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Critical Differences in Hematopoiesis and Lymphoid Development Between Humans and Mice

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Abstract

During the last five decades, elegant mouse models of hematopoiesis have yielded most of the seminal insights into this complex biological system of self-renewal and lineage commitment. More recent advances in assays to measure human stem and progenitor cells as well as high resolution RNA profiling have revealed that although the basic roadmap of blood development is generally conserved across mammals, evolutionary pressures have generated many differences between the species that have important biological and translational implications. To enhance the utility of the mouse as a model organism, it is more important than ever that research data are presented with regard to how they might be influenced by the species of origin as well as the developmental source of the hematopoietic tissue.

Introduction

The evolution of diverse life forms from a common ancestor and the consequent conservation of certain biological pathways between species have allowed researchers to model human physiology and disease in other animals and study biological questions that would be otherwise impossible to answer. Interestingly, among all the animal species, the mouse (*mus musculus*) has emerged as the principal biomedical laboratory research model. The ascent of mice to model stardom can be traced back to Dr Clarence Little's work a century ago. Early on in his career, Dr Little was mentored by Dr William Castle, a geneticist at the Bussey Institute of Harvard University. At the time, Dr Castle's group was studying Mendelian genetics in a variety of mammalian species. Dr Little's pioneering experiments to create genetically homogeneous models for the study of cancer genetics led to the generation of several inbred mouse lines. He went on to establish Jackson Laboratories, which now supplies laboratory mice to researchers all over the world¹. Small size, high breeding capacity, low maintenance requirements, easy transportability, short lifespan, susceptibility to some diseases that afflict humans, reproducible disease manifestations, genetic and disease phenotype similarities with humans, and easy availability of genetically homogeneous strains caused the mouse to evolve into the default species for human development and disease research (<http://research.jax.org/mousegenetics/>)

[advantages/advantages-of-mouse.html](#)). However, from a historical perspective, the choice of mice over other mammalian species appears to be the result of chance and logistical breeding considerations rather than any evidence that the mouse is a better representative of human biology than other mammals.

The field of hematopoiesis research is no exception to the phenomenon of murine model dominance. Since the concept of the hematopoietic stem cell (HSC) was first developed in mice from bone marrow transplantation experiments by Till and McCullough in the 1960s², the overwhelming majority of the literature on hematopoietic stem and progenitor cell biology has been based on murine studies. A primary reason for this dependence on mice, is that mechanistic studies into human hematopoiesis are hampered by difficulties in direct gene manipulation, and the lack of a physiological human microenvironment for sustained hematopoiesis from HSC in xenogeneic and in vitro models. Significant experimental challenges are also caused by the tremendous genotypic and phenotypic variability among humans, and by limitations on the availability of human tissue. Large animals, particularly non-human primates more closely reflect human physiology and provide essential pre-clinical models, but their use in basic biology research is somewhat limited by cost and similar methodological limitations to studies in humans. In contrast, the ability to perform experimental transplantation studies in genetically in-bred strains of mice and the development of elegant transgenic and knockout mouse models have revealed invaluable insights into mechanisms of normal hematopoiesis and blood diseases in both mice and humans. However, the dominance of murine studies has led surprisingly often to an assumption that the findings revealed using in-bred strains of experimental mice can be universally applied to all hematopoiesis.

The ongoing development of humanized xeno-transplantation models, in vitro culture systems and improved methods to manipulate gene expression are now allowing more targeted and mechanistic studies in human hematopoiesis^{3, 4}. Although these studies have shown that the overall hematopoietic differentiation scheme is conserved between mice and humans, they have also revealed many critical differences in phenotype, function, and regulatory mechanisms of stem cell maintenance and lineage differentiation between human and mouse HSC and progenitors. The biological importance of these species differences and their practical relevance for translational research cannot be overemphasized.

Differences at the HSC level

Accurate immunophenotypic characterization of human HSC and progenitors is essential for any subsequent molecular analysis of lineage commitment as well as clinical diagnostic and therapeutic studies of hematopoiesis. In addition, since the cell surface molecules that provide immunophenotypic definitions often have functional roles, differences between human and murine immunophenotypes may reflect deeper mechanistic species differences, for example, in cytokine and adhesion molecule pathways.

HSC immunophenotypes are not conserved between humans and mice. Differential expression of Sca-1, c-kit, CD150 and CD48 enable the isolation of HSC (lin-Sca+kit+CD150+CD48-) from murine adult bone marrow. One in two lin-sca+kit^{hi}CD150+CD48- cells provides long term HSC activity in transplantation assays⁵. In contrast, CD150, CD48, and sca-1 are not useful for the isolation of human HSC⁶. In humans, HSC and hematopoietic progenitor cells (HPC) do not express CD150, and CD48 is expressed by both HSC and HPC⁶. Human long term HSC activity resides in the CD34+CD38-lin- fraction of cord blood and bone marrow, which expresses the cytokine receptor Flt-3^{7,8,9}. In cord blood, the CD34+CD38-Thy1+CD45RA-CD49f+ immune phenotype is highly enriched for human HSC⁷. Murine HSC on the other hand do not express either CD34 or Flt-3, and

do express CD38^{7, 10}. These immunophenotypic differences may signify functional differences in stem cell maintenance, differentiation, and microenvironmental interaction pathways, between murine and human hematopoiesis. CD150, a member of the signaling lymphocyte activation molecule (SLAM) family has been suggested to play a role in the maintenance of the murine HSC niche¹¹. In mice, Flt-3 signaling is important for lymphopoiesis but not for HSC survival or myelopoiesis¹². Kit Ligand has been shown to be a more potent survival factor than Flt3 ligand in vitro for mouse bone marrow HSC, but the opposite appears to be true for human HSC^{8,13}. The species difference in the effects of cytokines on survival of HSC in vitro has important implications for the design of systems for ex vivo expansion and transduction of human HSC.

Despite numerous similarities in basic cellular mechanisms, there are important differences between HSC of mice and humans in specific roles of transcription factors and cellular behavior such as cycling and DNA damage responses. For instance, mouse HSC have been described as dividing once every 30–50 days⁷ whereas human HSC tend to be more quiescent, dividing every 175–350 days⁷. Irradiation induced DNA damage in murine HSC activates a p53 dependent non-homologous end joining (NHEJ) DNA repair response that promotes cell survival¹⁴. Imperfect repair during NHEJ can result in the persistence of HSC with genomic aberrations and instability⁷. In contrast, irradiation activates a p53 dependent apoptotic response in human HSC⁷. Teleologically one can think of the HSC response to irradiation in mice as being geared toward repairing DNA damage, albeit sometimes imperfectly, and continued survival of the repaired HSC, while that in humans leads to the sacrifice of cells with DNA damage to avoid persistence of cells with genomic perturbations. Functional and cell cycle kinetic differences between HSC from the two species have important implications for the application of results of murine HSC transduction and transplantation studies to the design of gene and cell therapy clinical trials¹⁵.

Differences in the innate immune system

The innate immune system constitutes an antimicrobial defense that appeared during the early part of multicellular organism evolution. It consists of mechanisms that are broadly conserved across species ranging from drosophila to humans. However, the cross talk between the innate and adaptive immune systems has led to important evolutionary changes in the innate pathways that are divergent between species¹⁶. Differences between human and mouse innate systems encompass the dendritic, natural killer, toll like receptor, and defensin components.

Functionally distinct mouse dendritic cells (DC) subsets have been immunophenotypically characterized using differences in expression patterns of CD11b, CD11c, CD8α, CD317, Siglec-H (Sialic acid-binding Ig-like lectin-H) and Ly6. In contrast, Human DC subsets are identified by differential expression of CD303 and CD1c. Comparative genomic studies between mouse and human DC subsets have shown similarities in DC gene expression signatures between the two species. However, with the exception of plasmacytoid dendritic cells, functional characterization of human dendritic cell subsets is still at an early stage¹⁷. One important difference has been reported in the responses of human and mouse DC to VEGF (vascular endothelial growth factor) which may underlie inconsistencies in tumor immune responses between human patients and mouse models¹⁸.

Human Natural killer cell subsets are immunophenotypically defined by differential expression of CD56 and CD16. Mouse NK cells do not express CD56; rather NK1.1¹⁹, CD11c and CD27 are useful markers for the isolation of murine NK cell subsets. Species specific mechanisms underlie NK cell interactions with MHC class I and non MHC ligands.

For instance, human NK cells interact with class I MHC ligands through killer immunoglobulin receptors, whereas murine NK cells interact with these ligands through the structurally different lectin like Ly49 receptors. The NKG2D receptor, which is involved in NK mediated tumor cell destruction, is activated by different ligands in humans and mice. Among the non MHC NK cell receptors, humans express one NKR-P1 receptor subtype whereas a much larger repertoire of NKR-P1 receptor subtypes has been reported in mice²⁰.

13 members of the toll like receptor (TLR) family have been described among humans and mice^{21,22}. Of these, TLR 10 is present in humans but is represented by a pseudogene in mice, and TLR 11–13 are present in mice but represented by a pseudogene in humans^{22,23}. The other 9 TLR are conserved in both species²³. Differences in gene regulatory sequences, cell type distribution, and inducibility of human and mouse TLR genes suggest species specific regulation mechanisms for TLR genes²⁴. Species differences in functional features of TLR include the recognition of single stranded RNA by human TLR8 (in mice the corresponding role is played by TLR7)²⁵ and lipopolysaccharide (a TLR4 agonist) induced gene expression changes in macrophages²⁶.

Species specific tissue distributions of antimicrobial peptides include the expression of a wide variety of defensins in the murine intestine and the high expression of defensins in human neutrophils. In contrast murine neutrophils do not express defensins and the human intestine expresses only two defensins²⁷.

NKT1 cells, which border the innate and adaptive systems, show a wider repertoire of TCR beta expression in mice (V β 8, V β 7 or V β 2) than in humans (V β 11). From a functional standpoint, the specificity of NKT1 cell antigen receptors is directed toward different portions of the glycolipid molecule in the two species²⁸.

Species differences in innate pathways have critical implications for the design of murine models for human immune diseases, and the clinical translation of NK and NKT immunotherapies.

Differences in the Adaptive Immune System

Genetic mutations associated with human immune deficiencies have shown that there are specific differences in the regulation of lymphoid differentiation between human and mice. IL-7 signaling through the cytokine common gamma chain receptor (aka IL2RG) plays an indispensable role in murine B lymphopoiesis but based on the phenotypes seen in genetic mutations in X-linked and Jak3-deficient human Severe Combined Immune Deficiency, common gamma chain signaling is not essential for human B lymphopoiesis²⁷. Consistent with its functional role, surface expression of IL-7 receptor alpha (IL7R α) defines mouse lymphoid progenitors but is not included in immunophenotypic definitions of human lymphoid progenitors⁷. Defects in BLNK and ZAP70 produce different degrees of lymphoid differentiation arrest in mice and humans, suggesting lymphoid developmental stage-specific species differences in these lymphocyte signaling pathways²⁷.

The earliest phase of lymphoid differentiation from bone marrow HSC is marked by a so-called “lymphoid primed multipotent progenitor” (LMPP). In murine studies, LMPP are identified by cell surface expression of Flt3, which is upregulated from the flt3^{neg} HSC stage¹³. Recent studies in human bone marrow have now identified a functionally similar progenitor to the murine LMPP based on high expression of L-selectin (CD62L); although flt3 mRNA is higher in human LMPP than in HSC, flt3 protein expression is not useful in human lymphoid progenitor studies as it is expressed at similar levels in HSC and LMPP⁹.

Major species differences exist between the immunophenotype of thymocytes prior to development of CD4+CD8+ (DP) cells. The earliest stages of murine thymopoiesis are found in the CD4–CD8– (Double Negative) population, which is further subdivided into 4 developmental stages (DN1-4) based on the expression of CD25 and CD44²⁹. In humans however, CD44 and CD25 are not useful for identifying subsets of the DN population. Rather human DN thymic progenitors can be subdivided into a primitive CD34+CD1a– stage and a more differentiated CD34+CD1a+ stage³⁰. Although most CD34+CD1a– cells express CD7, a small subset of CD34+CD1a–CD7– thymocytes exist that have multilineage potential and a gene expression profile reflecting a recent transition from HSC³¹. In contrast to the murine DN1 population, which does not express CD25 (IL-2 receptor alpha), a significant proportion of the most immature human thymic progenitor cells (CD34+CD7–) express CD25³¹. In addition to these immunophenotypic differences, critical events during T cell differentiation occur at different stages in the mouse and human thymus. CD1a expression marks the earliest T-lineage committed thymic progenitors in humans but not in mice. Beta T cell selection takes place at different stages in murine (the DN3 progenitor stage) and human thymopoiesis (during the immature single progenitor to double positive progenitor stage transition)^{29,32}.

Mature B and T lymphocytes have species-specific expression patterns for certain cell surface markers that probably reflect underlying differences in adaptive immune responses. Functional differences in lymphocytes from the two species encompass immunoglobulin subtypes. The evolutionary divergence of mouse and human immune genes and the consequent lymphoid differences may be a manifestation of differences in pathogen exposure, lifespan, and selection related to the non immune functions of certain immune genes²⁷.

Differences in hematopoietic gene regulation networks

Gene regulation networks governing self-renewal, differentiation, lineage commitment and immune diversity in hematopoiesis consist of transcription factors, microRNAs, long non coding RNAs, epigenetic modifiers of chromatin and post translational modifications. Many, but not all, of the same genes specifically expressed in murine HSC are also expressed in human CD34+CD38–lin– HSC fractions⁷. However, the need for genomic fidelity and a wider immune repertoire over a several fold longer human lifespan makes it likely that there are evolutionary differences in hematopoietic gene regulation between humans and mice. One such example is the transcription factor *HoxB4*, the over-expression of which induces a 1000 fold expansion of murine HSC but only a 2–4 fold expansion of human HSC, suggesting that regulation of self-renewal is similar but not identical in mice and humans⁷. Advances in sequencing and array technologies that interrogate regulatory mechanisms like non coding RNAs and epigenetic modifiers will no doubt reveal even more such species differences in hematopoietic molecular mechanisms beyond expression of transcription factors. Examples already uncovered include the epigenetic mechanisms controlling hemoglobin beta-globin gene expression³³, and hematopoietic lineage-specific expression of certain microRNAs³⁴.

Conclusion

Humans and mice are thought to have diverged from a common placental mammalian ancestor 65–110 million years ago³⁵. Differences in pathogen exposures, body sizes and lifespans have resulted in an evolutionary accumulation of genomic changes that account for the biologic differences between humans and mice. These changes include species specific duplications of transcription factors and immune genes³⁵.

By providing a means for hematopoietic tissue specific gene manipulation, murine models constitute a useful tool for answering mechanistic questions in an in vivo context. However, functional characteristics and immunophenotypes vary even between HSC from different mice strains^{36, 37}. Unknown bias introduced by the genetic background of the mouse strain, and the genetic homogeneity of the strain could yield results that are not applicable to a genetically heterogeneous human population. Murine immune and hematopoietic studies in controlled artificial environments may not replicate the interactions of the human hematopoietic system with a diverse microbial environment³⁸.

The development of hematopoietic cell therapy and the study of human leukemia and bone marrow failure syndromes all rest on a better understanding of normal human hematopoiesis than currently exists. Work with mouse models will continue to provide vital breakthroughs in knowledge that can often be applied, at least conceptually and often specifically, to human hematopoiesis. Nonetheless, it is crucial that the limitations in interpretation of these studies be made explicit to encourage a thorough understanding and appreciation of how data can and cannot be applied to human biology and ultimately whether it can be used clinically. With this challenge in mind, *we encourage authors and journals to include in titles and abstracts, the species used when publishing original studies, even if the species is the mouse*. It is particularly important that review articles make explicit the species from which they are citing prior studies as these formats are often turned to for universal truths by readers with less specialized knowledge of the area. When citing data from murine (or other non-human species) it would also be helpful to acknowledge when human data on the issue are either contradictory or absent. For similar reasons, reports of human studies should be careful to make clear how the developmental source of the hematopoietic cells under study (fetal liver vs. cord blood vs. bone marrow vs. mobilized peripheral blood), the potential limitations of xenogeneic and other assay models, and the ability of immunophenotype based isolation strategies to enrich for human functional HSC may affect interpretation of results. Such species awareness will ensure that research in non-human and human hematopoiesis will continue to sustain and enhance the evolution of both fields.

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