Sex differences in normal and malignant hematopoiesis

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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. HSCs are located at the top of the hematopoietic hierarchy and give rise to progenitor cells that gradually differentiate into lineage-restricted cells. Hematopoiesis is strictly controlled by a complex network of cell-intrinsic factors and cell-extrinsic modulators to maintain the hematopoietic homeostasis. Dysregulation may occur at any stage of hematopoiesis and can cause hematological malignancies.

Males and females are similar in many aspects. However, the considerable differences in biological characteristics and behaviors between them account for the differences in clinical incidence, manifestation, and outcome of many widespread diseases and affect the approach to health care. 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. 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.

2.1. HSC self-renewal and proliferation

In 2014, Nakada et al 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. Nakada et al detected little or no ERβ, progesterone (PG) receptor or androgen receptor expression in HSCs (CD150+CD48 Lin Sca-1+ c-kit+) and MPPs. However, in a murine bone marrow-derived hematopoietic stem/progenitor cell (HSCP) subset (Sca-1+Lin CD45+), and a CD34+Lin CD45+ population isolated from human umbilical cord blood, expression 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. 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. CD34+ cells sorted from mice with 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. 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 expression of the LH receptor is highly restricted to mouse HSCs after birth and peaks after sexual maturation. Human and mouse long-term self-renewing HSCs expanded ex vivo when stimulated with LH. Another pituitary sex hormone, FSH, was reported to mobilize Lin−CD235a−CD45+CD133+ HSPCs into peripheral blood.

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. Before the introduction of recombinant human erythropoietin in 1987, androgen was used as a red cell stimulant. 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. 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. In an early study, prolactin, as well as plasma from pregnant mice, was shown to promote proliferation of female but not male erythroid progenitor cells in vitro. The same group, indicating sex as a prognostic factor for the overall survival of myelodysplastic syndrome.

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. Overall, males are at greater risk and have worse prognosis compared with females for most cancers. 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.

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). 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. 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. 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. 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. 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, most of the remaining cases are acute myeloid leukemia (AML), which occurs about equally among boys and girls. In adults, sex-biased differences in leukemias become more evident. 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. 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.
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). 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.

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. Estrogen receptor alpha (ERα), but not ERβ, is highly expressed in HSCs. Estrogen promotes HSC proliferation in both male and female HSCs, but female HSCs experience more self-renewing divisions than male HSCs. Estrogen selectively inhibits B lymphopoiesis in females. Estrogen has been shown to increase the number of myeloid cells while suppressing the proliferation of B lymphocyte precursors. During the pregnancy and lactation in female mouse, more HSCs were found in the bone marrow and spleen during pregnancy. In lactating mouse, increased level of prolactin was found to stimulate erythropoiesis. 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. Testosterone increases the proliferation of female but not male erythroid progenitors. In human adult, estrogen increase the number of myeloid progenitor colonies. In malignant hematopoiesis, boys developed more ALL than girls. Higher incidence of MDS, leukemia and non-Hodgkin lymphoma are reported in males than females, suggesting the sex disparity in hematologic malignancy. Two signaling pathways are reported to become active when sex hormones bind their receptors in HSPCs, MAPKp42/p44, and AKT-dependent signaling pathways, which results in cell proliferation (Fig. 3).
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. In females, there are two X chromosomes. The dosage disparity between males (XY) and females (XX) is balanced by the X chromosome inactivation (XCI) process. 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. Hematologic malignancies originate as a result of altered gene expression and XCI escaper mutation. 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. It is an X chromosome-located histone H3K27me3 demethylase gene. In vivo knockdown of KDM6A reduces HSPC colony formation and suppresses the proliferation of several leukemia cell lines, suggesting its potential role as an oncogene. 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. It rescues KDM6A deficiency-induced leukemia development, further supporting the tumor suppressor function of KDM6A/KDM6D genes in vivo. 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. 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. 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.

Furthermore, mosaic loss of chromosome Y (mLOY), which is common in hematopoietic cells, causes DNA damages in HSPCs and accelerates leukemogenesis. The frequency and level of mLOY increase significantly with age. 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 (Table 1).

5. CONCLUSIONS

In both healthy and malignant hematopoiesis, there is sex dimorphism. Through receptors that are selectively expressed...
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.

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