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Human and murine erythropoiesis

Xiuli An^{a,b,c}, Vincent P. Schulz^d, Narla Mohandas^b, and Patrick G. Gallagher^{d,e}

^aLaboratory of Membrane Biology, the New York Blood Center, New York, New York, USA

^bRed Cell Physiology Laboratory, the New York Blood Center, New York, New York, USA

^cCollege of Life Science, Zhengzhou University, Zhengzhou, Henan, China

^dDepartment of Pediatrics, Yale University School of Medicine, New Haven, Connecticut, USA

^eDepartment of Pathology and Genetics, Yale University School of Medicine, New Haven, Connecticut, USA

Abstract

Purpose of review—Research into the fundamental mechanisms of erythropoiesis has provided critical insights into inherited and acquired disorders of the erythrocyte. Studies of human erythropoiesis have primarily utilized in-vitro systems, whereas murine models have provided insights from in-vivo studies. This report reviews recent insights into human and murine erythropoiesis gained from transcriptome-based analyses.

Recent findings—The availability of high-throughput genomic methodologies has allowed attainment of detailed gene expression data from cells at varying developmental and differentiation stages of erythropoiesis. Transcriptome analyses of human and murine reveal both stage and species-specific similarities and differences across terminal erythroid differentiation. Erythroid-specific long noncoding RNAs exhibit poor sequence conservation between human and mouse. Genome-wide analyses of alternative splicing reveal that complex, dynamic, stage-specific programs of alternative splicing program are utilized during terminal erythroid differentiation. Transcriptome data provide a significant resource for understanding mechanisms of normal and perturbed erythropoiesis. Understanding these processes will provide innovative strategies to detect, diagnose, prevent, and treat hematologic disease.

Summary—Understanding the shared and different mechanisms controlling human and murine erythropoiesis will allow investigators to leverage the best model system to provide insights in normal and perturbed erythropoiesis.

Keywords

alternative splicing; erythrocyte; erythropoiesis; next-generation sequencing; noncoding RNA; RNA seq; transcriptome

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Correspondence to Patrick G. Gallagher, Department of Pediatrics, Yale University School of Medicine, 333 Cedar Street, P. O. Box 208064, New Haven, CT 06520-8064, USA. Tel: +1 203 688 2896; fax: + 203 785 6974; patrick.gallagher@yale.edu.

Conflicts of interest

None of the authors have any conflicts of interest to report.

INTRODUCTION

This is a review of recent advances in our understanding of human and murine erythropoiesis gained from transcriptome-based analyses. Advances in genomic technologies, particularly next-generation ultrahigh-throughput sequencing, have transformed our understanding of gene expression and gene regulation, as well as our understanding of mechanisms of human disease [1]. Comprehensive information on the composition of cellular transcriptomes obtained by RNA sequencing (RNA-seq) has provided us with detailed, unbiased knowledge about transcript composition and abundance, including knowledge about novel transcripts, novel isoforms, alternative splicing, and allele-specific isoform expression [2–4].

Studies of fundamental mechanisms of erythropoiesis in both human and mouse have provided critical insights into inherited and acquired disorders of the erythrocyte. Analysis of human erythropoiesis has primarily utilized in-vitro systems, whereas murine models have provided insights from both in-vitro and in-vivo studies. Despite their widespread utilization, detailed comparisons of human and murine erythropoiesis have not been performed. Although the essential body plan and critical physiologic axes are well conserved, humans and mice have diverged significantly. At the genomic DNA level, about half of human genomic DNA can be aligned to murine genomic DNA, with only a small percentage (~5%) under purifying selection in mammals [5]. This report reviews recent insights into human and murine erythropoiesis obtained from transcriptome studies during terminal erythroid differentiation.

HUMAN AND MURINE ERYTHROPOIESIS

It has long been known that there are fundamental differences between human and murine erythrocytes. Human erythrocytes have larger mean corpuscular volume (90 vs. 52 fl), longer life span (120 vs. 42 days), higher oxygen affinity (P50 25 vs. 40mm Hg), and lower levels of 2,3-diphosphoglycerate. Known differences between human and mouse exist in membrane protein structure and function, glucose utilization, vitamin C metabolism, signaling pathways, regulation of ion content and cell size, and mechanisms of stress erythropoiesis [6–13]. The variations in globin gene composition and developmental regulation between human and mouse are well documented [13,14]. Differences between human and murine erythrocytes persist *ex vivo*, as murine erythrocytes exhibit a much shorter half-life during storage [15]. Limited information on transcript isoform composition generated by alternate splicing in erythroid cells, such as the differences in exon composition of the delta-aminolevulinate synthase-2 gene cDNAs between mouse and human, is available [16]. Until recently, detailed analyses of transcript type and abundance in human or murine cells during terminal erythroid differentiation have been lacking [17–23].

TRANSCRIPTOME ANALYSES ACROSS TERMINAL ERYTHROID DIFFERENTIATION

An *et al.* isolated pure populations of human and murine erythroblasts at distinct stages in erythroid development using FACS-based methods to purify morphologically and functionally discrete populations of cells, each representing specific stages of terminal erythroid differentiation [24–26]. RNA from these cells underwent RNA-seq analyses, to create differentiation stage-specific transcriptomes [17■].

Bioinformatic analyses of these transcriptomes revealed that there was tight clustering of biologic replicates from the different stages of terminal erythroid differentiation. There were remarkable differences between the individual stages at the transcriptional levels in both man and mouse. There were both shared and dissimilar gene expression profiles defining each stage of terminal erythroid differentiation within transcriptional space. These temporal changes in gene expression across differentiation revealed that each stage possesses a unique transcriptome. Clustering and network analyses revealed that differing stage-specific patterns of expression observed across erythroid differentiation were transcriptionally enriched for genes of varying function.

These observations supported, at the transcriptional level, the long-held tenet that the daughter cells produced during erythroid differentiation are structurally and functionally different than the mother cell from which they are derived. There are numerous phenotypic differences across the developmental and differentiation stages of erythropoiesis, such as changes in cell size and shape, hemoglobin composition and content, membrane structure and function, metabolic programs, nuclear alterations, and, ultimately, enucleation. These have led to the working hypothesis that erythropoiesis is a unique process in which each cell division is simultaneously coupled with a stage of differentiation [24,26–28]. This is in stark contrast to most cell types, wherein each cell division generates two daughter cells almost identical to the mother cell. These observations were true in both human and murine terminal erythroid differentiation, with the major difference being murine cells undergoing one less cell division from the proerythroblast to the orthochromatic erythroblast stages.

There were several major differences between human and murine transcriptomes. The most striking observation from these comparisons was that in contrast to human, there was a near-global decrease in gene expression during murine terminal erythroid differentiation. This was true across many clusters of genes. For instance, there were a variety of patterns of expression of transcription factor genes in human cells, whereas in murine cells, transcription factor expression exhibited the global steady decrease in gene expression across murine terminal erythroid differentiation.

Differences in both individual genes, as suggested by prior studies, for example, *ALAS2*, *GLUT1*, (Fig. 1) and entire groups of clusters of genes were observed between human and mouse (Fig. 2). Differences in signaling pathways, for example, the mitogen-activated protein kinase pathway, and ubiquitination, for example, the E3 ubiquitin ligase pathway, showed major differences between species. These altered patterns mostly mirrored the global decrease in gene expression observed in murine terminal erythroid differentiation,

with genes upregulated in human but downregulated in mouse. Biologic studies have identified similar differences. RHEX, a recently identified regulator of erythroid cell expansion and erythroblast development, is present in human, but not mouse, rat, and lower vertebrates [29].

TRANSCRIPTOMES, CONSERVATION, AND DIVERGENCE

Pishesha *et al.* [19] performed global comparative gene expression analyses of terminal erythroid differentiation using morphologically identical stage-matched populations of human and murine erythroid cells, from early to late erythroblasts. Although the induction and repression of major erythroid transcription factors were mostly conserved between human and mouse, at a global level, there was substantial divergence between species at comparable stages during erythroid differentiation. Exceptions were *SCL/TAL1* and *MYB* genes encoding critical transcriptional regulatory proteins. In humans, *SCL/TAL1* is upregulated only in the polychromatophilic and orthochromatic erythroblast stages, whereas mouse *Scf/Tall* is upregulated earlier in differentiation at the basophilic erythroblast stage. The authors hypothesized that these two differences could significantly alter patterns of gene expression regulated by these two factors and their co-regulatory factors. Computational analyses predicted regulation by similar key transcription factors, GATA1, NF-E2, and KLF1/EKLF, in the promoters of expressed genes at similar stages of erythroid differentiation in both species. These data suggested that key erythroid transcription factors direct groups of developmental and differentiation-stage specific genes in patterns that have evolved throughout evolution.

Investigation of major membrane protein gene expression revealed similar patterns of gene expression in both human and mouse. Genes encoding SPTA1, SPTB, EPB42, EPB41, TMOD1, and EPB49 increased during terminal erythroid differentiation. However, divergence between species did exist, for example, the human *ACTB* and *TNFRSF1A* genes showed no significant changes across differentiation stages, but their mouse orthologs decreased in late-stage erythroblasts, whereas human *ANK1* and *ADD1* gene expression showed minimal changes during differentiation but their orthologs increased during differentiation in mice. *ADD3* gene expression increased in humans, but *Add3* decreased in mice. The interpretation of these findings was that the composition of erythrocyte membranes is globally conserved in mammals; differences are present in certain proteins necessary for species-specific membrane maintenance.

A caveat of both of these studies is that no correlation between gene expression and protein composition is provided. For instance, although gamma adducin mRNA increased during erythroid differentiation in human cells and decreased during differentiation in murine cells, minimal to no gamma adducin protein is present in mature human erythrocytes, whereas it is readily detected in murine erythrocytes [30,31]. In addition, much of the data from these studies were derived from cultured erythroid cells. Obtaining unbiased transcriptomes from uncultured primary erythroid cells at varying developmental and differentiation stages is a priority for our understanding of erythropoiesis in both human and mouse.

ALTERNATE SPLICING

Studying patterns of alternative premessenger RNA splicing across the stages of human terminal erythroid differentiation, Pimentel *et al.* [32■] discovered a complex program of alternative splicing enriched in genes controlling cell cycle, chromatin function, organelle organization, and RNA processing, with numerous alternative splicing events controlled in a differentiation stage-specific manner. Alterations in exon inclusion/exclusion efficiency were prominent in late-stage erythroblasts, paralleling the pancellular alterations associated with the final stages of terminal erythroid differentiation. Interestingly, a subset of splicing alterations was observed that introduce premature translation termination codons thereby decreasing the proportion of full-length coding mRNAs and downregulate gene expression via nonsense-mediated decay (Fig. 3) [32■]. Utilization of posttranscriptional RNA processing pathways, particularly via premature termination codon usage/nonsense mediated decay, appears to be a signification mechanism regulating gene expression at the late stages of terminal erythroid differentiation. These data support the conclusion that a complex, dynamic, stage-specific program of alternative splicing is essential for human terminal erythroid differentiation, playing a critical role in cellular proliferation and differentiation in human erythropoiesis. It will be interesting to examine whether such a program also exists in murine erythropoiesis.

NONCODING RNAs

Utilization of high-throughput sequencing methodology for transcriptome analyses led to the observation that many noncoding RNAs (ncRNAs) are produced within the cell [33]. These ncRNAs are classified as housekeeping RNAs, microRNAs, siRNAs, PIWI-interacting RNAs, small ncRNAs (<200 nt in length), and long ncRNAs (lncRNAs, >200 nt in length).

Several studies have addressed the role of lncRNAs in erythropoiesis. Alvarez-Dominguez *et al.* [22■] identified erythroid-specific lncRNAs in BFU-E, CFU-E, and erythroblasts and demonstrated that these lncRNAs demonstrated dynamic patterns of expression throughout erythropoiesis. Alterations in lncRNA expression during erythropoiesis were reflected at the chromatin level, as patterns of gene expression correlated well with patterns of histone architecture reflecting active and repressive chromatin, and erythroid transcription factors bound the promoter regions of erythroid cell expressed lncRNAs.

Paralkar *et al.* [21] studied lncRNAs obtained from transcriptome analyses of murine fetal liver erythroblasts, megakaryocytes, and megakaryocyte–erythroid progenitor cells. Remarkable lineage specificity was demonstrated for lncRNAs, with ~30% of high stringency lncRNAs detectable in only one of the three cell types examined. When compared with human, murine erythroid lncRNAs were very poorly conserved in both nucleotide sequence and expression, yet they were conserved across eight different mouse strains.

Together, these studies fit well with observations that lncRNA transcription is tightly regulated by cellular developmental or differentiation stage, external environment, and so on [34], and that there is poor conservation of lncRNA sequence across species [35].

TRANSCRIPTIONAL AND REGULATORY NETWORKS

The ENCODE Consortium mapped transcription, replication domains, DNase I hypersensitivity, chromatin architecture, transcription factor occupancy, and replication-timing domains, and compared these in human and mouse [36–38,39■]. Comparison of features obtained from mouse compared with human cells revealed several key results [36]. Although there is significant conservation of patterns of gene expression between species, expression profiles of many murine genes in specific biological pathways show significant divergence from their human orthologues. Much of the *cis*-regulatory landscape has diverged between mouse and human, but this divergence varies widely between different classes of regulatory elements in different cellular contexts. In addition, mouse and human transcription factor networks are much more conserved than *cis*-regulatory DNA. Chromatin domains, as studied via genome-wide analysis of DNA replication timing, are developmentally stable and evolutionarily conserved. A significant caveat to these studies is that they were completed on immortalized cell lines.

IMPLICATIONS

The availability of these data sets is essential for interpreting the transcriptional architecture of erythropoiesis. They can be leveraged to better understand steady state and stress erythropoiesis. These data can be used to create transcriptional circuits during hematopoietic cell development.

These data sets can be utilized to better understand disorders of erythropoiesis, including the bone marrow failure syndromes, aplastic anemia, the myelodysplasia syndromes, and erythroid disorders with prominent ineffective erythropoiesis. Comparative analyses between wild type and variant cells may provide insight into disease pathobiology, allowing understanding of mechanisms of abnormal erythropoiesis over time in specific diseases, and may provide insights into identification of potential therapeutic targets.

As noted by Pishesha *et al.* [19■], global comparisons allow integration of data between human and mouse erythropoiesis, providing insight into why some human hematologic disorders are not recapitulated in mouse models and highlight the problems in translating therapeutic observations from mice to human.

CONCLUSION

Genome-wide based studies are rapidly advancing our knowledge of the transcriptomes of human and murine cells during hematopoietic development and differentiation. Understanding the features that regulate conserved and divergent features of human and murine erythropoiesis is critical. Comparing and contrasting the similarities and differences between human and murine erythropoiesis will provide novel insights into these processes while expanding our understanding of both. Together, these data can be leveraged to improve disease detection and diagnosis, understand and predict disease-specific complications, and develop novel therapeutic strategies for patients with hematologic disease.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

1. Sankaran VG, Gallagher PG. Applications of high-throughput DNA sequencing to benign hematology. *Blood*. 2013; 122:3575–3582. [PubMed: 24021670]
2. Garber M, Grabherr MG, Guttman M, Trapnell C. Computational methods for transcriptome annotation and quantification using RNA-seq. *Nat Methods*. 2011; 8:469–477. [PubMed: 21623353]
3. McGettigan PA. Transcriptomics in the RNA-seq era. *Curr Opin Chem Biol*. 2013; 17:4–11. [PubMed: 23290152]
4. Trapnell C, Williams BA, Pertea G, et al. Transcript assembly and quantification by RNA-Seq reveals unannotated transcripts and isoform switching during cell differentiation. *Nat Biotechnol*. 2010; 28:511–515. [PubMed: 20436464]
5. Waterston RH, Lindblad-Toh K, Birney E, et al. Mouse Genome Sequencing C. Initial sequencing and comparative analysis of the mouse genome. *Nature*. 2002; 420:520–562. [PubMed: 12466850]
6. Subramanian S, Tsai R, Discher DE. The 'metabolon', CD47, and the 'phagocytic synapse': molecular co-localization and species divergence. *Transfus Clin Biol*. 2006; 13:31–38. [PubMed: 16581280]
7. Huang ZY, Barreda DR, Worth RG, et al. Differential kinase requirements in human and mouse Fc-gamma receptor phagocytosis and endocytosis. *J Leukoc Biol*. 2006; 80:1553–1562. [PubMed: 16921024]
8. Wandersee NJ, Olson SC, Holzhauer SL, et al. Increased erythrocyte adhesion in mice and humans with hereditary spherocytosis and hereditary elliptocytosis. *Blood*. 2004; 103:710–716. [PubMed: 12947004]
9. Varki A, Kornfeld S. An autosomal dominant gene regulates the extent of 9-O-acetylation of murine erythrocyte sialic acids. A probable explanation for the variation in capacity to activate the human alternate complement pathway. *J Exp Med*. 1980; 152:532–544. [PubMed: 7411019]
10. Chen D, Kaul DK. Rheologic and hemodynamic characteristics of red cells of mouse, rat and human. *Biorheology*. 1994; 31:103–113. [PubMed: 8173039]
11. Delpire E, Mount DB. Human and murine phenotypes associated with defects in cation-chloride cotransport. *Annu Rev Physiol*. 2002; 64:803–843. [PubMed: 11826289]
12. Montel-Hagen A, Kinet S, Manel N, et al. Erythrocyte Glut1 triggers dehydroascorbic acid uptake in mammals unable to synthesize vitamin C. *Cell*. 2008; 132:1039–1048. [PubMed: 18358815]
13. Hardison RC. Evolution of hemoglobin and its genes. *Cold Spring Harb Perspect Med*. 2012; 2:a011627. [PubMed: 23209182]
14. Peterson KR. Hemoglobin switching: new insights. *Curr Opin Hematol*. 2003; 10:123–129. [PubMed: 12579037]
15. Makley AT, Goodman MD, Friend LA, et al. Murine blood banking: characterization and comparisons to human blood. *Shock*. 2010; 34:40–45. [PubMed: 20090565]

16. Conboy JG, Cox TC, Bottomley SS, et al. Human erythroid 5-aminolevulinate synthase. Gene structure and species-specific differences in alternative RNA splicing. *J Biol Chem.* 1992; 267:18753–18758. [PubMed: 1527005]
- 17■. An X, Schulz VP, Li J, et al. Global transcriptome analyses of human and murine terminal erythroid differentiation. *Blood.* 2014; 123:3466–3477. [PubMed: 24637361] This is a detailed study of human and murine transcriptomes at varying stages of terminal erythroid differentiation. Detailed bioinformatics analyses are included.
18. Mitchell JA, Clay I, Umlauf D, et al. Nuclear RNA sequencing of the mouse erythroid cell transcriptome. *PLoS One.* 2012; 7:e49274. [PubMed: 23209567]
- 19■. Pishesha N, Thiru P, Shi J, et al. Transcriptional divergence and conservation of human and mouse erythropoiesis. *Proc Natl Acad Sci U S A.* 2014; 111:4103–4108. [PubMed: 24591581] This is a series of analyses of human and murine transcriptome data available in databases across erythroid differentiation. Numerous gene groups are compared between human and mouse.
20. Marques AC, Hughes J, Graham B, et al. Chromatin signatures at transcriptional start sites separate two equally populated yet distinct classes of intergenic long noncoding RNAs. *Genome Biol.* 2013; 14:R131. [PubMed: 24289259]
21. Parakar VR, Mishra T, Luan J, et al. Lineage and species-specific long noncoding RNAs during erythro-megakaryocytic development. *Blood.* 2014; 123:1927–1937. [PubMed: 24497530]
- 22■. Alvarez-Dominguez JR, Hu W, Yuan B, et al. Global discovery of erythroid long noncoding RNAs reveals novel regulators of red cell maturation. *Blood.* 2013; 123:570–581. [PubMed: 24200680] References [20,21,22■] provide detailed analyses of noncoding RNAs in erythroid cells during erythroid development and differentiation.
23. Hattangadi SM, Wong P, Zhang L, et al. From stem cell to red cell: regulation of erythropoiesis at multiple levels by multiple proteins, RNAs, and chromatin modifications. *Blood.* 2011; 118:6258–6268. [PubMed: 21998215]
24. Chen K, Liu J, Heck S, et al. Resolving the distinct stages in erythroid differentiation based on dynamic changes in membrane protein expression during erythropoiesis. *Proc Natl Acad Sci U S A.* 2009; 106:17413–17418. [PubMed: 19805084]
25. Liu J, Zhang J, Ginzburg Y, et al. Quantitative analysis of murine terminal erythroid differentiation in vivo: novel method to study normal and disordered erythropoiesis. *Blood.* 2013; 121:e43–e49. [PubMed: 23287863]
26. Hu J, Liu J, Xue F, et al. Isolation and functional characterization of human erythroblasts at distinct stages: implications for understanding of normal and disordered erythropoiesis in vivo. *Blood.* 2013; 121:3246–3253. [PubMed: 23422750]
27. Dzierzak E, Philipsen S. Erythropoiesis: development and differentiation. *Cold Spring Harb Perspect Med.* 2013; 3:a011601. [PubMed: 23545573]
28. Wong P, Hattangadi SM, Cheng AW, et al. Gene induction and repression during terminal erythropoiesis are mediated by distinct epigenetic changes. *Blood.* 2011; 118:e128–e138. [PubMed: 21860024]
- 29■. Verma R, Su S, McCrann DJ, et al. RHEX, a novel regulator of human erythroid progenitor cell expansion and erythroblast development. *J Exp Med.* 2014; 211:1715–1722. [PubMed: 25092874] This report describes a new phosphoprotein that regulates human erythroid cell expansion and supports the final stages of terminal erythroid differentiation.
30. Pasini EM, Kirkegaard M, Salerno D, et al. Deep coverage mouse red blood cell proteome: a first comparison with the human red blood cell. *Mol Cell Proteomics.* 2008; 7:1317–1330. [PubMed: 18344233]
31. Pasini, EM.; Thomas, AW.; Mann, M. Red blood cells: proteomics, physiology and metabolism. In: Beaumont, C.; Beris, Y.; Beuzard, C.; Brugnara, C., editors. *ESH handbook on disorders of erythropoiesis, erythrocytes and iron metabolism.* European School of Haematology; 2008.
- 32■. Pimentel H, Parra M, Gee S, et al. A dynamic alternative splicing program regulates gene expression during terminal erythropoiesis. *Nucleic Acids Res.* 2014; 42:4031–4042. [PubMed: 24442673] This report describes creation of a novel algorithm to study alternate splicing and applies it to provide new insights in terminal erythroid differentiation.

33. Sabin LR, Delas MJ, Hannon GJ. Dogma derailed: the many influences of RNA on the genome. *Mol Cell*. 2013; 49:783–794. [PubMed: 23473599]
34. Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. *Cell*. 2013; 152:1298–1307. [PubMed: 23498938]
35. Cabili MN, Trapnell C, Goff L, et al. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. *Genes Dev*. 2011; 25:1915–1927. [PubMed: 21890647]
36. Yue F, Cheng Y, Breschi A, et al. A comparative encyclopedia of DNA elements in the mouse genome. *Nature*. 2014; 515:355–364. [PubMed: 25409824]
37. Stergachis AB, Neph S, Sandstrom R, et al. Conservation of trans-acting circuitry during mammalian regulatory evolution. *Nature*. 2014; 515:365–370. [PubMed: 25409825]
38. Cheng Y, Ma Z, Kim BH, et al. Principles of regulatory information conservation between mouse and human. *Nature*. 2014; 515:371–375. [PubMed: 25409826]
39. Pope BD, Ryba T, Dileep V, et al. Topologically associating domains are stable units of replication-timing regulation. *Nature*. 2014; 515:402–405. [PubMed: 25409831] Detailed genomic studies, including transcriptome data, from the mouse ENCODE project are reported in references [36–38,39]. Comparisons with human genomic data are provided.

KEY POINTS

- There are many differences in programs regulating human and murine erythropoiesis.
- There are significant functional differences in human and murine mature erythrocytes.
- Genome-wide transcriptome profiling during erythropoiesis shows species-specific profiles.
- LncRNAs are poorly conserved between human and murine erythroid cells.

FIGURE 1.

Human and murine erythroid cells have distinct expression profiles at the *SLC2A1* locus. RNA obtained from human and murine erythroid cells at different stages of erythroid differentiation underwent RNA-seq. Integrated genome browser views of normalized mapped RNA-seq read coverage at the *SLC2A1* locus in human and mouse. There is robust expression in human cells at all stages of erythroid differentiation, whereas there is no expression in murine erythroid cells at any stage.

FIGURE 2.

Transcriptome analyses. Human and murine erythroid cells have distinct expression profiles. RNA obtained from human and murine erythroid cells at different stages of erythroid differentiation underwent RNA-seq. The figure demonstrates graphical depiction of a pattern of gene expression levels of a cluster of 318 differentially expressed genes in human and mouse cells. Bioinformatic analyses predict this cluster is related to protein processing.

FIGURE 3.

Stage-specific premature chain termination (PCT) splicing events in human erythroblasts.

(a) Transcripts in which PCT isoforms are more abundant in late erythroblasts because of upregulation of PCT-exons. (b) Transcripts in which PCT transcripts are relatively more abundant in early erythroblasts because of exon skipping events that alter translational reading frame. Gene names and differentiation stage are indicated above each lane, whereas calculated percent spliced in (PSI) values are shown below each lane. Arrowheads indicate PCR bands representing PCT isoforms. * indicates genes for which PCR results indicate larger splicing changes than were predicted bioinformatically. Reprinted with permission from [32■].