From Developmental Transition to Functional Divergence: Transcriptomic Profiling of Placenta and Bone Marrow Identifies Bone Marrow–Specific Links to Hematologic and Immune Disorders

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Abstract

Hematopoiesis during human development occurs in sequential anatomical sites, with the placenta acting as a transient hematopoietic niche and the bone marrow assuming lifelong function. This study aimed to compare gene expression profiles between bone marrow and placenta to assess their function in immune and blood system development. RNA-seq data for three biological replicates of each tissue were obtained from the Human Protein Atlas and analyzed using edgeR. Differentially expressed genes (FDR < 0.05, logFC > 1 and logFC < 1) were functionally annotated using GO, KEGG, and DisGeNET in Enrichr and DAVID. Bone marrow was enriched for immune and hematopoietic processes, while placenta genes were associated with structural and developmental pathways. STRING-based network analysis identified key hub genes such as MPO, BPI, ELANE in bone marrow and linked them to disorders like leukemia, SCID, juvenile arthritis, thalassemia, lymphoma, multiple myeloma, diamond blackfan anemia and SLE. The lack of hematopoietic enrichment in placenta supports its limited role in blood formation during late gestation. These findings emphasize the biological and clinical importance of bone marrow gene expression in hematologic and immune health.

Introduction

Placenta is a highly vascularized organ essential for oxygen and nutrient transport for healthy development of the fetus. It also serves as a site for the formation of Hematopoietic Stem Cells in fetus before bone marrow becomes responsible for this function. In an adult, bone marrow is the primary organ to produce hematopoietic stem cells. These cells act as precursor to all the blood cells including red blood cells, white blood cells and platelets. Though placenta and bone marrow have shared function, they are active at different stages - placenta during early to mid-gestation and bone marrow throughout postnatal life. Bone marrow is a lifelong supplier of blood cells

whereas placenta is responsible for the overall embryonic development including nutrient and waste exchange between mother and fetus. [7]

To better understand the developmental timeline of hematopoiesis, it is important to consider the sequence of anatomical transitions. Human yok sac begins generating primitive erythroid cells leading to the formation of blood 16 days after the conception. At day 19, the intra-embryonic splanchnopleura (AGM) also known as aorta-gonad mesonephros becomes hematopoietic. Shortly after the AGM shows signs of hematopoiesis, macrophage-like cells and hemangioblastic cords arise from mesenchymal cells. Day 24 marks the day when primitive erythroblast cells that morphologically resemble those in yolk sac fill placenta. Around day 30, week 5, liver is colonized by the erythroid progenitor cells for the first time. By week 6, HSCs are found both in CD34+ and CD34- fraction in placenta vasculature. This indicates different stages of stem cell activation and dormancy. During week 8 to 10 there is no sign of hematopoiesis in yok sac. 3 weeks later, second colonization of the liver takes place by multilineage progenitor cells. Leukocytes start to express CD45, a marker of mature immune cells in placenta during week 12-14. At week 15, all progenitor cells express CD34+ in placenta as the proliferation increases and gradually migrate to the final site of hematopoiesis. By week 16 and onwards, bone marrow becomes hematopoietic and supports life-long formation of hematopoietic stem cells making it an essential part of the human body [1]. Term placenta still contains some progenitors but is no longer a hematopoietic organ. It is yet uncertain if placental HSCs are retained in CD34+ and CD34- fractions in term placenta as they are in umbilical cord blood. It remains an open question if the placenta serves merely as a reservoir for hematopoietic progenitor and stem cells during fetal development or whether this organ plays crucial role in definitive hematopoiesis.

The hypothesis driving this project is that low expression of genes involved in hematopoiesis and immune regulation in placenta compared to bone marrow may not support long-term production of blood cells, potentially contributing to blood disorders and immunodeficiencies.

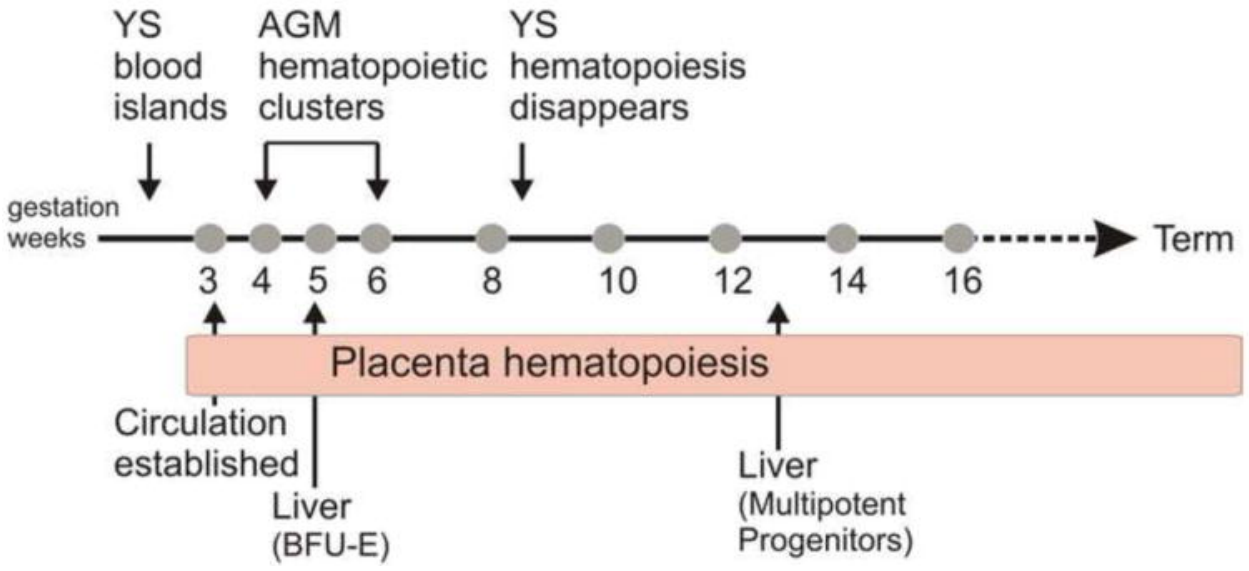

Fig 1. Hematopoiesis timeline in Human

Shows the sequence of anatomical transitions of hematopoiesis in human [1]

Materials and Methods

Data Collection:

RNA-seq data of placenta and bone marrow each with three biological replicates were used for differential gene expression study. The sample data was sourced from Human Protein Atlas (HPA), particularly those reported in the publication by [2]. These tissue samples were collected from healthy individuals who exhibited no signs of disease at the time of collection. Samples were handled in accordance with Swedish legal and ethical standards and were derived through the Department of Pathology, Uppsala University Hospital, and governed by the Uppsala Biobank. All samples were anonymized to ensure compliance with ethical guidelines.

Quality Control and Trimming:

Raw fastq.gz files were examined using **FastQC** (v0.11.9) to evaluate the samples based on per base sequence quality and content, adapter content, sequence length distribution and overrepresented sequences. The sequence quality was high for most of the reads, but some warnings were noted for per sequence quality score and adapter content. Such low-quality reads

(Q<30) and short reads (<50bp) were trimmed using **Trim Galore** (v0.0.6) and **Cutadapt.** This ensured clean reads for accurate mapping.

Mapping and Alignment:

Filtered reads with high quality were mapped to **GRCh38,** human reference genome using **HISAT2** (v2.2.1). Read alignment rates for both placenta and bone marrow samples exceeded 99% indicating high quality sequencing and effective mapping to the reference genome. The resulting files were stored in BAM format.

Counting:

Gene counts were quantified using **HTSeq-count** (v 2.0.1) and the resulting text files were segregated into tissue specific genes are served as input for differential gene expression analysis.

Differential Expression:

Differential gene expression analysis was carried out using **edgeR** (v3.36.0) package in R. The raw count data was normalized to minimize the biases and adjust the differences in library size, thereby enabling accurate comparison of expression levels across all samples. **exactTest** function helped to statistically evaluate differential expression between both the samples by estimating dispersion and testing for tissue-specific expression. Genes were statistically significant if they met a p-value threshold of < 0.05 and represent log 2-fold change greater than or less than 1. A total of 10,682 genes were identified to be differentially expressed.

R Packages:

R packages such as GeneFilter, RcolorBrewer, DESeq2, edgdeR, pheatmap were used to visualize tissue-specificity among genes by plotting Multi-Dimensional Scaling plot and Principal Component Analysis Plot. Biological Co-efficient Variant plot, Smear plot, Correlation matrix and Heatmap reported the differential expression pattern of genes.

Enrichment Analysis:

The differential gene expression list was categorized into two groups based on tissue specificity. All genes with a positive logFC (logFC > 0) and p-value less than 0.05 were categorized as upregulated placenta genes, 6186 genes exhibited higher expression in placenta compared to bone marrow. Conversely, genes with negative logFC (logFC < 0) and p-value less than 0.05 were grouped as upregulated bone marrow genes. 4496 genes were highly expressed in bone marrow compared to placenta. GO terms and Kegg pathways associated with these significant genes were identified using **Enrichr** (MaayanLab v2025) and **DAVID** knowledgebase (v 2025_1). **DisGeNET** from Enrichr was used to study diseases caused by these genes.

Network Visualization:

Protein-protein interaction (PPI) and gene-disease association network was built using **Cytoscape** (v3.10.3) and **STRINGdb** (v2.2.0). Cytoscape and STRING was used to study the interaction of top upregulated bone marrow genes, where network topological parameters such as node degree was used to identify hub nodes and peripheral nodes. Additionally, STRINGdb was employed to construct gene-disease network, linking upregulated bone marrow genes to hematological and immunological disorders.

Results

Preprocessing:

Table 1. Sequencing quality evaluation

Sample	Tissue	Total reads Processed	Reads with Adapters	%reads removed for low quality	% reads filtered out due to short length
Bonemarrow_5a	Bone marrow	20,000,000	7,27,769,781 (36.3%)	3.80%	4.60%
Bonemarrow_6a	Bone marrow	20,000,000	8,301,042 (41.5%)	2.90%	2.60%
Bonemarrow_6b	Bone marrow	20,000,000	8,169,896 (40.8%)	2.80%	2.60%
Placenta_3a	Placenta	20,000,000	9,088,194(45.4%)	5%	5.40%
Placenta_6a	Placenta	20,000,000	8,726,820(43.6%)	2.9%	3.1%
Placenta_6b	Placenta	20,000,000	9,137,705(45.7%)	2.80%	2.90%

The table shows RNA-seq quality metrics for bone marrow and placenta samples. All samples had 20 million reads. Placenta samples had higher adapter content (~44–46%) than bone marrow (~36–42%). Quality and short-read filtering percentages were low in all samples (2.8–5.4%).

Differential Gene Expression:

Top 10 differentially expressed genes are shown in Table 2. Among the top differentially expressed genes, several placenta-upregulated genes were associated with developmental and structural functions. DLK1, a negative regulator of hematopoietic stem cell expansion, showed high expression in the placenta with logFC value of 14.62, supporting the tissue's limited hematopoietic capacity. EGFL6, involved in angiogenesis and tissue remodeling, and CAPN6, which regulates microtubule dynamics and cytoskeletal organization, were also significantly elevated (logFC = 15.03 and 15.42, respectively). Additionally, COL4A1, a key component of the basement membrane, showed strong upregulation (logFC = 12.22), highlighting extracellular matrix activity in the placenta.

Conversely, bone marrow-upregulated genes reflected its hematopoietic and immune roles. MPO (logFC = –10.56), AZU1 (–11.64), and CTSG (–10.52) were significantly upregulated in bone

marrow, consistent with their known functions in innate immunity, antimicrobial activity, and inflammation regulation. These findings reinforce the functional divergence between the two tissues, with placenta supporting structural and developmental roles and bone marrow driving immune and hematopoietic processes.

Table 2. Top Genes with Differential Expression in Placenta and Bone marrow

Gene	LogFC	LogCPM	p-value	FDR
DLK1	14.62288	9.978944	3.174601e-75	2.454316e-70
EGFL6	15.03279	8.701953	2.706645e-71	1.046267e-66
COL4A2	11.95712	10.400691	9.248565e-69	2.383386e-64
CAPN6	15.42297	7.145907	104617e-68	7.933302e-64
COL4A1	12.21574	10.897552	5.950892e-68	9.201389e-64
PAGE4	15.46058	7.183490	3.187225e-67	4.106793e-63
MPO	-10.56083	11.579160	8.343941e-67	9.215406e-63
AZU1	-11.63981	9.744137	1.631443e-66	1.576607e-62
LIPG	12.71926	7.186288	3.880884e-66	3.333722e-62
CTSG	-10.51636	9.637341	6.096452e-66	4.713228e-62

Genes such as DLK1, EGFL6, COL4A2 with positive logFC values were upregulated in placenta and genes such as MPO, AZU1, CTSG with negative logFC values were highly expressed in bone marrow.

Mapping and Alignment:

Placenta and bone marrow both showed high read alignment rates of 99% demonstrating high sequence quality and efficient read alignment to the human reference genome GRCh38. This high mapping rate reflects minimal contamination or technical noise, ensuring the reliability of downstream differential expression analysis.

Multidimensional Scaling (MDS) and Principal Component Analysis (PCA) Reveal Tissue-Specific Expression Patterns

The bone marrow and placenta samples formed two distinct clusters in MDS plot (Fig 2) and PCA plot (Fig 3) indicating sharp divergence in gene expression patterns between the two samples.

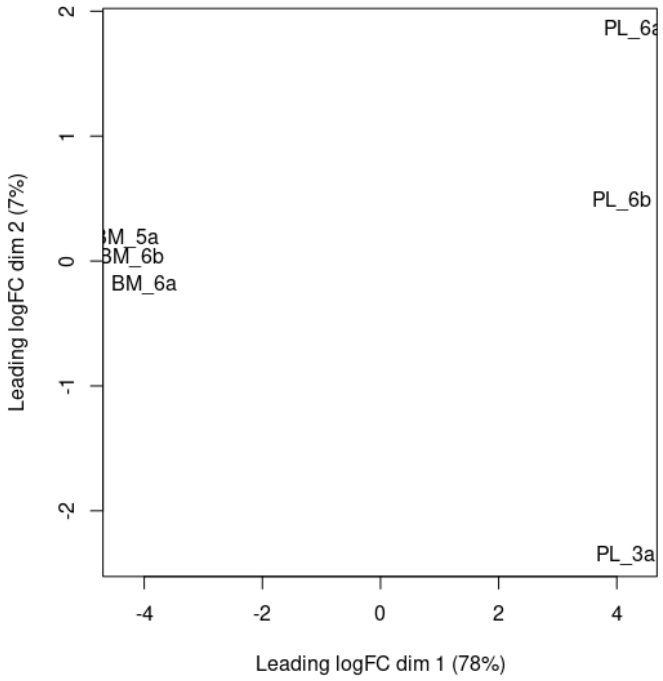

Fig2. MDS Plot

The tight clustering of replicates within each tissue indicates minimal within-group variability

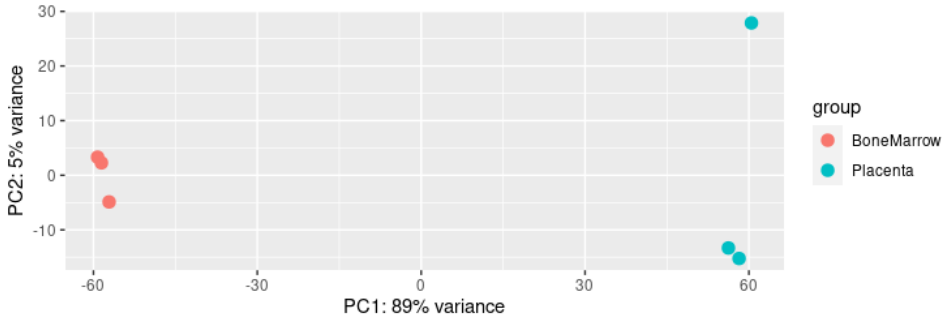

Fig 3. PCA Plot

PC1 accounting for 89% variance distinguishes bone marrow and placenta samples into non-overlapping groups.

Variability of Gene Expression

BCV plot (Fig 4) provides insights into variability of gene expression compared to average expression levels across samples.

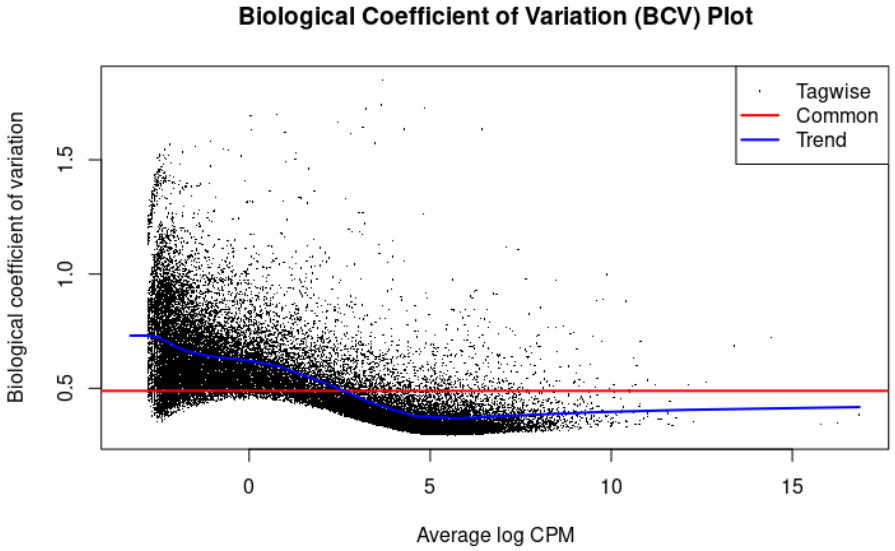

Fig 4. BCV Plot

BCV plot displays reduced gene expression variability with increase in expression level. The trend line dips below common line indicating lower biological variation for moderately expressed genes.

Distribution of Differentially Expressed Genes

Differentially expressed genes can be visualized by a smear plot (Fig 5) which helps identify genes with both statistically significant and biologically meaningful changes in expression.

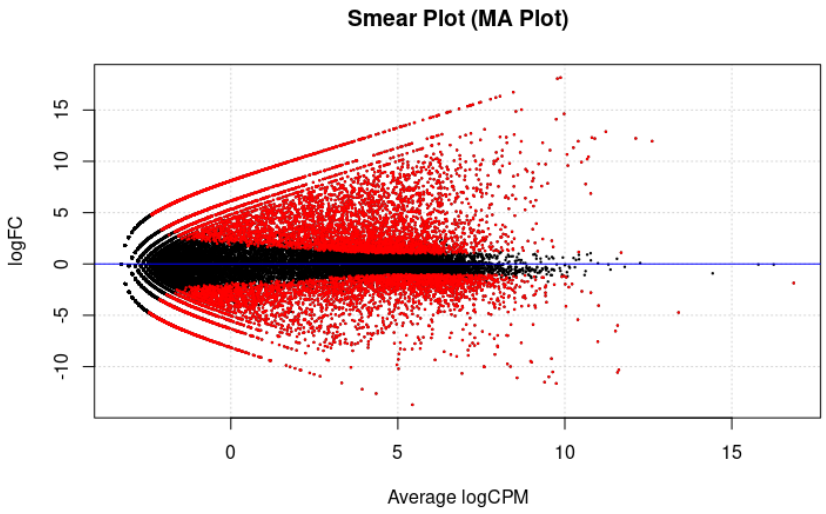

Fig 5. Smear Plot

Red dots represent differentially expressed significant genes. The symmetrical distribution of differentially expressed genes at logFC = 0 indicated upregulated and downregulated genes.

Correlation Matrix:

Correlation matrix (Fig 6) was generated to visualize sample-to-sample distance based on gene expression profile. It clusters samples based on Euclidian distance.

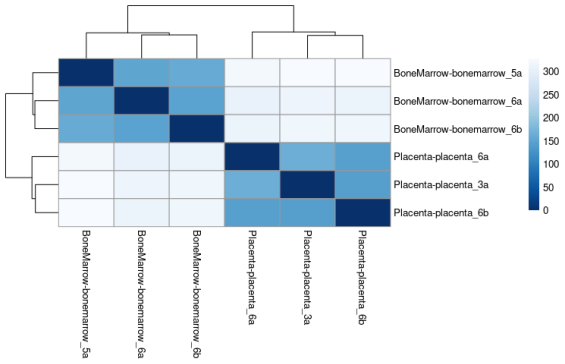

Fig 6. Correlation Matrix

The strong intra-group clustering indicates high biological reproducibility within each tissue type

Expression Pattern of top 50 Differentially Expressed Genes

Heatmap (Fig 7) provides overview of how certain genes are silenced in a tissue type indicating their downregulation in that tissue.

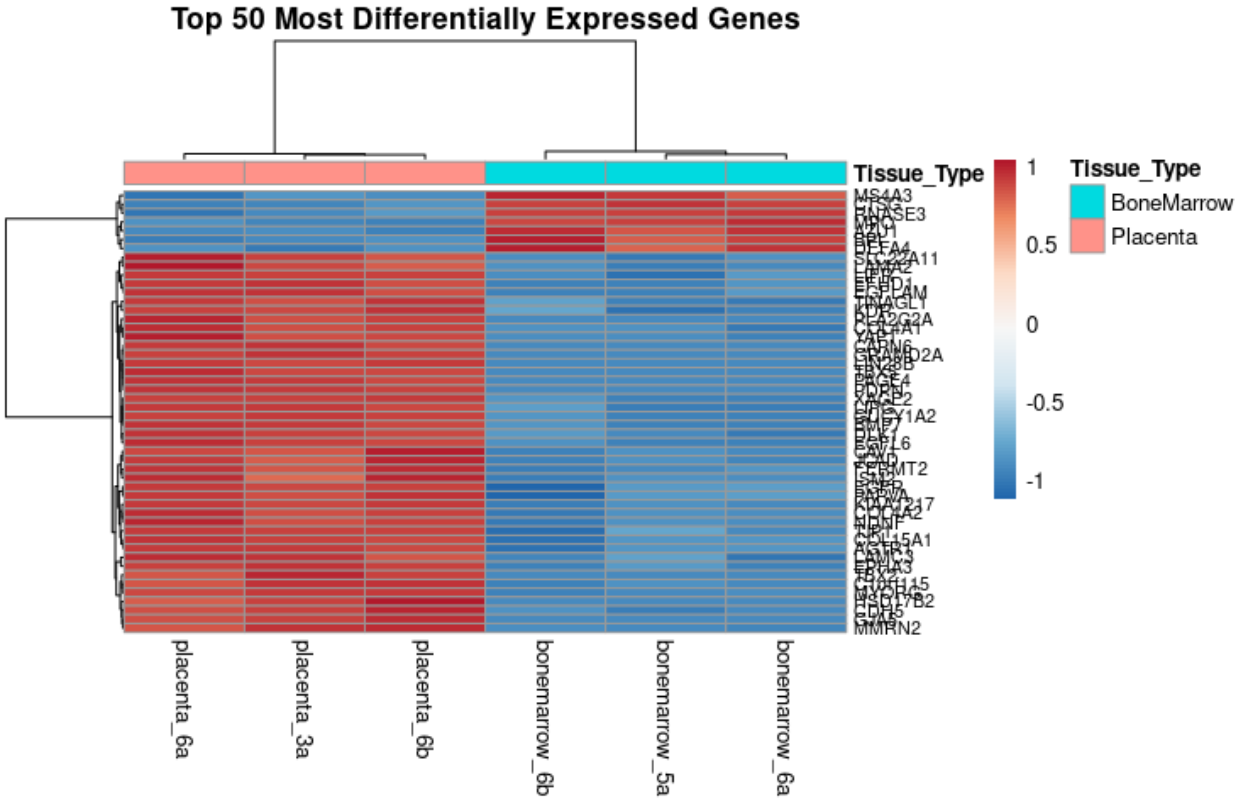

Fig 7. Heatmap

The heatmap clearly separates the samples into two distinct clusters corresponding to placenta (pink) and bone marrow (cyan), confirming a strong transcriptional difference between the two tissues. Genes such as MS4A3, MPO, and DEFA4—known for their roles in hematopoiesis, microbicidal activity, and neutrophil function, respectively—are highly expressed in bone marrow but minimally expressed in placenta. This supports the bone marrow's role in immune defense and blood cell development. In contrast, placenta-enriched genes like SLC22A11, which protects the fetus by transporting organic anions, and LAMA2, a structural component of the basement membrane, are upregulated in placental tissue.

Enrichment Analysis:

Functional enrichment analysis of upregulated bone marrow genes revealed that these genes are active in erythrocyte differentiation, myeloid cell differentiation, antigen receptor mediated signaling, T-cell receptor signaling (Table 3). Further analysis of GO cellular component and molecular function indicates the presence of Major Histocompatibility complex and Fc receptor

bearing cells. KEGG pathways include primary immunodeficiency and hematopoietic cell lineage. This confirms that bone marrow upregulated genes are enriched for immune regulation and stem cell division control.

Upregulated placenta gene expression profile shows the involvement of placenta upregulated genes in extracellular matrix organization, regulation of cell migration and osteoblast differentiation (Table 3). The most enriched cellular components are collagen containing extracellular matrix, basement membrane and cell junctions. These genes perform molecular function such as cell adhesion and growth factor signaling. Key pathways such as Hippo signaling pathway and ECM receptor interaction for development of organs and maintenance of tissue structure underline the placenta's role in supporting fetal growth.

Table 3. Gene Ontology Analysis of Hematopoietic and Immune Processes in Bone Marrow vs. Placenta

GO Term (Biological Process)	**Tissue**	**p-value**	**FDR**	**Interpretation**
Erythrocyte Differentiation (GO:0030218)	Bone Marrow	1.81e-5	0.0045	Strong evidence for red blood cell formation
Myeloid Cell Differentiation (GO:0030099)	Bone Marrow	4.57e-4	0.0425	Strong enrichment of granulocyte formation
Antigen Receptor-Mediated Signaling (GO:0050851)	Bone Marrow	3.39e-10	1.52e-6	Highly significant adaptive immune activation
T Cell Receptor Signaling (GO:0050852)	Bone Marrow	1.04e-7	6.64e-5	Robust T-cell mediated immune function
Regulation of Cytokine-Mediated Signaling (GO:0001959)	Bone Marrow	8.19e-9	1.83e-5	Regulates immune signaling
Humoral Immune Response via Immunoglobulin (GO:0002455)	Placenta	0.1875	0.6607	Weak immune activity
Regulation of Humoral Immune Response (GO:0002920)	Placenta	0.235	0.7673	Not significant
Positive Regulation of Adaptive Immune Response (GO:0002821)	Placenta	0.3495	0.9254	Not significant
Hematopoietic Stem Cell Proliferation (GO:0071425)	Placenta	0.3179	0.8841	Not significant
Hematopoietic Stem Cell Differentiation (GO:0060218)	Placenta	0.7258	1.000	Not significant

Myeloid Cell Differentiation (GO:0030099)	Placenta	0.872	1.000	Not enriched

This table suggests that bone marrow shows strong enrichment for hematopoietic stem cell production and immune response generation but placenta's role in blood cell production and immune regulation is very low implying it does not contribute to long term blood cell generation.

Hypothesis Refinement

The functional enrichment of RNA seq data shows that hematopoietic related processes are not significantly enriched (negligible) in placenta. It was majorly involved in extracellular matrix organization, cell proliferation, organ development. This indicates that the samples were from later period of gestation when the hematopoietic function has already shifted to bone marrow making the samples unfit to test the hypothesis. This was further confirmed from Human Protein Atlas [3] from where the placenta RNA-seq data was collected. HPA analyses gene expression profiles in fully developed human tissues. The HPA's methodology, histology and data reveals that placenta samples collected might be at or near full term as placenta appears to be immunologically and hematologically quiet which is biologically consistent with the known timeline of fetal hematopoiesis which occurs during early gestation and gradually shifts to bone marrow.

This data limitation led to the proposal of a refined hypothesis- The placenta exhibits low or no expression of hematopoietic and immune related genes during later gestation suggesting it is not equipped to support long term blood cell production. Therefore, proper expression of bone marrow genes is critical for immune and blood system development and any disruptions in these genes may lead to hematologic and immunologic disorders.

Protein-Protein Interaction Network

A cytoscape and STRING based protein-protein interaction network (Fig 8) of upregulated bone marrow genes identified cluster of hub nodes including MPO, BPI, ELANE, DEFA4, PGLYRP. Myeloperoxidase heavy chain is a part of host defense system to polymorphonuclear leukocyte. Bactericidal Permeability Increasing protein is associated with human neutrophil granules and has antimicrobial activity against gram negative organisms. Another central gene is ELANE (Elastase enzyme) plays a role is degenerative inflammatory disease through proteolysis of elastin.

Defensin is an antimicrobial and cytotoxic peptide involved in host defense. Peptidoglycan recognition protein 1 is involved in antimicrobial humoral immune response.

Genes such as FLT3, GFI1, SERPINB10 were in the periphery. Receptor type tyrosine protein kinase regulates differentiation, proliferation and survival of hematopoietic progenitor and dendritic cells. Zinc finger protein Gfi-1 (GFI1) is a transcriptional repressor essential for hematopoiesis. Serpin B10 is a protease inhibitor that plays a role during hematopoiesis.

The PPI network shows that the hub genes contributed to immune defense and neutrophil function. On the contrary, peripheral genes influenced the process of hematopoiesis. These findings suggest that upregulated bone marrow genes are highly involved in immune and blood cell development.

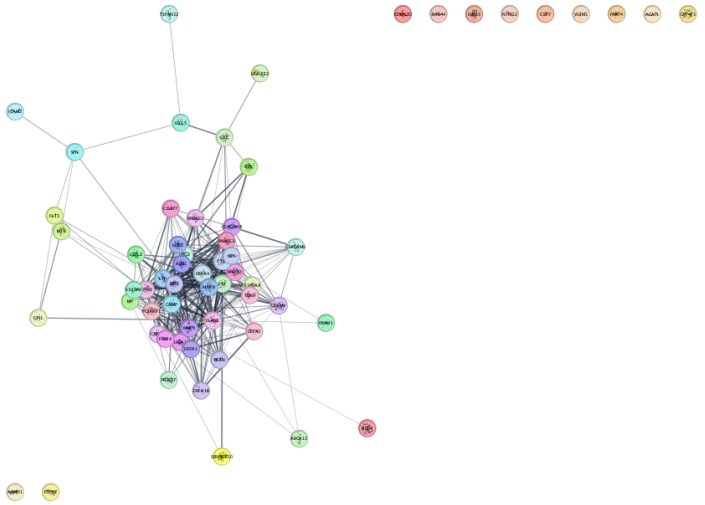

Fig 8. PPI

Protein -protein interaction showing hub genes and peripheral genes

Gene – Disease Network Analysis:

Gene disease association analysis using STRINGdb uncovered that multiple genes that are significantly upregulated in bone marrow are associated with several hematologic and immune related disorders indicating the importance of these genes in immune response regulation and hematopoiesis. (Fig 9) (Table 4) These findings are also supported by publications.

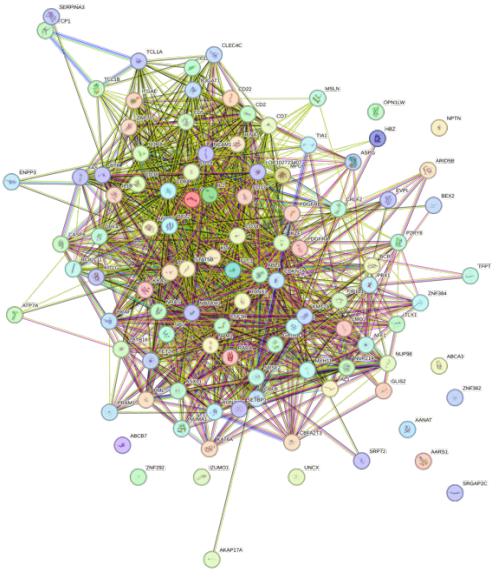

Fig 9a. Leukemia

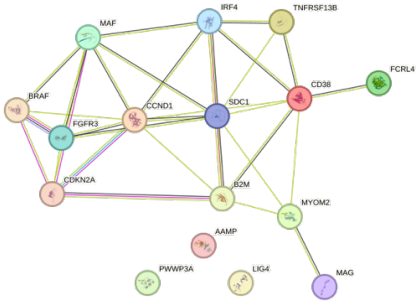

Fig 9b. Multiple Myeloma

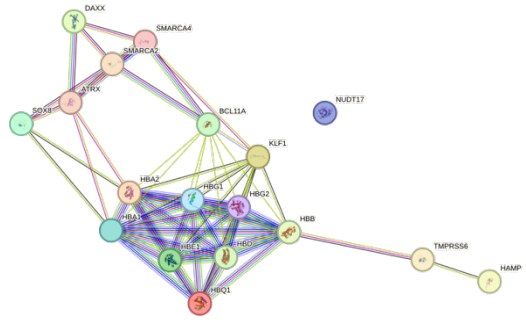

Fig 9c. Thalassemia

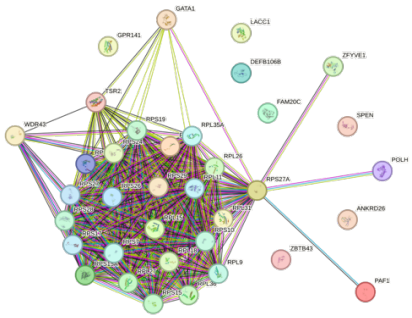

Fig 9d. Diamond Blackfan anemia

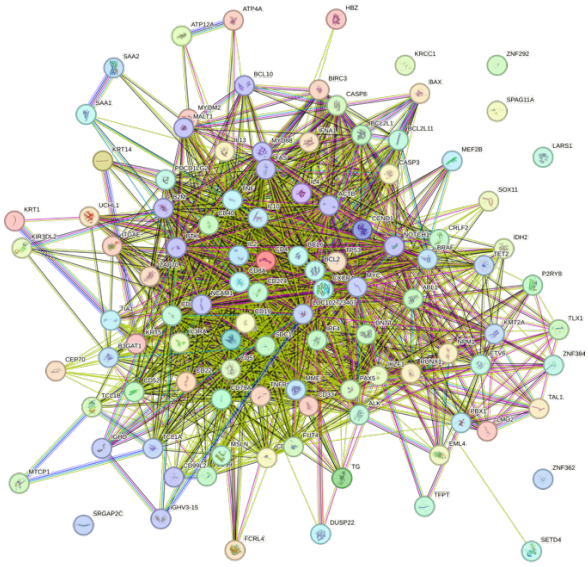

Fig 9e. Lymphoma

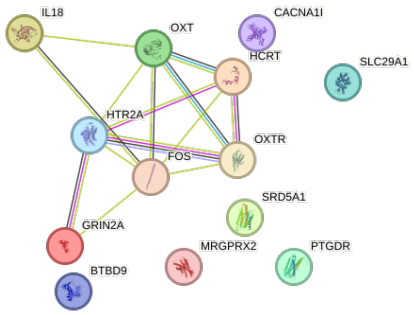

Fig 9f. SLE

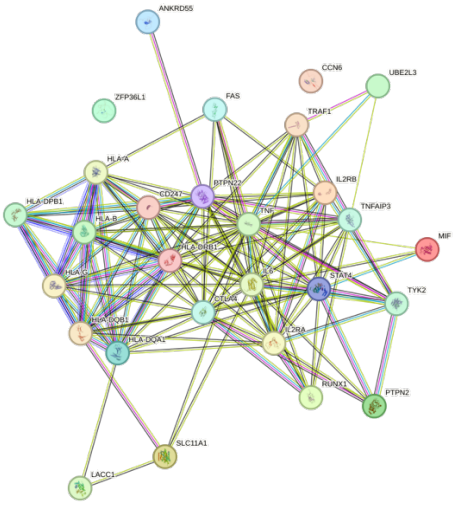

Fig 9g. Juvenile arthritis

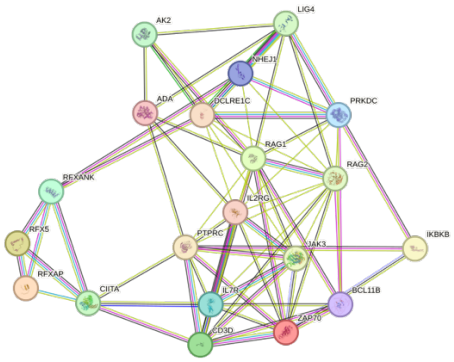

Fig 9h. SCID

Table 4. Disease Mapping of Bone Marrow genes

S.No.	Disease	Type of Disease	Associated Genes
1.	Leukemia	Hematologic Disorder	FLT3 [6] , CD19 [5] , RUNX1, GRAMD1B, IKZF1
2.	Multiple Myeloma	Hematologic Disorder	CD38, CD19 [5], IRFA, BRAF
3.	Thalassemia	Hematologic Disorder	HBA1, HBA2, BCL11A, HBB [5]
4.	Diamond Blackfan anemia	Hematologic Disorder	GATA1 [9] , WDR43, ZBTB43
5.	Lymphoma	Immunologic Disorder	CD19 [5], CD8A, MYD88, CXCR4, GRAMD1B
6.	SLE	Immunologic Disorder	CD8A, MSH5, LY6G5B, PTPN22 [10]
7.	Juvenile arthritis	Immunologic Disorder	IL1B, PTPN22, PTPN2, PSMG2, SH2BB
8.	SCID	Immunologic Disorder	IL2RG, RAG1, JAK3 [12] , DCLREIC, CD8A

The intersection between bone marrow–upregulated genes and key regulators of immune and hematologic diseases suggests that dysregulation of these genes may contribute to blood and immune disorders.

Clinical Implications:

Diseases associated with individual genes was studied using Enrichr DisGeNET. This analysis highlights the clinical relevance of individual bone marrow–upregulated genes, showing that each gene is associated with multiple distinct diseases. Disruption of even 1 gene can have can contribute to a spectrum of diseases including hematologic and immune disorders, emphasizing their potential as biomarkers or therapeutic targets in disease diagnostics and management.

Table 5. Disorders Linked to Individual Gene Dysregulation

Gene	Associated Diseases
CD19	• Trisomy 4 • Plasma cell inflammation • Primary immunoglobin A nephropathy • Cutaneous lymphoma • Infant leukemia
MPO	• Hematological abnormality • Keratoma • Abnormality of immune system • Infant leukemia
AZU1	• Tumor progression • Influenza • Carcinogenesis • Coinfection
CD8A	• Spontaneous abortion • Respiratory tract infection • Prone to bacterial infection • Megakaryocyte leukemia
GATA1	• Hemoglobin increased • Trisomy 21 syndrome • Ineffective erythropoiesis

These findings feature the crucial regulatory role these genes play in maintaining hematologic and immune homeostasis

Discussions:

The results of this study strongly support the refined hypothesis that bone marrow is transcriptionally active in genes essential for hematopoiesis and immune regulation. The clear segregation of tissue-specific gene expression profiles in MDS and PCA plots, combined with strong alignment rates and reproducibility between replicates, indicate that the dataset is robust and suitable for meaningful biological interpretation. The identification of differentially expressed genes such as **MPO, ELANE, CTSG** in bone marrow and **DLK1, EGFL6, COL4A1** in placenta highlights the functional dissimilarity between these tissues. Gene Ontology and KEGG pathway analyses showed that bone marrow genes are highly enriched for hematopoietic processes and immune functions (T cell receptor signaling, myeloid differentiation, antigen receptor signaling), while placenta genes were predominantly enriched for structural and developmental processes of the fetus such as extracellular matrix organization, cell adhesion, and growth signaling. This finding aligns with published literature showing that the placenta plays a transient role in hematopoiesis, supporting HSC expansion only during early gestation and is no longer a hematopoietic organ by term- "despite the presence of cells with an HSC phenotype and CFU-Cs, week 5-6 human placentas lack definitive HSCs" [4]

The gene–disease network analysis further strengthens the biological relevance of these findings. Many of the bone marrow–upregulated genes (e.g., **CD19, FLT3, IL2RG**) are implicated in hematologic and immune disorders such as **leukemia, SCID, and autoimmune diseases** [12] **,** suggesting that these genes serve as critical regulatory nodes in immune system function. The presence of hub genes such as **MPO and BPI** in the PPI network indicates their central role in neutrophil-mediated host defense.

However, one key limitation of this study lies in the nature of the placenta samples, which were sourced from the Human Protein Atlas and likely represent **full-term tissues**. Since hematopoiesis in the placenta predominantly occurs during early gestation, it is plausible that many hematopoietic or immune-related transcripts were not captured in the dataset. This limitation restricted the ability to detect immune- or blood-related disease associations for the placenta-upregulated genes.

Future analyses incorporating **early gestation placenta RNA-seq data**—especially from weeks 6 to 15 could provide a more comprehensive understanding of the placenta's role in fetal hematopoiesis and immunity.

Prospective Research:

1. Placenta RNA-seq data from early gestation (week 3-15) can be used to capture its full hematopoietic potential and uncover disease associations that may be missed in term tissue.

2. Gene knockout or gene editing techniques such as CRISPR cas-9 can be employed to evaluate the role of identified genes in hematopoiesis and immune development.

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