun X, Shi M, Cai Z, Wang B, Zhong M, Li J, Lu Z, Gu N, Zhang X, Goodman L, Bolund L, Wang J, Yang H, Kristiansen K, Dean M, Li Y, Wang J (2012) Single-cell exome sequencing reveals single-nucleotide mutation characteristics of a kidney tumor. Cell 148(5):886–895
79. Li Z, White P, Tuteja G, Rubins N, Sackett S, Kaestner KH (2009) Foxa1 and Foxa2 regulate bile duct development in mice. J Clin Invest 119(6):1537–1545
80. Patrone C, Cassel TN, Pettersson K, Piao YS, Cheng G, Ciana P, Maggi A, Warner M, Gustafsson JA, Nord M (2003) Regulation of postnatal lung development and homeostasis by estrogen receptor beta. Mol Cell Biol 23(23):8542–8552
81. Wada-Hiraike O, Hiraike H, Okinaga H, Imamov O, Barros RPA, Morani A, Omoto Y, Warner M, Gustafsson JA (2006) Role of estrogen receptor beta in uterine stroma and epithelium: insights from estrogen receptor beta-/- mice. Proc Natl Acad Sci U S A 103(48):18350–18355
82. Wada-Hiraike O, Imamov O, Hiraike H, Hultenby K, Schwend T, Omoto Y, Warner M, Gustafsson JA (2006) Role of estrogen receptor beta in colonic epithelium. Proc Natl Acad Sci U S A 103(8):2959–2964
83. Yu CP, Ho JY, Huang YT, Cha TL, Sun GH, Yu DS, Chang FW, Chen SP, Hsu RJ (2013) Estrogen inhibits renal cell carcinoma cell progression through estrogen receptor-beta activation. PLoS One 8(2):e56667
84. Passarelli MN, Phipps AI, Potter JD, Makar KW, Coghill AE, Wernli KJ, White E, Chan AT, Hutter CM, Peters U, Newcomb PA (2013) Common single-nucleotide polymorphisms in the estrogen receptor beta promoter are associated with colorectal cancer survival in postmenopausal women. Cancer Res 73(2):767–775
85. Press OA, Zhang W, Gordon MA, Yang D, Lurje G, Iqbal S, el-Khoueiry A, Lenz HJ (2008) Gender-related survival differences associated with EGFR polymorphisms in metastatic colon cancer. Cancer Res 68(8):3037–3042
86. Feng H, Cheng ASL, Tsang DP, Li MS, Go MY, Cheung YS, Zhao GJ, Ng SS, Lin MC, Yu J, Lai PB, To KF, Sung JJY (2011) Cell cycle-related kinase is a direct androgen receptor-regulated gene that drives beta-catenin/T cell factor-dependent hepatocarcinogenesis. J Clin Invest 121(8):3159–3175
87. Ma WL, Hsu CL, Yeh CC, Wu MH, Huang CK, Jeng LB, Hung YC, Lin TY, Yeh S, Chang C (2012) Hepatic androgen receptor suppresses hepatocellular carcinoma metastasis through modulation of cell migration and anoikis. Hepatology 56(1):176–185
88. Han HJ, Heo JS, Lee YJ (2006) Estradiol-17beta stimulates proliferation of mouse embryonic stem cells: involvement of MAPKs and CDKs as well as protooncogenes. Am J Phys Cell Phys 290(4):C1067–C1075
89. Nakada D, Oguro H, Levi BP, Ryan N, Kitano A, Saitoh Y, Takeichi M, Wendt GR, Morrison SJ (2014) Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. Nature 505(7484):555–558
90. Gupta PB, Proia D, Cingoz O, Weremowicz J, Naber SP, Weinberg RA, Kuperwasser C (2007) Systemic stromal effects

of estrogen promote the growth of estrogen receptor-negative cancers. Cancer Res 67(5):2062–2071
91. Hartman J, Lindberg K, Morani A, Inzunza J, Strom A, Gustafsson JA (2006) Estrogen receptor beta inhibits angiogenesis and growth of T47D breast cancer xenografts. Cancer Res 66(23):11207–11213
92. Masuda H, Kalka C, Takahashi T, Yoshida M, Wada M, Kobori M, Itoh R, Iwaguro H, Eguchi M, Iwami Y, Tanaka R, Nakagawa Y, Sugimoto A, Ninomiya S, Hayashi S, Kato S, Asahara T (2007) Estrogen-mediated endothelial progenitor cell biology and kinetics for physiological postnatal vasculogenesis. Circ Res 101(6): 598–606
93. Sieveking DP, Lim P, Chow RWY, Dunn LL, Bao S, McGrath KCY, Heather AK, Handelsman DJ, Celermajer DS, Ng MKC (2010) A sex-specific role for androgens in angiogenesis. J Exp Med 207(2):345–352
94. Fish EN (2008) The X-files in immunity: sex-based differences predispose immune responses. Nat Rev Immunol 8(9):737–744
95. Mode A, Gustafsson JA (2006) Sex and the liver - a journey through five decades. Drug Metab Rev 38(1–2):197–207
96. van Bemmel JG, Mira-Bontenbal H, Gribnau J (2016) Cis- and trans-regulation in X inactivation. Chromosoma 125(1):41–50
97. Northcott PA, Jones DTW, Kool M, Robinson GW, Gilbertson RJ, Cho YJ, Pomeroy SL, Korshunov A, Lichter P, Taylor MD, Pfister SM (2012) Medulloblastomics: the end of the beginning. Nat Rev Cancer 12(12):818–834
98. Benyoucef A, Palii CG, Wang C, Porter CJ, Chu A, Dai F, Tremblay V, Rakopoulos P, Singh K, Huang S, Pflumio F, Hébert J, Couture JF, Perkins TJ, Ge K, Dilworth FJ, Brand M (2016) UTX inhibition as selective epigenetic therapy against TAL1-driven T-cell acute lymphoblastic leukemia. Genes Dev 30(5):508–521
99. Murakami S, Ninomiya W, Sakamoto E, Shibata T, Akiyama H, Tashiro F (2015) SRY and OCT4 are required for the acquisition of cancer stem cell-like properties and are potential differentiation therapy targets. Stem Cells 33(9):2652–2663
100. Murakami S, Chishima S, Uemoto H, Sakamoto E, Sato T, Kurabe N, Kawasaki Y, Shibata T, Akiyama H, Tashiro F (2014) The male-specific factor Sry harbors an oncogenic function. Oncogene 33(23):2978–2986
101. Kido T, Lo RCL, Li Y, Lee J, Tabatabai ZL, Ng IOL, Lau YFC (2014) The potential contributions of a Y-located protooncogene and its X homologue in sexual dimorphisms in hepatocellular carcinoma. Hum Pathol 45(9):1847–1858
102. Li S, Mo C, Huang S, Yang S, Lu Y, Peng Q, Wang J, Deng Y, Qin X, Liu Y (2014) Over-expressed testis-specific protein Y-encoded 1 as a novel biomarker for male hepatocellular carcinoma. PLoS One 9(2):e89219
103. Lau YF, Li Y, Kido T (2009) Gonadoblastoma locus and the TSPY gene on the human Y chromosome. Birth Defects Res C Embryo Today 87(1):114–122
104. Kido T, Ou JH, Lau YF (2011) The X-linked tumor suppressor TSPX interacts and promotes degradation of the hepatitis B viral protein HBx via the proteasome pathway. PLoS One 6(7):e22979
105. Tsuei DJ, Hsu HC, Lee PH, Jeng YM, Pu YS, Chen CN, Lee YC, Chou WC, Chang CJ, Ni YH, Chang MH (2004) RBMY, a male germ cell-specific RNA-binding protein, activated in human liver cancers and transforms rodent fibroblasts. Oncogene 23(34): 5815–5822
106. Tsuei DJ, Lee PH, Peng HY, Lu SL, Su DS, Jeng YM, Hsu HC, Hsu SH, Wu JF, Ni YH, Chang MH (2011) Male germ cell-specific RNA binding protein RBMY: a new oncogene explaining male predominance in liver cancer. PLoS One 6(11):e26948
107. (1998) *Tamoxifen in treatment of hepatocellular carcinoma: a randomised controlled trial. CLIP Group (Cancer of the Liver Italian Programme)*. Lancet 352(9121):17–20
108. Chou WC, Su IJ, Tien HF, Liang DC, Wang CH, Chang YC, Cheng AL (1996) Clinicopathologic, cytogenetic, and molecular studies of 13 Chinese patients with Ki-1 anaplastic large cell lymphoma. Special emphasis on the tumor response to 13-cis retinoic acid. Cancer 78(8):1805–1812
109. Lasset C, Bonadona V, Chauvin F, Mignotte H, Brémond A (1998) Risk of endometrial cancer in premenopausal women on tamoxifen. Lancet 352(9138):1476
110. Araki K, Miyazaki J, Hino O, Tomita N, Chisaka O, Matsubara K, Yamamura K (1989) Expression and replication of hepatitis B virus genome in transgenic mice. Proc Natl Acad Sci U S A 86(1):207–211
111. Breidbart S, Burk RD, Saenger P (1993) Hormonal regulation of hepatitis B virus gene expression: influence of androgen receptor. Pediatr Res 34(3):300–302
112. Chen CC, Ko TM, Ma HI, Wu HL, Xiao X, Li J, Chang CM, Wu PY, Chen CH, Han JM, Yu CP, Jeng KS, Hu CP, Tao MH (2007) Long-term inhibition of hepatitis B virus in transgenic mice by double-stranded adeno-associated virus 8-delivered short hairpin RNA. Gene Ther 14(1):11–19
113. DeLoia JA, Burk RD, Gearhart JD (1989) Developmental regulation of hepatitis B surface antigen expression in two lines of hepatitis B virus transgenic mice. J Virol 63(9):4069–4073
114. Guidotti LG, Eggers CM, Raney AK, Chi SY, Peters JM, Gonzalez FJ, McLachlan A (1999) In vivo regulation of hepatitis B virus replication by peroxisome proliferators. J Virol 73(12): 10377–10386
115. Julander JG, Colonno RJ, Sidwell RW, Morrey JD (2003) Characterization of antiviral activity of entecavir in transgenic mice expressing hepatitis B virus. Antivir Res 59(3):155–161
116. Peltekian C, Gordien E, Garreau F, Meas-Yedid V, Soussan P, Willams V, Chaix ML, Olivo-Marin JC, Bréchot C, Kremsdorf D (2005) Human MxA protein participates to the interferon-related inhibition of hepatitis B virus replication in female transgenic mice. J Hepatol 43(6):965–972
117. Buzzetti E, Parikh PM, Gerussi A, Tsochatzis E (2017) Gender differences in liver disease and the drug-dose gender gap. Pharmacol Res 120:97–108
118. Carbone M, Mells GF, Pells G, Dawwas MF, Newton JL, Heneghan MA, Neuberger JM, Day DB, Ducker SJ, UK PBC Consortium, Sandford RN, Alexander GJ, Jones DE (2013) *Sex and age are determinants of the clinical phenotype of primary biliary cirrhosis and response to ursodeoxycholic acid*. Gastroenterology 144(3):560–569 e7 quiz e13–4