Blood Science

Sex differences in normal and malignant hematopoiesis

Xiaojing Cui[a], Xinghui Zhao[a], Ying Liang[a],*

[a]Department of Toxicology and Cancer Biology, University of Kentucky, Lexington, KY

Abstract

Hematopoiesis is a continuous and well-regulated process requiring both the capacity for self-renewal and the potential for differentiation of hematopoietic stem cells. Multiple studies indicate that sex hormones exert significant effects on not only hematopoietic stem and progenitor cells, but also the development of hematopoietic lineages, resulting in sexual dimorphisms in normal hematopoiesis. Hematologic malignancies comprise a wide variety of cancers affecting the blood, bone marrow, and lymphatic system, such as leukemia, lymphoma, myeloma, myelodysplastic syndrome, and myeloproliferative diseases. Overall, males are at greater risk and have worse prognosis for most of these malignancies compared with females. A better understanding of the differences between male and female could be of substantial value in research as well as clinical management.

Key Words: Hematopoietic stem cells; Malignant hematopoiesis; Normal hematopoiesis; Sex hormones; Sexual dimorphism

1.INTRODUCTION

Hematopoiesis is a process that is continuous and well regulated. It requires the capacity for self-renewal and the potential for differentiation of hematopoietic stem cells (HSCs). Hematopoiesis eventually gives rise to all the various mature blood and immune cell lineages, such as mast cells which do not typically circulate in the blood.[1] HSCs are located at the top of the hematopoietic hierarchy and give rise to progenitor cells that gradually differentiate into lineage-restricted cells.[2] Hematopoiesis is strictly controlled by a complex network of cell-intrinsic factors and cell-extrinsic modulators to maintain the hematopoietic homeostasis.[3] Dysregulation may occur at any stage of hematopoiesis and can cause hematological malignancies.[4]

Males and females are similar in many aspects. However, the considerable differences in biological characteristics and behaviors between them[5] account for the differences in clinical incidence, manifestation, and outcome of many widespread diseases[6–10] and affect the approach to health care.[5] Male and female differences may be influenced by both sex and gender. "Sex differences" are based on the biological factors, such as the X and Y chromosomes, reproductive organs and sexual hormones. By contrast, "gender differences" are determined by social factors related to behavior, lifestyle, and life experience.[5,11] In this review, we summarize what is known about sex differences in normal and malignant hematopoiesis, provide examples, and discuss possible mechanisms that drive the differences.

2. SEX DIFFERENCES IN NORMAL HEMATOPOIESIS

Multiple studies have identified differences involved in male and female hematopoietic systems, including HSCs, lineage-committed progenitors, and niche components.[12,13]

2.1. HSC self-renewal and proliferation

In 2014, Nakada et al[14] reported that although males and females have similar basal numbers of HSCs and their immediate progeny, multipotent progenitor cells (MPPs), female mice exhibited increased frequency of proliferation of these cells without depletion of the stem cell pool. This indicates that female HSCs undergo more frequent self-renewing divisions. The enhanced proliferation of HSCs in females is driven by endogenous estrogens and mediated mainly by intrinsic estrogen receptor alpha (ERα), which is highly expressed in HSCs. During pregnancy, more HSCs were detected in the bone marrow and spleen relative to non-pregnant female mice. Significant increases in spleen cellularity, erythropoiesis, and myelopoiesis were also observed during pregnancy with elevated estrogen levels, highlighting the importance of sex hormones in HSC activity.[14,15]

Nakada et al[14] detected little or no ERβ, progesterone (PG) receptor or androgen receptor expression in HSCs (CD150$^+$CD48$^-$Lin$^-$Sca-1$^+$c-kit$^+$) and MPPs.[14] However, in a murine bone marrow–derived hematopoietic stem/progenitor cell (HSPC) subset (Sca-1$^+$Lin$^-$CD45$^+$)[16] and a CD34$^+$Lin$^-$CD45$^+$ population isolated from human umbilical cord blood,[17] expressions of receptors for gonadal sex hormones including estrogens,

androgen, and PG, as well as the pituitary sex hormone receptors, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin, were detected.[16–18] In vivo administration of sex hormones, including LH, enhances BrdU incorporation into Sca-1+Lin−CD45+HSPCs and accelerates hematopoietic recovery in sublethally irradiated mice.[16] CD34+ cells sorted from human umbilical cord blood stimulated with the sex hormones (including estradiol and LH) in vitro exhibit an increase in the number of clonogenic BFU-E, CFU-GM, CFU-Meg, and more primitive CFU-Mix progenitors.[17] Further detailed studies indicate that expression of the LH receptor is highly restricted to mouse CD150+/−CD48−Lin−Sca-1+c-Kit HSC/MPPs, is activated on HSCs after birth and peaks after sexual maturation.[19] Human and mouse long-term self-renewing HSCs expanded ex vivo when stimulated with LH.[20] Another pituitary sex hormone, FSH, was reported to mobilize Lin−CD235a−CD45+CD133+ HSPCs into peripheral blood.[21]

2.2. Hematopoietic progenitors

Sex hormones exert significant effects on not only hematopoietic stem and progenitor cells, but also on the development of hematopoietic lineages.

Associations between sex hormones and erythropoiesis have been known for several decades. The initial observations that men have a higher blood cell mass than women and administering androgens to various animals causes an increase in hemoglobin levels call attention to the possible specific roles that androgen plays in erythropoiesis.[22] Before the introduction of recombinant human erythropoietin in 1987, androgen was used as a red cell stimulant.[22] On the other hand, erythrocytosis is the most common dose-limiting adverse event associated with testosterone therapy, and aged men appear more sensitive to the stimulatory effect on erythropoiesis of testosterone than young men.[23] Interestingly, addition of testosterone to culture of human erythroid progenitors expanded from umbilical cord blood of male and female newborns in vitro significantly promotes proliferation of female but not male erythroid progenitors.[24] In an early study, prolactin, as well as plasma from pregnant or lactating mice, was found to stimulate erythropoiesis.[25] Administration of estradiol, also known as E2, which is the predominant estrogen in females, induces erythropoiesis in the spleens of both male and female mice.[14] In the same study, more erythroid cells in the spleen were found in female mice during pregnancy with increased estrogen levels.[14]

Several lines of evidence suggest that sex hormones might participate in or contribute to the steady state regulation of B lymphopoiesis.[26] Marked reduction in pre-B cells and a corresponding reduction in interleukin -7–responding precursors were found in the bone marrow of normal pregnant mice,[27] and treatment of estrogen selectively inhibits the B lymphocyte precursors without affecting myeloid progenitors in male and female mice.[28] Although PG alone has no influence on B lymphopoiesis, it increases the sensitivity of precursors of B lymphocytes to estrogen.[28] Conversely, reduced levels of circulating sex hormones stimulate B lymphopoiesis in the bone marrow.[26] For example, B lymphocyte precursors are selectively accumulated in bone marrow in ovariectomized mice and can be reversed by estrogen replacement.[29] In addition, androgen receptor-deficient testicular feminization mice show selective expansion of B cell production in the bone marrow.[26] Dramatic and long-lived enhancement of B lymphopoiesis was observed in castrated male mice.[30,31] The castration-induced expansion of B cell populations is reversible with androgen replacement in the bone marrow, but not in the spleen.[32]

Multiple studies have shown that precursors of human and murine myeloid cells are responsive to estrogen.[33] E2 in physiological concentrations augments the number of granulocyte/macrophage progenitor cell colonies (CFU-GM) developed from human peripheral blood or cord blood mononuclear cells in vitro.[34] In an ex vivo culture system for GM-CSF–supported dendritic cells (DC) differentiation from murine bone marrow myeloid precursors, E2 preferentially promotes the differentiation of CD11c+ CD11bint DC population from BM precursor cells, suggesting that estrogen could increase the number of potent antigen-presenting cells.[35] However, the production rate in murine bone marrow of another subset of DC, plasmacytoid DC, are not affected by in vivo E2 treatment.[36] In a study examining DC differentiation from the same highly purified myeloid progenitor cells in both GM-CSF- and Flt3 Ligand-driven culture models, E2 promotes DC differentiation in GM-CSF cultures, but decreases viable cell numbers in Flt3 Ligand-culture with a consequent reduction in differentiated DC.[37]

3. SEX DIFFERENCES IN MALIGNANT HEMATOPOIESIS

A wide range of cancer types that are unrelated to reproductive functions have exhibited sexual dimorphism in incidence, prognosis and mortality.[38] Overall, males are at greater risk and have worse prognosis compared with females for most cancers.[7,39] Hematologic malignancies comprise a wide variety of cancers affecting the blood, bone marrow and lymphatic system, such as leukemia, lymphoma, myeloma, myelodysplastic syndrome, and myeloproliferative diseases.[6]

Leukemia is caused by uncontrolled clonal expansion of leukemic cells in the bone marrow and blood. The subtypes of leukemia are determined by and classified according to their cell origins (lymphocytic or myeloid) as well as their stage of maturation arrest (acute or chronic).[40] According to the International Agency for Research on Cancer's GLOBOCAN database, in 2018, leukemia represented the 15th leading cause of cancer occurrence and 11th leading cause of cancer mortality worldwide, accounting for 437,033 new cases and 309,006 deaths.[40,41] Altogether, males have higher age-standardized incidence and mortality rates of leukemia (6.1 and 4.2 per 100,000) than females (4.3 and 2.8 per 100,000) in 2018.[40] Another report using data from the Global Burden of Disease shows that between 1990 and 2017, the age-standardized incidence rate of leukemia was higher in males than in females, and a more pronounced decrease occurs in females compared with males.[42] It is worth noting that as the most common type of pediatric cancer, leukemia accounts for about one-third of all cancers diagnosed in children under 15 years old.[43] Within this population, about 3 out of 4 leukemia diagnoses are acute lymphocytic leukemia (ALL) which develops slightly more frequently in boys than in girls[43,44]; most of the remaining cases are acute myeloid leukemia (AML), which occurs about equally among boys and girls.[43] In adults, sex-biased differences in leukemias become more evident.[6,39] As we know, sex hormones remain in low concentrations in children before puberty, which indicates an important role that sex hormones play in mediating these effects.

Myelodysplastic syndrome is typically considered a heterogeneous collection of clonal myeloid neoplasms characterized by ineffective hematopoiesis, progressive cytopenia, and increased risk of developing AML. A higher age-adjusted incidence rate is found in males, with a male/female ratio of 1.67.[45] Male myeloid dysplastic syndrome (MDS) patients, regardless of age and race, show a higher probability of mortality compared with females in the same group, indicating sex as a prognostic factor for the overall survival of myelodysplastic syndrome.[46]

Non-Hodgkin lymphomas, involving heterogeneous groups of lymphoproliferative malignancies with diverse patterns of behaviors, represent 1 of the 2 major types of lymphoma. By the latest GLOBOCAN statistics, the overall non-Hodgkin lymphoma incidence is approximately 50% higher among males than females (6.7 vs 4.7 per 100,000, respectively), and the mortality rates also reflect a male predominance (3.3 vs 2.0).[40]

Considerable variation exists in male to female incidence rate ratios (IRRs) by non-Hodgkin lymphoma subtype. The male predominance was most pronounced for mantle cell (IRR = 3.07) and Burkitt lymphoma (IRR = 2.79), and less pronounced for marginal zone (IRR = 1.05) and follicular lymphomas (IRR = 1.18).[40,47] HIV/AIDS is known as a strong risk factor for Burkitt lymphoma and may contribute to the strong male predominance, since HIV/AIDS is more prevalent in males than females.[40,47]

4. MECHANISMS UNDERLYING SEX DIMORPHISM IN NORMAL AND MALIGNANT HEMATOPOIESIS

4.1. Sex hormones

Although males and females are alike in many aspects, important differences exist between the 2 genders. In normal hematopoiesis, multiple sex hormone receptors are detected in blood cells, and more and more evidence proves that sex hormones exert significant effects on hematopoietic stem and progenitor cells as well as the development of hematopoietic lineages in both mouse and human. Sex hormone expression changes along development stages from birth, puberty through the adulthood. Even in adult, especially in female, sex hormone levels undergo dramatic changes during the pregnancy, lactation, and menopause. However, there is little research on the effects of sex hormones on hematopoiesis, and the majority of studies have been done in adults.

In mouse (Fig. 1), receptors for estrogen, androgen, PG, FSH, LH, and prolactin (PRL) were found to be expressed in HSPC.[16] Estrogen receptor alpha (ERα), but not ERβ, is highly expressed in HSCs.[14] Estrogen promotes HSC proliferation in both male and female HSCs, but female HSCs experience more self-renewing divisions than male HSCs.[14] Estrogen selectively inhibits B lymphopoiesis[28] in females. Estrogen has been shown to increase the number of myeloid cells while suppressing the proliferation of B lymphocyte precursors.[28,35] During the pregnancy and lactation in female mouse, more HSCs were found in the bone marrow and spleen during pregnancy.[14] In lactating mouse, increased level of prolactin was found to stimulate erythropoiesis.[25] In human (Fig. 2), cord blood–derived CD34+ cells are widely used to study sex hormone effect on hematopoiesis. It was found that receptors for sex hormones such as estrogens, androgens, PG, FSH, LH, and PRL were expressed in cord blood HSPCs.[17] Testosterone increases the proliferation of female but not male erythroid progenitors.[24] In human adult, estrogen increase the number of myeloid progenitor colonies.[34] In malignant hematopoiesis, boys developed more ALL than girls.[44] Higher incidence of MDS, leukemia and non-Hodgkin lymphoma are reported in males than females, suggesting the sex disparity in hematologic malignancy.[40,42,45,46] Two signaling pathways are reported to become active when sex hormones bind their receptors in HSPCs, MAPKp42/44, and AKT-dependent signaling pathways, which results in cell proliferation (Fig. 3).[16,17]
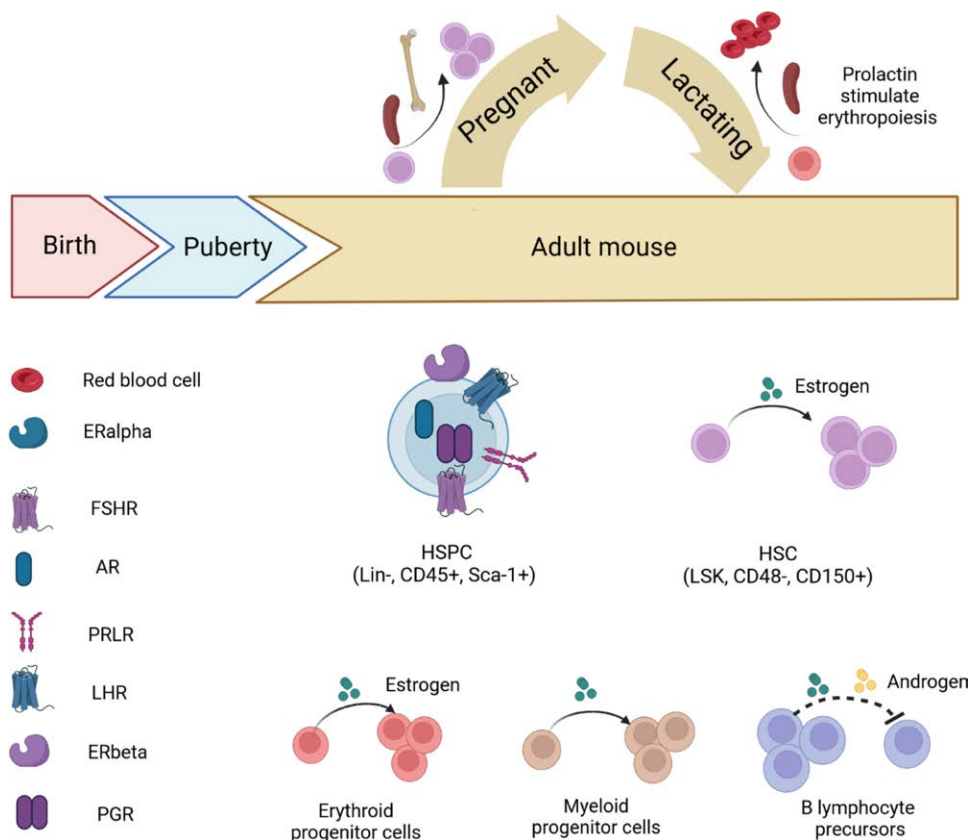

Figure 1. Role of sex hormones in the regulation of murine hematopoiesis. In the murine HSPC, estrogen, androgen, PG, FSH, LH, and PRL receptors were found to be expressed. Estrogen promotes HSC proliferation via ER alpha, which is highly expressed in HSCs. Female HSCs experience more self-renewing divisions than male HSCs. Estrogen increases the number of myeloid cells while suppressing the proliferation of B lymphocyte precursors. During the pregnancy and lactating time of female mouse, more HSCs were found in the bone marrow and spleen during pregnancy. Lactating mouse prolactin was discovered to stimulate erythropoiesis. HSPCs are defined by cell surface markers Lin-, CD45+ and Sca-1+ in flow cytometry. HSCs are defined as Lin-, Sca1+, c-kit+ (LSK), CD48, and CD150+ cells. Majority of studies are performed in adult hematopoiesis. AR = androgen receptor, ER = estrogen receptor, FSH = follicle-stimulating hormone, FSHR = follicle stimulating hormone receptor, HSC = hematopoietic stem cell, HSPC = hematopoietic stem/progenitor cell, LH = luteinizing hormone, LHR = luteinizing hormone receptor, PG = progesterone, PGR = prostaglandin receptor, PRL = prolactin, PRLR = prolactin receptor.
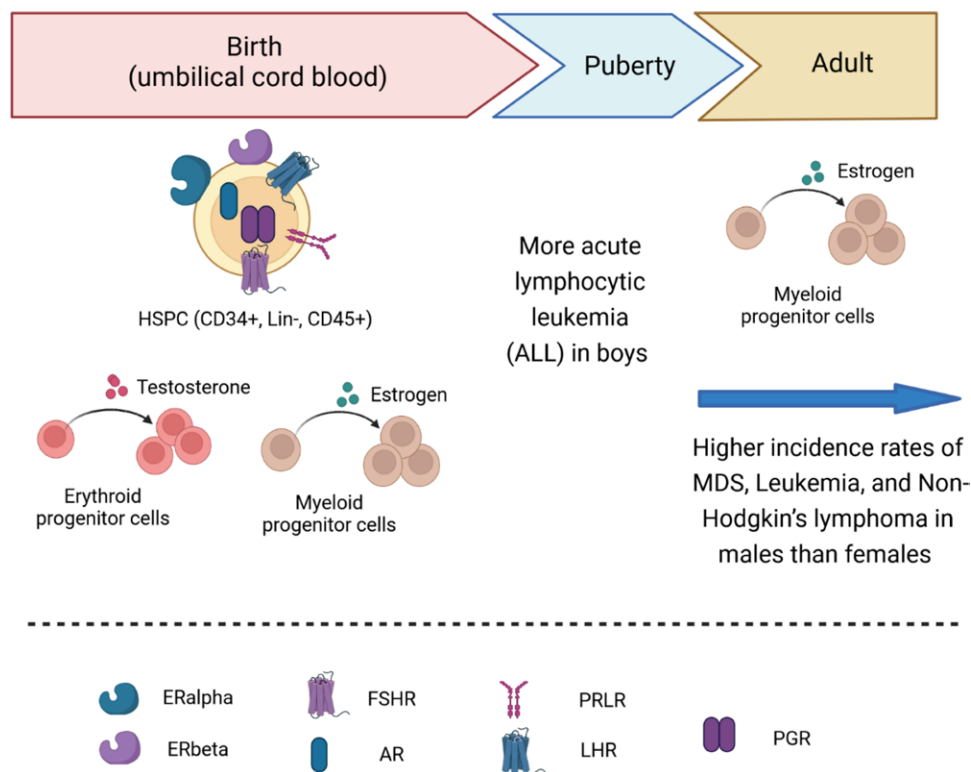
Figure 2. Role of sex hormones in the regulation of human hematopoiesis. Human cord blood–derived HSPCs expressed receptors for sex hormones such as estrogens, androgens, PG, FSH, LH, and PRL. The addition of testosterone to an in vitro culture of human erythroid progenitors significantly increases the proliferation of female but not male erythroid progenitors. Boys developed more acute lymphocytic leukemia than girls in pediatric hematological malignancy. In human adult, estrogen increase the number of myeloid progenitor colonies. Higher incidence of MDS, leukemia, and non-Hodgkin lymphoma are reported in males than females. Cord blood HSPCs are defined by cell surface markers Lin-, CD45+, and CD34+ in flow cytometry. AR = androgen receptor, FSH = follicle-stimulating hormone, FSHR = follicle stimulating hormone receptor, HSPC = hematopoietic stem/progenitor cell, LH = luteinizing hormone, LHR = luteinizing hormone receptor, MDS = myeloid dysplastic syndrome, PG = progesterone, PGR = prostaglandin receptor, PRL = prolactin, PRLR = prolactin receptor.

4.2. Sex chromosome related genes in the regulation of normal and malignant hematopoiesis

The sex chromosome, in addition to sex hormone, is a significant contributor to gender differences.[48] In females, there are 2 X chromosomes. The dosage disparity between males (XY) and females (XX) is balanced by the X chromosome inactivation (XCI) process.[49] Twenty-five percent of human genes have been shown to escape the XCI, and expression of these genes is doubled in females compared with males.[49] Hematologic malignancies originate as a result of altered gene expression and XCI escaper mutation.[48,50]

The X chromosome accounts for 5% of all genetic material in humans, and has about 900 genes. In contrast, the Y chromosome is one-third the size of the X chromosome. It accounts for 2% of the human genome, and has approximately 55 protein-coding genes (https://www.genome.gov/about-genomics/fact-sheets/Y-Chromosome-facts). However, very few genes were discovered to be involved in both normal and malignant hematopoiesis. Recently, it was reported that KDM6A (lysine-specific demethylase 6A) regulates hematopoiesis.[51] It is an X chromosome-located histone H3K27me3 demethylase gene.[52] In vitro knockdown of KDM6A reduces HSPC colony formation and suppresses the proliferation of several leukemia cell lines, suggesting its potential role as an oncogene.[51] However, in vivo deletion of KDM6A in the knockout (KO) mouse model showed enhanced self-renewal of HSCs, myeloid expansion and a block in lymphoid and erythroid/megakaryocytic differentiation. At the age of 22 months, around 63% of the mice spontaneously developed AML. With a secondary oncogenic hit of AML-ETO, KDM6A KO mice had a significantly accelerated AML development and death, suggesting that KDM6A deletion confers HSC a pre-leukemic state. KDM6D is the Y chromosome homolog of KDM6A.[53] It rescues KDM6A deficiency-induced leukemia development, further supporting the tumor suppressor function of KDM6A/KDM6D genes in vivo.[53] Another sex chromosome located gene is CRLF2 (cytokine receptor-like factor 2). It is located on the Xp22.3/Yp11.3 chromosome, and its mutation has been identified as an oncogene in more than 7% of B-ALL cases.[54] CSF2RA encodes the granulocyte-macrophage colony-stimulating factor receptor subunit alpha (GM-CSFR), which is found on the X chromosome in humans. GM-CSFR protects chronic lymphocytic leukemia (CLL) cells from apoptosis, and high CSF2RA expression was also found in AML patients, indicating its potential role in hematologic malignancy.[55,56] X-linked tumor suppressor gene *PHF6* is found mutated and deleted almost exclusively in males in T-ALL, and genetic alterations in *PHF6* are seven times more prevalent in males than in females with AML.[57]

Furthermore, mosaic loss of chromosome Y (mLOY), which is common in hematopoietic cells, causes DNA damages in HSPCs and accelerates leukemogenesis.[58] The frequency and level of mLOY increase significantly with age.[59] In both human and mouse AML with mLOY, 29 genes are downregulated. KDM5D (lysine-specific demethylase 5D) is one of 29 H3K4 demethylase genes on the Y chromosome. KDM5D deficiency promotes DNA damages in HSPCs. Overexpression of KDM5D, on the other hand, prevents DNA damage and leukemogenesis[60] (Table 1).

5.CONCLUSIONS

In both healthy and malignant hematopoiesis, there is sex dimorphism. Through receptors that are selectively expressed
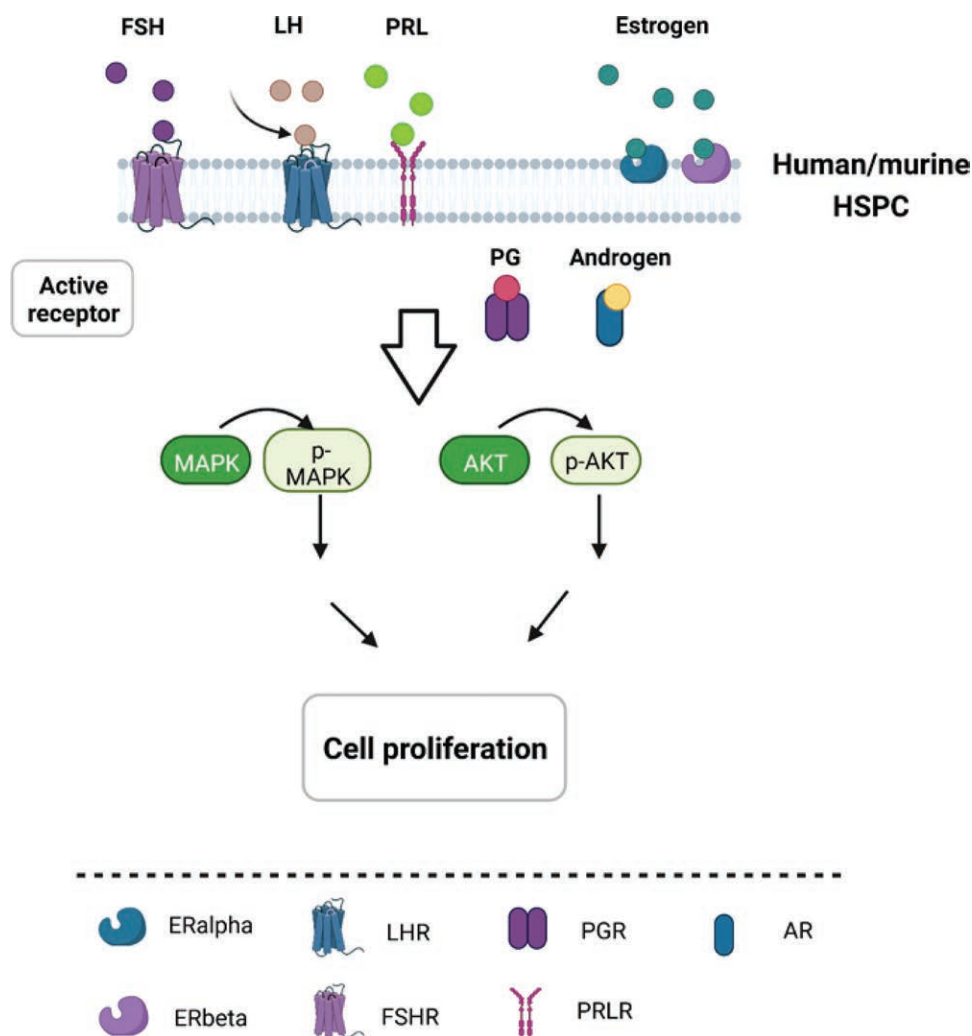
Figure 3. Sex hormone signaling pathways in the regulation of hematopoietic cells. Both human and murine HSPCs expressed receptors for sex hormones such as estrogens, androgens, PG, FSH, LH, and PRL. In response to these sex hormones, MAPKp42/44 and AKT-dependent signaling pathways were activated, resulting in cell proliferation. AR = androgen receptor, FSH = follicle-stimulating hormone, FSHR = follicle stimulating hormone receptor, HSPC = hematopoietic stem/progenitor cell, LH = luteinizing hormone, LHR = luteinizing hormone receptor, PG = progesterone, PRL = prolactin, PRLR = prolactin receptor.

Table 1

Genes found on both sexes and their roles in normal and malignant hematopoiesis.

Gene name	Sex chromosome	Normal hematopoiesis	Malignant hematopoiesis	References
KDM6A	X	Kdm6a deletion enhances self-renewal of HSCs, myeloid expansion and a block in lymphoid and erythroid/megakaryocytic differentiation	Kdm6a deletion induces spontaneous leukemia, accelerates leukemia development in combination with other oncogenic hit	51–53
KDM5D	Y	Loss of KDM5D promotes the DNA damage in HSPCs	Overexpression of KDM5D prevents the DNA damages and suppresses leukemogenesis	60
CRLF2	X		Mutation occurs in over 7% of B-ALL	54
CSF2RA	X		High CSF2RA expression was detected in AML patients	55,56
PHF6	X		Mutation is more prevalent in male T-ALL and AML	57

ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, HSC = hematopoietic stem cell, HSPC = hematopoietic stem/progenitor cell.

in various populations of stem/progenitor cells, sex hormone controls their self-renewal, differentiation, and proliferation in steady state. Males are more susceptible to and have worse prognoses in the majority of malignant hematopoiesis than females. Genes associated with the sex chromosomes are significant contributors to the sex discrepancy in hematologic malignancy. Both research and clinical management could benefit greatly from a greater knowledge of the variations between men and women.

REFERENCES

[1] Laurenti E, Göttgens B. From haematopoietic stem cells to complex differentiation landscapes. *Nature* 2018;553(7689):418–426.

[2] Zhang Y, Gao S, Xia J, Liu F. Hematopoietic hierarchy – an updated roadmap. *Trends Cell Biol* 2018;28(12):976–986.

[3] Pinho S, Frenette PS. Haematopoietic stem cell activity and interactions with the niche. *Nat Rev Mol Cell Biol* 2019;20(5):303–320.

[4] Hu D, Shilatifard A. Epigenetics of hematopoiesis and hematological malignancies. *Genes Dev* 2016;30(18):2021–2041.

[5] Regitz-Zagrosek V. Sex and gender differences in health. Science & Society Series on Sex and Science. *EMBO Rep* 2012;13(7):596–603.

[6] Ben-Batalla I, Vargas-Delgado ME, Meier L, Loges S. Sexual dimorphism in solid and hematological malignancies. *Semin Immunopathol* 2018;41(2):251–263.

[7] Clocchiatti A, Cora E, Zhang Y, Paolo Dotto G. Sexual dimorphism in cancer. *Nat Rev Cancer* 2016;16(5):330–339.

[8] Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016;16(10):626–638.

[9] Sampathkumar NK, Bravo JI, Chen Y, et al. Widespread sex dimorphism in aging and age-related diseases. *Hum Genet* 2019;139(3):333–356.

[10] Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex differences in cardiovascular pathophysiology. *Circulation* 2018;138(2):198–205.

[11] Goldstein JM, Rich-Edwards JW, Kaiser UB, Chen GL, Manson JE. Sex and gender differences research design for basic, clinical, and population studies: essentials for investigators. *Endocr Rev* 2018;39(4):424–439.

[12] Heo HR, Chen L, An B, Kim KS, Ji J, Hong SH. Hormonal regulation of hematopoietic stem cells and their niche: a focus on estrogen. *Int J Stem Cells* 2015;8(1):18–23.

[13] Kovats S. Estrogen receptors regulate innate immune cells and signaling pathways. *Cell Immunol* 2015;294(2):63–69.

[14] Nakada D, Oguro H, Levi BP, et al. Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. *Nature* 2014;505(7484):555–558.

[15] Leeman DS, Brunet A. Stem cells: sex specificity in the blood. *Nature* 2014;505(7484):488–490.

[16] Mierzejewska K, Borkowska S, Suszynska E, et al. Hematopoietic stem/progenitor cells express several functional sex hormone receptors—novel evidence for a potential developmental link between hematopoiesis and primordial germ cells. *Stem Cells Dev* 2015;24(8):927–937.

[17] Abdelbaset-Ismail A, Suszynska M, Borkowska S, et al. Human haematopoietic stem/progenitor cells express several functional sex hormone receptors. *J Cell Mol Med* 2015;20(1):134–146.

[18] Ratajczak MZ. Why are hematopoietic stem cells so "sexy"? on a search for developmental explanation. *Leukemia* 2017;31(8):1671–1677.

[19] Peng YJ, Yu H, Hao X, et al. Luteinizing hormone signaling restricts hematopoietic stem cell expansion during puberty. *EMBO J* 2018;37(17):e98984.

[20] Velardi E, Tsai JJ, Radtke S, et al. Suppression of luteinizing hormone enhances HSC recovery after hematopoietic injury. *Nat Med* 2018;24(2):239–246.

[21] Zbucka-Kretowska M, Eljaszewicz A, Lipinska D, et al. Effective mobilization of very small embryonic-like stem cells and hematopoietic stem/progenitor cells but not endothelial progenitor cells by follicle-stimulating hormone therapy. *Stem Cells International* 2016;2016:1–8.

[22] Shahani S, Braga-Basaria M, Maggio M, Basaria S. Androgens and erythropoiesis: past and present. *J Endocrinol Invest* 2009;32(8):704–716.

[23] Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab* 2008;93(3):914–919.

[24] Leberbauer C, Boulmé F, Unfried G, Huber J, Beug H, Müllner EW. Different steroids co-regulate long-term expansion versus terminal differentiation in primary human erythroid progenitors. *Blood* 2005;105(1):85–94.

[25] Jepson JH, Lowenstein L. Effect of prolactin on erythropoiesis in the mouse. *Blood* 1964;24:726–738.

[26] Smithson G, Couse JF, Lubahn DB, Korach KS, Kincade PW. The role of estrogen receptors and androgen receptors in sex steroid regulation of B lymphopoiesis. *J Immunol* 1998;161(1):27–34.

[27] Medina KL, Smithson G, Kincade PW. Suppression of B lymphopoiesis during normal pregnancy. *J Exp Med* 1993;178(5):1507–1515.

[28] Medina KL, Kincade PW. Pregnancy-related steroids are potential negative regulators of B lymphopoiesis. *Proc Natl Acad Sci USA* 1994;91(12):5382–5386.

[29] Masuzawa T, Miyaura C, Onoe Y, et al. Estrogen deficiency stimulates B lymphopoiesis in mouse bone marrow. *J Clin Invest* 1994;94(3):1090–1097.

[30] Wilson CA, Mrose SA, Thomas DW. Enhanced production of B lymphocytes after castration. *Blood* 1995;85(6):1535–1539.

[31] Olsen NJ, Kovacs WJ. Effects of androgens on T and B lymphocyte development. *Immunol Res* 2001;23(2-3):281–288.

[32] Viselli SM, Reese KR, Fan J, Kovacs WJ, Olsen NJ. Androgens alter B cell development in normal male mice. *Cell Immunol* 1997;182(2):99–104.

[33] Nalbandian G, Kovats S. Understanding sex biases in immunity: effects of estrogen on the differentiation and function of antigen-presenting cells. *Immunol Res* 2005;31(2):91–106.

[34] Maoz H, Kaiser N, Halimi M, et al. The effect of estradiol on human myelomonocytic cells. 1. Enhancement of colony formation. *J Reprod Immunol* 1985;7(4):325–335.

[35] Paharkova-Vatchkova V, Maldonado R, Kovats S. Estrogen preferentially promotes the differentiation of CD11c+ CD11b(intermediate) dendritic cells from bone marrow precursors. *J Immunol* 2004;172(3):1426–1436.

[36] Harman BC, Miller JP, Nikbakht N, Gerstein R, Allman D. Mouse plasmacytoid dendritic cells derive exclusively from estrogen-resistant myeloid progenitors. *Blood* 2006;108(3):878–885.

[37] Carreras E, Turner S, Paharkova-Vatchkova V, Mao A, Dascher C, Kovats S. Estradiol acts directly on bone marrow myeloid progenitors to differentially regulate GM-CSF or Flt3 ligand-mediated dendritic cell differentiation. *J Immunol* 2008;180(2):727–738.

[38] Rubin JB, Lagas JS, Broestl L, et al. Sex differences in cancer mechanisms. *Biology of Sex Differences* 2020;11(1):17.

[39] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70(1):7–30.

[40] Bispo JAB, Pinheiro PS, Kobetz EK. Epidemiology and etiology of leukemia and lymphoma. *Cold Spring Harb Perspect Med* 2020;10(6):a034819.

[41] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68(6):394–424.

[42] Dong Y, Shi O, Zeng Q, et al. Leukemia incidence trends at the global, regional, and national level between 1990 and 2017. *Exp Hematol Oncol* 2020;9:14.

[43] Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: a review. *Environ Health Perspect* 2007;115(1):138–145.

[44] Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med* 2015;373(16):1541–1552.

[45] Zeidan AM, Shallis RM, Wang R, Davidoff A, Ma X. Epidemiology of myelodysplastic syndromes: why characterizing the beast is a prerequisite to taming it. *Blood Rev* 2019;34:1–15.

[46] Wang F, Ni J, Wu L, Wang Y, He B, Yu D. Gender disparity in the survival of patients with primary myelodysplastic syndrome. *J Cancer* 2019;10(5):1325–1332.

[47] Teras LR, DeSantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin* 2016;66(6):443–459.

[48] Ben-Batalla I, Vargas-Delgado ME, Meier L, Loges S. Sexual dimorphism in solid and hematological malignancies. *Semin Immunopathol* 2019;41(2):251–263.

[49] Slavney A, Arbiza L, Clark AG, Keinan A. Strong constraint on human genes escaping X-inactivation is modulated by their expression level and breadth in both sexes. *Mol Biol Evol* 2016;33(2):384–393.

[50] Kim HI, Lim H, Moon A. Sex differences in cancer: epidemiology, genetics and therapy. *Biomol Ther (Seoul)* 2018;26(4):335–342.

[51] Liu J, Mercher T, Scholl C, Brumme K, Gary Gilliland D, Zhu N. A functional role for the histone demethylase UTX in normal and malignant hematopoietic cells. *Exp Hematol* 2012;40(6):487–98.e3.

[52] Hübner MR, Spector DL. Role of H3K27 demethylases Jmjd3 and UTX in transcriptional regulation. *Cold Spring Harb Symp Quant Biol* 2010;75:43–49.

[53] Gozdecka M, Meduri E, Mazan M, et al. UTX-mediated enhancer and chromatin remodeling suppresses myeloid leukemogenesis through noncatalytic inverse regulation of ETS and GATA programs. *Nat Genet* 2018;50(6):883–894.

[54] Russell LJ, Capasso M, Vater I, et al. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid

transformation in B-cell precursor acute lymphoblastic leukemia. *Blood* 2009;114(13):2688–2698.

[55] Matsuura S, Yan M, Lo MC, et al. Negative effects of GM-CSF signaling in a murine model of t(8;21)-induced leukemia. *Blood* 2012;119(13):3155–3163.

[56] Li P, Harris D, Liu Z, et al. STAT3-activated GM-CSFRα translocates to the nucleus and protects CLL cells from apoptosis. *Mol Cancer Res* 2014;12(9):1267–1282.

[57] Van Vlierberghe P, Patel J, Abdel-Wahab O, et al. PHF6 mutations in adult acute myeloid leukemia. *Leukemia* 2010;25(1):130–134.

[58] Danielsson M, Halvardson J, Davies H, et al. Longitudinal changes in the frequency of mosaic chromosome Y loss in peripheral blood cells of aging men varies profoundly between individuals. *Eur J Hum Genet* 2020;28(3):349–357.

[59] Thompson DJ, Genovese G, Halvardson J, et al. Genetic predisposition to mosaic Y chromosome loss in blood. *Nature* 2019;575(7784):652–657.

[60] Zhang Q, Zhao L, Yang Y, Li S, Liu Y, Chen C. Mosaic loss of chromosome Y promotes leukemogenesis and clonal hematopoiesis. *JCI Insight* 2022;7(3):e153768.