Unique Gene Expression Patterns in Hematopoietic Stem Cells from Various Sources

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ABSTRACT Hematopoietic stem cells are involved in the production of blood cells. These cells are derived from various origins. In this study, we examined, using microarray software GeneSpring GX, whether HSCs derived from four different origins i.e., cord blood, liver, bone marrow and peripheral blood, exhibit unique gene expression pattern. A total of 23 individual normal hematopoietic cell expression profiles were identified in NCBI's GEO database -10 normal CD34+ bone marrow sample, 4 normal CD34+ liver sample, 5 normal CD34+ cord blood sample and 4 normal CD34+ peripheral blood sample. These studies were performed using U133A array platform. The data analysis was done by GeneSpring GX Microarray software 7.3 version. Our results indicated that HSCs derived from various origins exhibited unique gene expression patterns. We also determined the specific biological function of HSCs using upregulated genes that are uniquely expressed in each origin. We observed the following results - cord blood HSCs play an important role in development of embryos; Liver HSCs play an important role in apoptosis, angiogenesis and neural transdifferentiation; Bone marrow HSCs play an important role in cell proliferation, cell migration and cell retention and peripheral blood HSCs play an important role in nucleosome assembly. These HSCs genes present in peripheral blood, when altered, get involved in Systemic Lupus Erythematosus Pathway.

INTRODUCTION

Stem cell biology is currently one of the most exciting areas of biomedical research. Enthusiasm for the application of this technology in regenerative medicine continues to expand (Sylvester and Longaker 2004). Stem cells are clonogenic cells capable of both self renewal and multilineage differentiation (Sharma 2006). There are many potential sources for stem cells. The two important types of stem cells are embryonic stem cells and adult stem cells. The adult stem cell includes mesenchymal stem cells and hematopoietic stem cells (Baharvand et al. 2007). The HSCs are defined by two properties. First, they can produce more HSCs, a process of self renewal. Second, they have the potential to differentiate into various progenitor cells that eventually commit to further maturation along specific pathways. The hematopoietic system is responsible for the production and maintenance of all types of blood and immune cells. They play an important role in hematopoiesis. The highly orchestrated process of blood cell production and homeostasis is termed hematopoiesis (Smith 2003). In mammals, hematopoiesis is divided into two main systems, the primitive embryonic system and the definitive system. It encompasses cellular proliferation, lineage commitment, lineage progression, lineage expression, cellular inhibition and regulated apoptosis. Stem cells exhibit a number of behaviors including quiescence, migration, division, death, self-renewal and differentiation that are orchestrated throughout development and into adulthood within multicellular organisms (Schaffer 2010). HSCs are the best characterized stem cell population in adult organisms. They differentiate into all blood lineages and self-renew to keep a constant pool of HSCs throughout life (Ciriza and Ojeda 2010).

In this study we hypothesized that HSCs derived from different origins will exhibit unique gene expression profiles. Using Genespring microarray software and the data collected from Geo Datasets, we have compared the gene expression profiles of four groups of CD34+ HSCs that were isolated from bone marrow, cord blood, foetal liver and peripheral blood. The CD34 cells, regarded as the population containing hematopoietic progenitor cells, were the valuable fraction when used for transplantation (Sun et al. 2009). CD34+ was the first differentiation marker to be recognized on primitive human HSCs and is the most common marker used to obtain enriched populations of human HSCs and progenitors for research or clinical use. The HSCs from various sources have their own advantages. For transplantation, traditionally, HSCs were obtained from the bone marrow. However, umbilical cord blood has been found to be especially rich in HSCs. During foetal

development, the liver is physiologically a part of the hematopoietic tissues. Although bone marrow has the highest percentage of CD34+ HSCs, an even higher number of CD34+ HSCs can be collected from peripheral blood after mobilization. For HSC transplantation all three types of HSCs are used, but for most other applications mobilized peripheral blood HSCs are most commonly used (Jin et al. 2008).

MATERIALS AND METHODS

Data Collection

Normal hematopoietic cell gene expression data were collected from the NCBI's Gene Expression Omnibus (GEO) database. Bone marrow, liver, HSCs, cord blood, peripheral blood, CD34+ cells were used as search terms to locate datasets containing gene expression profiles of normal HSCs from four different origins.

A total of 23 individual normal hematopoietic cell expression profiles were identified in NCBI's GEO database.10 normal CD34+ bone marrow sample, 4 normal CD34+ liver sample, 5 normal CD34+ cord blood sample and 4 normal CD34+ peripheral blood sample were taken from Geo datasets. These studies were performed using U133A array platform.

Data Analysis

Microarray-based studies of global gene expression have led to dramatic advances in understanding of various biological processes. There are many available platforms for microarray analysis, and newer technologies and better gene hematopoiesis annotations have led to constant refinement of these platforms (Ramasamy et al. 2008). The data analysis was done by GeneSpring GX Microarray software 7.3 version (The application can be installed from CD or can be downloaded from the Silicon Genetics web site), which was used to determine unique gene expression for HSCs from four different origins. It is a commercial software package for microarray data analysis developed by Agilent Technology. Its powerful visualization and analysis solution designed for use with genomic expression data allowed displaying and analyzing large data sets.

The Human Genome page is first uploaded and the Human Genome HG-U133A is display-

ed. The data obtained from Geo Datasets were then imported and analysis of the gene expression profiles was performed. After extracting the expression data, standard normalizations and transformations were performed. These are sensible normalizations and provide a good starting point. The file names are descriptive and so it is easy to figure out the origin of samples. In the add parameter window the "sample source" is made the parameter name and the origin names are added. The highly upregulated and downregulated gene expression compared with different origins were obtained by changing the fold change. Using Venn diagram the unique gene expressions of HSCs from four different origins were obtained.

RESULTS

After analyzing 23 samples from Geo Datasets using Genespring Microarray software, unique gene expressions from various origins were obtained. Total numbers of genes present in samples from four different origins are 22284 out of which 19,156 are common genes present in all the four origins (Fig. 1).
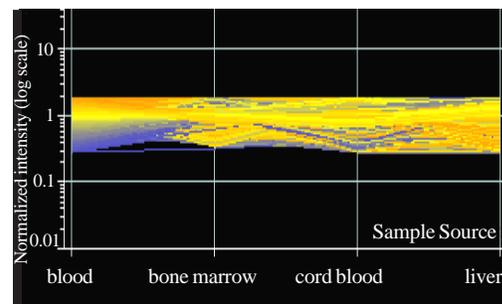
Fig. 1. Common genes present in the entire four origin using Gene Spring

Gene Expression in Cord Blood HSCs

The number of upregulated genes uniquely expressed in cord blood are 31 (Table 1) and the number of downregulated genes uniquely expressed are 27. Upregulated genes in cord blood are those involved in oxygen transport (HBG1, HBG2 and HBE1), cell adhesion (MFAP4 and DPP4), signal transduction (MFAP4, ASGR2 and FCGR2C), immune response (IFI44L, TPSAB1, CLEC10A, PRG3, FCGR2C and CD1C), oxidoreductase activity (SCD5 and

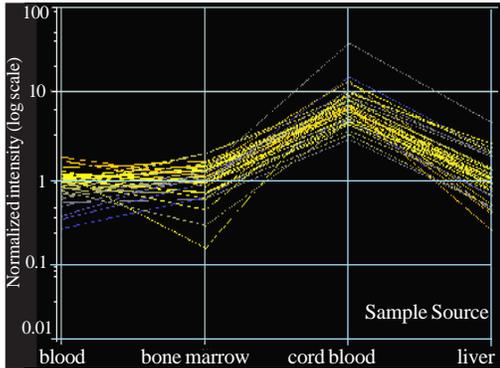EPX), and transcription regulation (ASS1 and ALAS2).

Fig. 2. Genes upregulated in cord blood using Gene Spring

Table 1: List of the genes that are upregulated in cord blood

HBG1	CLEC10A	PRG3	DPP4
HBG2	ASGR2	GYPA	S100P
HBE1	EPB42	SCD	EPX
KRT19	TPSB2	GYPB	TPSAB1
MFAP4	FCGR2C	KRT1	ALAS2
HBBP1	CD1C	RARRES1	ASS1
KCNQ1	CHAC1	FST	AMHR2
HPGD	NKG7	IFI44L	

Gene Expression in Liver HSCs

The number of upregulated genes uniquely expressed in liver are 17 (Table 2) and the number of downregulated genes uniquely expressed are 51. Upregulated genes in liver are those involved in signal transduction (LGR5, NTS, PLCH1, and FCN3) and cell-cell recognition (CLEC4M and RECM).
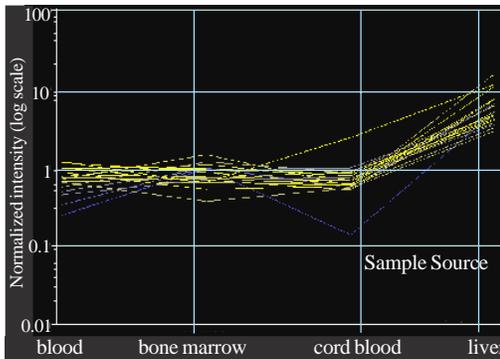

Fig. 3. Genes upregulated in liver using Gene Spring

Table 2: List of the genes that are upregulated in liver

CLEC4M	SNAP25	SCN3A
XIST	RELN	ANGPT2
PRSS2	TMEFF1	HMGA2
LGR5	MSH6	SPTBN1
NTS	GAS1	FCN3
HS3ST3A1	PLCH1	

Gene Expression in Bone Marrow HSCs

The number of upregulated genes uniquely expressed in bone marrow are 103 (Table 3) and the number of down regulated genes uniquely expressed are 6. Upregulated genes in Bone-marrow HSCs are those involved in inflammatory response (GALNAC4S-6ST, CCL18, CCL4, SELE and CCL3), cytokine production (GALNAC4S-6ST, CCL18, CCL4, CCL3, CXCL12, CCL8, AREG, FABP4, OSM and INHBA), immune response (C1QA, CCL18, CCL4, INHBA, VPREB1, POU2AF1, C1QB, HLA-C, CXCL12, CD14 and TREM1), cell-cell signaling (C1QA, MME, CCL3, AREG and INHBA), chemokine activity (CCL18, CCL4, CCL3, CXCL12 and CCL8), receptor activity (CCL4, NR4A2, PCDH21, FOLR2, ITGB5, MSR1 and OR7A5), signal transduction (CCL18, C13orf18, ELTD1, FCN1, MAP2K4, PLCE1, CCL3, IGFBP5, OR7A5, CCL8, HMOX1 and CDK2AP1) and cell adhesion (CCL4 and VCAN).
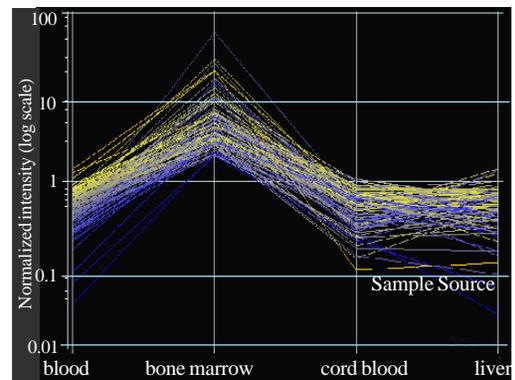

Fig. 4. Genes upregulated in bone marrow using Gene Spring

Gene Expression in Peripheral Blood HSCs

The number of upregulated genes uniquely expressed in peripheral blood are 27 (Table 4) and the number of downregulated genes uniquely

Table 3: List of the genes that are upregulated in bone marrow

IGHA1 /// IGHA2	VPREB3	CD24	HMOX1	PPARG
CXCL12	C1QA	VCAN	MME	NR4A2
S100A8	CCL18	C13orf18	PLCE1	CCL18
MAFB	CCL4	DNTT	FCN1	PCDH21
CD163	IGL@ /// IGLJ3 /// IGLV2-14 ///	CDNA: FLJ21499 fis,	MAP2K4	POU4F1
CD14	MSR1	C13orf18	C1QB	OR7A5
IFI6 /// IGH@ /// IGHG1 /// AREG ///	IGKC /// IGKV1-5 /// VPREB1	VCAM1 MME	HLA-C PALM	SELE FOLR2
CD24	LPL	S100A8	VCAN	NR4A2
GALNAC4S-6ST	CCL20	POU2AF1	THBD	AQP9
FABP4	NNMT	ELTD1	CD24	
CD163	CCL14 /// CCL15	DUSP26	CCL3	PDE4B
NNMT	CCL8	C5AR1	IGFBP5	IGLV2-14
SPARCL1 DKFZp564I083	TREM1	MCL1 (ANTI APAOPTO)	CXCL12	c D N A
TMEM118	SASH1	CXorf57	ZNF771	NR4A3
ITGB5 UG0651E06	EPHA7		FMO3	
TF	INHBA	CD38	MYO10	RNF6
OSM	F3	GJA1(hsa01430)	FLJ20581	SNF1LK
VCAN	MAGEA2 ///	NR4A3	MMP19	NR4A3
CETP	NMU	NR4A1	LPL	

expressed are 51. Upregulated genes in peripheral blood are those involved in cell adhesion (RHOB and SETBP), signal transduction (RHOB and DPXSL3) and nucleosome assembly (NAP1L2, HIST1H3D, H2BFS, HIST2H2AA3, HIST2H2AA4, HIST1H3G, HIST2H2BE, HIST1H3H, HIST1H2AC, HIST1H2BD, HIST1H2AE, HIST1H2BG and HIST1H2BC).

Table 4: List of the genes that are upregulated in peripheral blood

RHOB	HIST1H3D	HIST1H2BG	GBP2
NAP1L2 ARHGDIA	DPYSL3	HIST1H2BC///	
PRR16	JUND	HIST1H2BG HIST2H2AA3/// HIST2H2AA4	KLF9
SETBP1	H2BFS /// HIST1H2BK	HIST1H3G	KLF6
ZNF609	HIST1H2BD	HIST2H2BE	PBXIP1
PBXIP1 :	HIST1H2AE	HIST1H3H	AHNAK
TXNDC3	HIST1H2AC	EHD2	
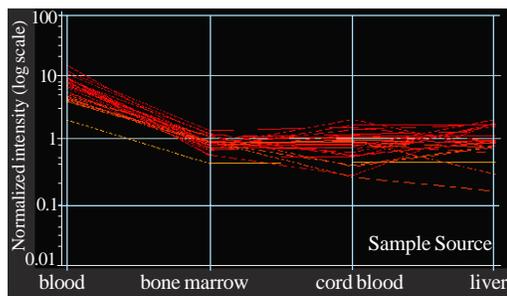
Fig. 5. Genes upregulated in peripheral blood using Gene Spring

DISCUSSION

Microarray analysis of global gene expression has led to rapid advances in our understanding of various physiological and pathological processes (Sohal et al. 2008). GeneSpring GX is versatile software that uses effective ways to compare the gene expressions from various data. The GeneSpring software is used in this study to find the gene expression of HSCs from four different origins.

The HSCs from bone marrow, cord blood, foetal liver and peripheral blood were taken and the unique gene expression pattern was found in each origin. There are various sources for HSCs and the function of the genes present in each origin differs. Hematopoietic stem cells (HSCs) follow a genetically programmed pattern of migration during development. Extracellular matrix and adhesion molecules, as well as chemokines and their receptors, are important in adult HSC migration (Ciriza and Ojeda 2010). The HSCs migrate from cord blood to liver, then to bone marrow and into peripheral blood. In this study the unique gene expression and biological function of these genes were found.

The important function of HSCs is Hematopoiesis. During primitive hematopoieis the first hematopoietic cells arise in the extraembryonic yolk sac and supply oxygen and nutrients to the developing tissues by circulating throughout the embryo (Almici et al.1995). The genes HBG1 (Hemoglobin, gamma A), HBG2 (Hemoglobin,

gamma B), HBE1 (Hemoglobin, epsilon 1) are found to be uniquely expressed in cord blood in this study, are involved in the transportation of oxygen which is essential for embryonic growth. During development in mammals, the first blood cells, called embryonic nucleated erythrocytes, appear in an extraembryonic yolk sac (Fuchs and Segre 2000).The gene EPB42 expressed in cord blood plays an important role in erythrocyte maturation.

Follistatin is an instrument of cellular differentiation. Follistatin (FST) is involved in the development of the embryo. It plays an important role in folliculogenesis within the ovary (Tsai et al. 2007). We found in this study that the gene FST that helps in the development of embryo is uniquely expressed in cord blood.

At a time during foetal development when hematopoiesis is beginning, a nascent immune system also begins to take form. Stem cells generate immune-related cells, such as common myelo-erythroid and lymphoid progenitors, which ultimately develop into the repertoire of differentiated immune cells that provide the body's defense against foreign attack (Kim et al. 2008). It is found in this study that the following genes IFI44L, TPSAB1, CLEC10A, PRG3, FCGR2C and CD1C are involved in the immune response. Thus the unique expression of these genes in cord blood shows that cord blood HSCs play an important role in embryonic development.

The suggestion that adult stem cells may transdifferentiate has in turn given rise to the concept of stem cell plasticity (Wagers and Weissman 2004).Certain genes that have the property of transdifferentiation are found to be uniquely expressed in the liver like NTS (neurotensin) that functions as a neurotransmitter or a neuromodulator, SNAP25 (synaptosomal associated protein) whose function is neurotransmitter secretion and uptake, RELN (reelin) that plays an important role in neuron migration.

Apoptosis is an important process of hematopoiesis. The genes involved in apoptosis include MSH6, GAS1, ANGPT2, which are uniquely expressed in the liver. Angiogenesis has been described as the development of new capillaries from pre-existing vessels and the final result is the formation of new capillary networks (Lee et al. 2008). The angiopoietin ANGPT2 uniquely expressed in the liver is involved in the process of angiogenesis. Thus, this study shows that liver HSCs plays an important role in angiogenesis, neural transdifferentiation and apoptosis.

The migration of HSCs occurs at specific times during development and sometimes in later life (Yu and Thomson 2008). The self-renewal and transdifferentiation capacities of stem cells are worthless unless their migration to target tissues can be appropriately orchestrated. During embryogenesis, blood-forming stem cells migrate from the fetal liver via the circulation, home into the bone marrow, and repopulate it with high numbers of immature and maturing blood cells of all lineages. These, in turn, are released into the circulation while maintaining a small pool of undifferentiated stem cells within the bone marrow. HSC recruitment (mobilization) and homing are mirror processes regulated by the interplay of cytokines, chemokines, and proteases. The homing of hemopoietic stem cells to the bone marrow is mediated by specific interactions occurring between CXCR4, which is expressed on hemopoietic stem cells, and its ligand, stromal cell-derived factor-1 (SDF-1), a CXC chemokine secreted by bone marrow stromal cells (Geminder et al 2001). SDF-1 is secreted by bone marrow stromal cells, and expression of CXCR4 on HSCs facilitates the attraction of the HSCs to the marrow microenvironment by means of chemokine gradient. SDF-1 represents the major chemokine for initiating stem cell migration. The majority of cytokines that mediate stem cell migration do so via modulation either of SDF-1 or of its receptor, CXCR4. Thus, the SDF-1/CXCR4 axis is central for stem cell mobilization from the bone marrow and homing to ischemic tissues (Smart and Riley 2008). The same gene CXCL12/SDF-1 that plays an important role in mobilization of hematopoietic cells is found to be uniquely expressed in the sample from bone marrow in this study thus validating that SDF-1 factor is necessary for mobilization of stem cells from liver to bone marrow.

It is possible that SCF-induced mobilization of stem and progenitor cells from the bone marrow into the blood may be mediated in part by alterations in the interactions of hematopoietic cell integrins with VCAM-1, but multiple mechanisms are likely to be involved. Normal hematopoietic progenitor cells express the integrins VLA-4 and VLA-5 and adhere to stromal cells that display VCAM-1 (Broudy 1997). The same gene VCAM-1 is found to be expressed in bone marrow sample and thus help in the mobilization of hemaopoietic stem cells from bone

marrow to peripheral blood. The most prominent characteristics of stem cells are self renewal and multi- potential differentiation, and homing and migration with ability to replace or treat the damaged tissues (Bahk 2008).

HSCs continuously provide blood components and maintain the immune system during an animal's lifespan. The hematopoietic system utilizes a variety of homeostatic mechanisms to regulate cell production and cell death, and thus maintains a normal level of blood cells throughout life. HSCs sustain blood homeostasis through extensive proliferation and differentiation. The majority of studies to date have focused upon the role of cytokine receptor signaling in stimulating cell proliferation (Watowich 1996). There are numerous types of cells in the body, including neurons, cardiac muscle cells, skeletal cells, kidney cells, liver cells, and so on. They all have the same origin and are made from stem cells which eventually develop the specific phenotypes. These stem cells are found in the bone marrow and proteins like cytokines help stimulate regeneration in stem cells. Hematopoietic stem cells are multi-potent stem cells with high regenerative abilities and are able to develop into a diverse range of cells. The genes having cytokine activity includes GALNAC4S-6ST, CCL18, CCL4, CCL3, CXCL2, AREG, CCL8, OSM, FABP4, and INHBA. They play a major role in cell proliferation, which is an important process in hematopoiesis and were found to be uniquely expressed in the samples from bone marrow in this study.

Chemokines are another class of compounds that are important regulators of hematopoiesis. Chemokines play a role in regulating hematopoietic stem cell functions, including migration, proliferation, and retention. The chemokines like CCL18, CCL4, CCL3, CXCL2 and CCL8 were found to be upregulated in samples from bone marrow. CCL18 is chemotactic for lymphocytes, particularly naive T cells and B cells, and for immature dendritic cells (Wimmer et al. 2006). The regulation of hemopoiesis by growth factors, cytokines and chemokines is mediated through binding to high affinity receptors like G-protein linked receptors. The genes like VCAN, ELTD1 and CCL3 associated with G-protein coupled receptor activity were found to be expressed in a bone marrow sample. This study shows that the bone marrows HSCs are involved in cell proliferation, cell migration and retention.

The proper and harmonious expression of a large number of genes is a critical component of normal growth and development, and the maintenance of proper health. Disruptions or changes in gene expression are responsible for many diseases (Daskalaki and Lazakidou 2006). Systemic Lupus Erythematosus (SLE) is an auto-immune disease that is characterized by the production of antinuclear auto-antibodies. In recent years, several studies have been published which suggest that not DNA itself, but DNA complexed to histones (nucleosomes) is the immunogenic particle involved both in induction of pathogenic anti-DNA antibodies, and in the pathophysiology of SLE (Tax et al. 1995). Nucleosome, complex of histone and DNA, is thought to have a pivotal role in pathogenesis of SLE. The concentration of nucleosome is elevated in SLE, probably related with disease activity. Anti-nucleosome antibody is highly positive in majority of SLE hence this antibody is thought as a diagnostic marker and probably an activity marker for SLE (Mukai 2006). Changes in DNA methylation and histone modifications, the major epigenetic marks, are a hallmark in genes that undergo epigenetic deregulation in this disease (Ballestar et al. 2006). The histone genes H2BFS, HIST1H2BK, HIST2H2AA3, HIST2H2AA4, HIST1H3G, HIST2H2BE, HIST1H3H, HIST1H2AC, HIST1H2BD, HIST1H2AE, HIST1H2BG, HIST1H2BC, HIST1H2BG are uniquely expressed in peripheral blood sample in my studies and are found to be involved in the SLE pathway. Histones are nucleosome assembly protein and are also found to be increased in the peripheral blood in SLE condition from above evidence. Common initial and chronic complaints are fever, malaise, joint pains, myalgias, fatigue, and temporary loss of cognitive abilities. Because they are so often seen with other diseases, these signs and symptoms are not part of the diagnostic criteria for SLE. Since there is no proper diagnosis for SLE, the unique expression of histone genes that are involved in the pathway related to SLE can be used for diagnosis by further studies. Complete deficiency of C1q is almost invariably associated with the development of systemic lupus erythematosus (Korb and Ahearn 1997). This gene is also found to be expressed in peripheral blood. Encouraging responses are raising new hope about the role of adult HSCs in systemic lupus erythematosus (Burt and Traynor 2003).

CONCLUSION

In conclusion, this study shows the unique gene expression pattern of HSCs and its functions in various origins like bone marrow, cord blood, liver and peripheral blood. This gene expression pattern can also be used to find the sample source. HSCs in cord blood play an important role in embryonic development. The bone marrow HSCs are involved in cell proliferation, cell migration and retention. They are also involved in immune response. The Peripheral blood HSCs are involved in nucleosome assembly and in abnormal conditions the histone genes are involved in SLE. The liver HSCs play an important role in angiogenesis, neural transdifferentiation and apoptosis.

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