Online Library Negative Regulators Of Hematopoiesis Studies On Their Nature Action And Potential Role In Cancer Therapy Annals Of The New York Academy Of Sciences Free Download Pdf

Identification of Chromatin Regulators Perturbed in Hematopoietic Stem and Progenitor Cell Aging Jan 27 2021

Functional Characterization of Homeodomain Transcription Factors and Retinoic Acid Signaling in Hematopoiesis Sep 03 2021 Improper regulation of hematopoiesis generates a spectrum of defects that range from anemia and embryonic lethality to leukemia. Identifying the molecular pathways that regulate hematopoiesis is therefore a major goal of both basic and clinical biology. Vertebrate hematopoiesis occurs in two embryonic waves. The first wave, primitive hematopoiesis, influences the morphology of the developing embryonic circulatory system and produces circulating erythrocytes that facilitate tissue oxygenation during periods of rapid embryonic growth. The second, definitive wave of hematopoiesis produces multipotent hematopoietic stem cells (HSCs) that are able to differentiate into all mature blood cell lineages, self-renew, and maintain adult hematopoiesis for life. A major challenge in developmental hematopoiesis is to determine the molecular cues that regulate each phase of hematopoiesis. Previous analyses using vertebrate models have identified molecular pathways that govern both primitive and definitive hematopoiesis. These pathways are conserved among vertebrates, and the critical mammalian hematopoietic genes have clear orthologues in zebrafish. Using zebrafish as a model organism, we have identified essential regulators of both primitive and definitive hematopoiesis. We have defined a critical role for the homeodomain transcription factors Meis1 and Pbx in regulating primitive erythropoiesis. Inhibiting zebrafish Meis1 and Pbx protein synthesis cripples the production of circulating erythrocytes, and generates defects in erythropoietic gene expression. Our data place Meis1 and Pbx upstream of gata1 in the erythropoietic transcription factor hierarchy. We have also elucidated a novel role for retinoic acid (RA) signaling in definitive hematopoiesis, as RA-depleted embryos fail to produce HSCs. Previous studies have implicated RA as a critical regulator of murine Notch1 signaling, and suggest that endothelial cells require RA in order to adopt a hemogenic fate. However, our research suggests that RA is required for HSC formation prior to the formation of dorsal aorta hemogenic endothelium and that, unlike in mice, zebrafish RA does not regulate HSC formation through the Notch1-signaling pathway. Previous research by our lab has implicated the homeodomain transcription factor Hmx4 as a critical regulator of zebrafish forebrain and ocular development, and has shown that Hmx4 modulates RA signaling.

However, prior to this work, the contribution of Hmx4 to embryonic hematopoiesis was unknown. We have identified putative RA-independent and dependent roles for Hmx4 in regulating primitive and definitive hematopoiesis, respectively.

Identification and Characterization of Molecular Regulators of Human Hematopoietic Stem Progenitor Cells May 31 2021

International Conference on Negative Regulators of Hematopoiesis ; 2 Feb 20 2023

Hematopoiesis Aug 14 2022 Hematopoiesis, the latest volume in the Current Topics in Developmental Biology, covers hematopoiesis, with contributions from an international board of authors. Its chapters provide a comprehensive set of reviews covering such topics as the regulation of blood stem cell development, epigenetic mechanisms controlling erythropoiesis, and regulatory RNAs/HSCs. Covers the area of hematopoiesis International board of authors Provides a comprehensive set of reviews covering such topics as regulation of blood stem cell development, epigenetic mechanisms controlling erythropoiesis, and regulatory RNAs/HSCs

Transcriptional Regulation of Hematopoietic Differentiation Sep 22 2020 Gene expression is critical for the development, patterning, and homeostasis of the organism. Precise temporal and spatial regulation of gene expression at the level of transcription requires a large network of sequence-specific factors, general transcription factors, co-factors, and epigenetic regulators. Malignancies of specific tissues often arise from perturbation of various gene expression levels. Hematopoiesis is one of the most sensitive biological processes to mis-regulation of transcription. To generate all blood cell types from embryonic development throughout the lifetime of the organism, hematopoiesis requires an intricate balance between the maintenance of a permanent stem cell pool and differentiation of multi-potent stem cells into cell types with unique functions. To generate a terminally differentiated, functional immune cell, multiple lineage-restricting steps are involved, with each governed by a specific transcription program. Therefore, gene expression regulation in hematopoietic differentiation is particularly important for an organism to properly develop, maintain oxygen transport to all tissues, and fight against infections. Furthermore, because of detailed understanding of how to isolate cells at different stages and lineages of hematopoietic differentiation, it provides an important model to study the development and differentiation of other adult tissues. Hematopoietic stem cells can be driven to differentiate along three main lineages: myeloid, erythroid, and lymphoid. Despite the discoveries of several transcription factors for specific lineages of hematopoietic differentiation, understanding the gene expression program that allow stem cells to make the decision to initiate lymphoid development still remains incomplete. For example, how is the preinititation complex of transcription (PIC) recruited to the gene promoters? Additionally, how are interactions, if any, coordinated among various sequence-specific factors that were identified via gene-by-gene knockout (KO) approaches? To form the PIC at any gene promoter, transcription factor (TF) IIA, B, D, E, F, and H, and RNA polymerase II (Pol II)

must coordinate their promoter-binding and enzymatic activities. TFIID, especially, is important for promoter recognition. As a multi-subunit complex containing TATA-box binding protein (TBP) and 13-14 TBP-associated factors (TAFs), TFIID binds to sequences in the proximal promoter and allows the recruitment of other TFs and Pol II. Previously thought to be invariant from one cell type to another, recently tissue-specific roles for certain TAFs have been uncovered. TAF4B is one of the first TAFs found to have cell-specific expression, since it was identified in human B cells {Dikstein:1996wk}, though a role for its function in hematopoiesis has remained elusive. I used a Taf4b KO mouse line to study its function in both myeloid and lymphoid differentiation. I found that Taf4b KO mice were able to generate myeloid and lymphoid progenitors as well as their wild-type (WT) littermates. Furthermore, both of these types of progenitors from Taf4b KO mice can terminally differentiate into mature cells as well as those from WT mice. Finally, TAF4B-null cells are as competent as heterozygous cells (equivalent to WT in terms of Taf4b expression) to reconstitute the hematopoietic compartment of lethally irradiated mice in all cell lineages tested. In conclusion, TAF4B is dispensable in both myeloid and B cell differentiation. This could be due to TAF4B's high sequence homology with TAF4A. Alternatively, TAF4B can play a role in fine-tuning expression levels of certain B cell or myeloid-specific genes, together with another transcription factor, which cannot be uncovered in a KO mouse approach. I have made a TAF4B-specific polyclonal antibody that can be used to identify its transcriptional targets, as well as identify any potential interaction partners. Though the basal machinery does not seem to play a role in hematopoietic lineage determination, sequence-specific factors have long been implicated in this process. A study using an inducible hematopoietic-specific KO mouse line found that myocyte enhancer factor 2c (MEF2C) is necessary for multi-potent progenitors to differentiate into the lymphoid lineage {StehlingSun:2009df}. Through a candidate approach, I have identified early B cell factor 1 (EBF1) to be a specific interacting partner of MEF2C. Together, they co-occupy and functionally co-activate many B cell specific genes. When MEF2C is depleted in mice, the animals had reduced B cell gene expression as well as increased myeloid gene expression, consistent with MEF2C's role as a lineage fate regulator. I have identified and confirmed several B cell-specific genes that are co-regulated by EBF1 and MEF2C through a genome-wide survey of their binding via chromatin immunoprecipitation followed by exonuclease treatment and deep-sequencing (ChIP-exo). Furthermore, I found that p38 MAPK is the pathway through which MEF2C is phosphorylated and activated to drive B cell differentiation. When phosphorylated, MEF2C prefers to bind its co-activator EBF1, and not its co-repressor HDAC7. Taken together, the results presented in this thesis elucidated the mechanism of activation, binding partners, and downstream targets by which MEF2C is able to regulate lymphoid-specific differentiation. This study contributes to understanding how transcriptional regulation of genes can drive progenitor cells to differentiate down a particular lineage, and provide a novel mechanism for a transcription repressor to switch to

an activator during cellular differentiation.

The Regulatory Role of Non-hematopoietic Bone Marrow Cells on Hematopoiesis in Steady-state and Inflammation Nov 05 2021

BCAP Functions as a Dynamic Regulator of Hematopoiesis and Myeloid Cell Development Jul 13 2022 Hematopoiesis governs the production of mature cells of the lymphoid, myeloid and erythroid lineages. This process occurs in the bone marrow of adult mammals, and generates these lineages throughout life. Furthermore, hematopoiesis is sensitive to multiple insults that drive demand for new hematopoietic cell differentiation, including infection, inflammation and myeloablation. These situations of demand alter hematopoietic differentiation to favor myeloid cell production, in a process known as emergency myelopoiesis. Both steady state hematopoiesis and emergency myelopoiesis are tightly regulated by a variety of signals in order to properly control the output of the different hematopoietic lineages. BCAP (B cell adaptor for PI-3 kinase) is a signaling adaptor protein expressed in hematopoietic cells, where it has a wide array of functions. Here we show that BCAP is expressed in the Hematopoietic Stem and Progenitor cells in the bone marrow, and acts as an inhibitor of myeloid cell development in both the steady state and during demand situations. Furthermore, we show that BCAP inhibits proliferation of the Long-Term Hematopoietic Stem cells, and therefore may regulate the quiescence and/or the self-renewal of this population in the BM. Overall, we have identified BCAP as a novel dynamic regulator of hematopoiesis and myeloid cell development.

Hematopoietic Stem Cell Biology Jan 15 2020 In the summer of 1988, my developmental biology professor announced to the class that hematopoietic stem cells (HSCs) had finally been purified. Somehow, I never forgot the professor's words. When I started working in Dr. Irv Weissman's labo- tory at Stanford as a postdoctoral fellow, I realized that the findings mentioned by the professor were from Weissman's laboratory and had been published in a 1988 edition of the journal Science. It has been over 20 years since the publication of that seminal paper, and since then tremendous advances in understanding the biology and maturation of HSCs, namely the process of hematopoiesis, which includes lymphocyte development, have been made. These discoveries were made possible in part by advancements in technology. For example, recent availability of user friendly fluorescence activated cell sorting (FACS) machines and monoclonal an- bodies with a variety of fluorescent labels has allowed more scientists to sort and analyze rare populations in the bone marrow, such as HSCs. All classes of hematopoietic cells are derived from HSCs. Stem cell biology draws enormous attention not only from scientists, but also from ordinary people because of the tremendous potential for development of new therapeutic application to diseases that currently lack any type of effective therapy. Thus, this type of "regenerative medicine" is a relatively new and attractive field in both basic science and clinical medicine.

Intrinsic and Extrinsic Regulators of Stem Cell Function in Normal and Malignant Hematopoiesis Feb 08 2022

Markers and Regulators Defining the Development of Hematopoietic Stem Cells and Their Niches Jul 01 2021 The future of personalized regenerative cellular medicine depends on the ability to faithfully differentiate pluripotent cells to tissue stem cells, or reprogram them from other cellular sources. So far, the efforts to generate transplantable multi-potent hematopoietic stem cells (HSC) in vitro have yielded hematopoietic cells with only limited functional potential. Thus, improved understanding of in vivo programs that direct specification of hematopoietic stem versus progenitor cells during embryonic development holds immense clinical implication. However, characterization of the unique properties of these cell populations is currently hindered by the inability to distinguish them prospectively due to the absence of discriminating cell surface markers or genes. Here, we uncovered lymphatic vessel endothelial receptor-1 (LYVE1) as a unique cell surface marker that identifies definitive hematopoietic stem and progenitor cells and their cellular precursor, the hemogenic endothelium, in the yolk sac. Furthermore, we showed that LYVE1-eGFP-hCre knock-in mouse is a powerful tool to separate the primitive erythropoiesis from definitive, even after the cell admixture upon onset of embryonic circulation. Using this tool, we provide in vivo evidence that the earliest progenitors to seed the fetal liver derive from the yolk sac. The mechanisms that establish multilineage differentiation potential in hemogenic endothelium are poorly understood. The vascular endothelial growth factor A (VEGF-A) is essential for endothelial development; however, its role in hemogenic endothelium has not been elucidated. Incorporating several unique mouse models of VEGF-A gene targeting, we document that proper VEGF-A dosage is critical for vascular remodeling and generating multipotent HS/PCs in embryonic hemogenic tissues. Our data support the fact that VEGF-A haploinsufficiency is able to establish primitive erythropoiesis and generate transient myelo-erythroid progenitors from the yolk sac. Moreover, we discover a new cellular source of VEGF-A in placental trophoblasts, and show that trophoblast VEGF-A is important for angiogenesis and hematopoiesis in distant hemogenic organs as well.

Regulatory Networks of Hematopoietic Stem Cells and Their Micro-environment Dec 14 2019

Hematopoiesis Sep 15 2022 Hematopoiesis, or the process of blood formation, has been extensively studied at both basic and clinical levels. Human diseases such as thalassemia, immunodeficiency, and leukemia represent defects in this process. Approaches to treat these disorders have required a basic understanding of the biology of blood cells. For instance, hemapoietic stem cell replacement or bone marrow transplantation has been used to ameliorate disease. This volume focuses on hematopoiesis at a cellular and molecular level, and establishes the basis for clinical manipulation of hematopoietic cells for therapeutic benefit. In Part I, the cellular characteristics of progenitors and stem cells are explored. Emphasis is placed on purification of stem cells and both in vitro and in vivo assays. The regulation of normal and leukemis stem cells is illustrated. An excellent discussion of potential use of these cells for gene therapy concludes this section. Hemapoiesis is easily

studied during embryogenesis. Part II develops the concept of the waves of hemapoiesis during development. Comparative hematology is making a major comeback as a field in the 1990's. One hope is that general principles of hematopoiesis will be established by studying many models and systems. Part III delves into critical factors that regulate hematopoiesis, including both intracellular and extracellular signals. Part IV and V describe lineage programs for myeloid and lymphoid lineages. These chapters are meant to be illustrative of the different cell fates, but are not exhaustive. Part VI examines the genetics of hematopoisis, particularly in animal models. The hematopoietic system is in constant contact with stromal cells and endothelial cells during development and in the adult. Evidence suggests that endothelial cells and blood cells may arise from a common progenitor, the hemangioblast. Part VII and VIII discuss the stromal and endothelial cells with the emphasis on their interaction with hematopoietic cells.

Identification and Characterization of Novel Regulators of Hematopoietic Stem Cell Fate Dec 18 2022

Myeloid Dendritic Cells Regulate Hematopoietic Stem and Progenitor Cell Trafficking in the Bone Marrow Jul 21 2020 Hematopoiesis is the process in which blood cells develop from hematopoietic stem and progenitor cells (HSPCs). In the healthy adult, the majority of HSPCs reside in specialized microenvironments surrounding the vasculature within the bone marrow, collectively referred to as the HSPC niche. In response to various forms of stimuli, including the administration of certain pharmacologic agents, the regulatory functions of niches are altered and allow HSPCs to exit the bone marrow and enter the periphery through a process known as mobilization. Granulocyte-colony stimulating factor (G-CSF) is the prototypic agent used clinically to mobilize HSPCs into the blood where they can be harvested for stem cell transplantation to treat a variety of hematologic conditions. However, the mechanisms by which G-CSF-induced signaling affect niche function to mobilize HSPCs are not completely understood. Our lab has previously shown that G-CSF signaling in monocytic cells is sufficient to induce a normal mobilization response of HSPCs. We first focused on identifying which of the monocytic cell subtypes in the bone marrow monocytes, macrophages, and myeloid dendritic cells (MDCs) are targeted by G-CSF. We identified MDCs as a previously uncharacterized cell type that localizes to perivascular HSPC niches in the bone marrow. G-CSF treatment results in a marked loss of MDCs from the bone marrow. Moreover, conditional ablation of MDCs results in HSPC mobilization and suppresses CXCL12 expression in arteriolar endothelial cells, a key stromal cell type of the HSPC niche, indicating a novel role for MDCs in regulating HSPC niche function. Our preliminary data suggests that monocyte-lineage activation of TGF-[beta] signaling in the bone marrow may mediate G-CSFs effects on bone marrow stromal cells. To test this hypothesis, we conditionally deleted Tgfbr2 from bone marrow mesenchymal progenitors and found altered hematopoiesis and stromal cell architecture. Further work will be required to fully characterize the changes in the stromal cell development in the marrow, how these

changes alter the HSPC niche, and how they affect HSPC maintenance.

Protease Proforms as Hematopoietic Regulators Feb 25 2021

Hematopoiesis: New Insights for the Healthcare Professional: 2012 Edition Nov 17 2022 Hematopoiesis: New Insights for the Healthcare Professional / 2012 Edition is a ScholarlyBrief™ that delivers timely, authoritative, comprehensive, and specialized information about Hematopoiesis in a concise format. The editors have built Hematopoiesis: New Insights for the Healthcare Professional / 2012 Edition on the vast information databases of ScholarlyNews.™ You can expect the information about Hematopoiesis in this eBook to be deeper than what you can access anywhere else, as well as consistently reliable, authoritative, informed, and relevant. The content of Hematopoiesis: New Insights for the Healthcare Professional / 2012 Edition has been produced by the world's leading scientists, engineers, analysts, research institutions, and companies. All of the content is from peer-reviewed sources, and all of it is written, assembled, and edited by the editors at ScholarlyEditions™ and available exclusively from us. You now have a source you can cite with authority, confidence, and credibility. More information is available at http://www.ScholarlyEditions.com/.

Isolation and Characterization of Genes which are Potential Regulators of Hematopoiesis (haemopoiesis). Oct 16 2022

MicroRNAs 155 and 125b Physiologically and Pathologically Regulate Hematopoiesis and Immunity Feb 14 2020

Advances in Hematopoietic Stem Cell Research Oct 04 2021 This book provides a comprehensive overview in our understanding of the biology and therapeutic potential of hematopoietic stem cells, and is aimed at those engaged in stem cell research: undergraduate and postgraduate science students, investigators and clinicians. Starting from fundamental principles in hematopoiesis, Advances in Hematopoietic Stem Cell Research assemble a wealth of information relevant to central mechanisms that may regulate differentiation, and expansion of hematopoietic stem cells in normal conditions and during disease.

Polycomb-like 2 (Mtf2/Pcl2) Mediated Epigenetic Regulation of Hematopoiesis and Refractory Leukemia Dec 26 2020 The Polycomb Repressive Complex 2 (PRC2) epigenetically regulates gene expression by methylating lysine 27 on histone 3 (H3K27me3). While the role of PRC2 core members during hematopoiesis has been elucidated, the role of PRC2 accessory protein, Mtf2, has not been well characterized outside of mouse embryonic stem cells. To investigate the role of Mtf2 in vivo, we created a gene-targeted knockout mouse model. Using this model, we discovered that Mtf2 was a critical regulator of hematopoiesis and its loss within the hematopoietic cells leads to loss of global H3K27me3 levels at the transcriptional start sites (TSS) therefore leading to the overexpression of multiple signalling networks. These findings presented in the first part of my thesis place Mtf2 as a critical regulator of hematopoiesis and expand the role of Mtf2 beyond a canonical accessory PcG protein. While our murine studies revealed that the loss of Mtf2 did

not cause leukemia in mice, our studies of MTF2 in human cells demonstrated that MTF2 deficiency within human Hematopoietic Stem and Progenitor Cells (HSPCs) causes a myelo-proliferative phenotype that is reminiscent of pre-leukemia. Furthermore, when we screened MTF2 expression within leukemic stem cell (LSC) enriched CD34+ CD38- cells isolated from primary Acute Myeloid Leukemia (AML) patient samples at diagnosis, we observed that MTF2 is miss-regulated in AML and its loss predicted refractory AML. Using MTF2 knockdown (KD) transcriptomic and ChIP-seq data, we drafted MTF2-PRC2 Gene Regulatory Network (GRN) in human HSPCs and LSC enriched cells. Finally, using the MTF2-PRC2 GRN, we uncovered a direct mechanism by which MTF2 regulates chemoresistance in AML and show that targeting this mechanism via MDM2 inhibitors sensitizes refractory AML to standard induction therapy. These findings presented in second part of my thesis demonstrate MTF2 as a novel prognostic marker for refractory AML and provide a novel therapy that helps target MTF2 deficient refractory AML.

Regulators of the Proliferation of Hematopoietic Stem and Progenitor Cells During Hematopoietic Regeneration Jan 07 2022 Regulators of the Proliferation of Hematopoietic Stem and Progenitor Cells During Hematopoietic Regeneration.

Alternative Polyadenylation in Hematopoiesis and Leukemia Oct 12 2019 Post-transcriptional regulation by RNA-binding proteins (RBPs) is an important layer of gene regulation implicated in both healthy hematopoiesis and hematologic malignancy. Among post-transcriptional mechanisms, alternative polyadenylation (APA) regulates gene expression and function, mediating normal cellular differentiation and malignant transformation across cellular systems. In hematology, APA plays a critical role in lymphocyte maturation and dysregulation contributes to multiple myeloma and lymphocytic leukemia. Despite its documented importance in immune cells, it is unknown whether APA plays a critical role in myeloid malignancy or in healthy hematopoietic stem cell (HSC) maintenance. Furthermore, RBPs that regulate APA in hematologic systems have not been identified. Here, we first addressed the prevalence and global function of APA in myeloid malignancy. We compared poly(A) site usage in acute myeloid leukemia (AML) blasts to usage in healthy hematopoietic stem and progenitor cells (HSPCs), uncovering global patterns and individual leukemia-promoting genes altered in malignancy. By targeting the RBP and APA regulator FIP1L1, we reversed the global trends in patients and observed cellular differentiation across diverse AML subtypes by disrupting leukemogenic signaling networks. In t(8;21) AML, we validated APA regulation of AML1-ETO, showing for the first time that expression of a prominent oncofusion is sensitive to this mode of post-transcriptional regulation. Altogether, our work defines a critical role for APA in AML and illuminates a new pathway that may be exploited for differentiation therapy in patients. We also studied the role of APA in healthy HSC pool maintenance by focusing on APA regulation of the critical hematopoietic transcription factor RUNX1. Polyadenylation upstream of the most distal 3'UTR produces a C-terminally truncated protein that antagonizes the pro-

differentiation function of full-length RUNX1 in HSCs. We modeled this relevant APA event using a dual fluorescent minigene reporter and used this reporter in a CRISPR screen targeting RBPs. We identified HNRNPA1 and KHDRBS1 as regulators of RUNX1 APA, assigning a new role to these RBPs in HSC fate. Overall, our work highlights the intersection between post-transcriptional regulation and transcription factor function in healthy hematopoiesis.

Polyfunctionality of Hemopoietic Regulators Nov 24 2020

Identification and Characterization of Novel Regulatory Genes of Post-embryonic Hematopoiesis Aug 22 2020

Hematopoiesis: New Insights for the Healthcare Professional: 2011 Edition Jun 19 2020 Hematopoiesis: New Insights for the Healthcare Professional: 2011 Edition is a ScholarlyBrief™ that delivers timely, authoritative, comprehensive, and specialized information about Hematopoiesis in a concise format. The editors have built Hematopoiesis: New Insights for the Healthcare Professional: 2011 Edition on the vast information databases of ScholarlyNews.™ You can expect the information about Hematopoiesis in this eBook to be deeper than what you can access anywhere else, as well as consistently reliable, authoritative, informed, and relevant. The content of Hematopoiesis: New Insights for the Healthcare Professional: 2011 Edition has been produced by the world's leading scientists, engineers, analysts, research institutions, and companies. All of the content is from peer-reviewed sources, and all of it is written, assembled, and edited by the editors at ScholarlyEditions™ and available exclusively from us. You now have a source you can cite with authority, confidence, and credibility. More information is available at http://www.ScholarlyEditions.com/.

2nd International Conference on Negative Regulators of Hematopoiesis May 11 2022

Molecular Mechanisms that Regulate GATA2 Transcription During Hematopoiesis Mar 17 2020

Negative Regulators of Hematopoiesis Jan 19 2023

Interleukin-1, a regulator of hematopoiesis Apr 10 2022

Bone Marrow Osteoblastic Niche as Key Regulator of Adult Hematopoiesis After Transplantation Oct 24 2020

Advances in Hematopoietic Stem Cell Research Dec 06 2021 This book provides a comprehensive overview in our understanding of the biology and therapeutic potential of hematopoietic stem cells, and is aimed at those engaged in stem cell research: undergraduate and postgraduate science students, investigators and clinicians. Starting from fundamental principles in hematopoiesis, Advances in Hematopoietic Stem Cell Research assemble a wealth of information relevant to central mechanisms that may regulate differentiation, and expansion of hematopoietic stem cells in normal conditions and during disease.

Endogenously Produced Protein Regulators Provide Feedback Signals that Regulate the Ex Vivo Expansion of Human Hematopoietic Stem and Progenitor Cells [microform] Apr 29

2021 The absence of effective strategies for the ex vivo expansion of human blood (hematopoietic) stem cells (HSCs) limits the development of many stem cell-based therapies. The focus of this study was to investigate in vitro processes responsible for regulating HSC proliferation and to utilize this information in the design of a robust methodology for expanding HSCs. Herein we show the existence of a negative feedback control mechanism whereby differentiated blood cells secrete soluble factors that limit HSC expansion. We demonstrate that global culture manipulation strategies including subpopulation selection and media dilution/exchange modulate this feedback mechanism to enable stem cell expansion. Using this approach, we were able to generate increased numbers of long term culture-initiating cells (LTC-ICs; 14.6-fold), rapid non-obese diabetic/severe combined immunodeficient (NOD/SCID) repopulating cells (R-SRCs; 12.1-fold), and long-term NOD/SCID repopulating cells (LT-SRCs; 5.2-fold), compared with input; outputs significantly higher than those obtained in unmanipulated control cultures. In order to enable this culture methodology for therapeutic applications, a closed-system bioprocess was designed which incorporated in-line subpopulation selection and media dilution/exchange processes. Experiments showed that the bioprocess was able to expand colony forming cells (CFCs), LTC-ICs and LT-SRCs in a manner consistent with results using standard tissue culture dishes. Studies to optimize the bioprocess operating conditions were also performed. In these studies it was found that non-specific cell loss, which occurred during the subpopulation selection step, could be decreased by increasing flow rate through the selection element. The ability to decrease cell loss is important since it should facilitate higher expansions of hematopoietic stem and progenitor cells within the bioprocess. Furthermore, optimization of the subpopulation selection process through the identification of specific inhibitory factor secreting cells may further augment the measured expansions. To initiate this goal, the gel microdrop (GMD) assay was developed as a means to measure protein secretion from individual cells in the context of cell surface phenotype. The development and use of the GMD assay represents the first step in the design of a second generation bioprocess which should have an even greater capacity for the ex vivo expansion of HSCs.

Summon Up the Blood Mar 29 2021

The Characterization of the Role of Myeloid Translocation Gene 16 in Hematopoietic Progenitor and Stem Cell Functions Mar 09 2022

Modeling Normal and Malignant Hematopoiesis in Vitro Aug 02 2021

Experimental Hematology Today—1985 May 19 2020 Experimental Hematology Today-1985 is a memento to the superb 14th Annual Meeting of the International Society for Experimental Hematology, held in Jerusa lem, Israel in July 1985. It represents a selection of the best presentations at the meeting. The manuscripts were selected by the local scientific committee and care fully reviewed by the editors. The yearbook is divided into five parts and represents the most recent advances in the basic sciences and clinical applications. Part I, under the leadership of Dr. L.A. Rozenszajn, is entitled "Hematopoietic Regulators." Papers

in this section discuss the most recent discoveries on the phys iological regulation of hematopoiesis. Part II, "Hematopoietic Microenvironment," introduced by Dr. J.S. Greenberger, deals with the involvement ofthe hematopoietic microenvironment in the control of hematopoiesis. Dr. M. Saito leads Part Ill, "Dif ferentiation of Normal and Leukemic Cells," while Part IV, "Leukemic Cells in Leukemogenesis," is introduced by Dr. A. Raghavacher. The important discussions on recent advances in "Bone Marrow Transplantation," Part V, are headed by Dr. M.M. Bortin. Recent findings in many disciplines in experimental and clinical hematology are presented in this yearbook. It should be of considerable value to experimental and clinical scientists. The Editors v Contents Part I. Hematopoietic Regulators L.A. Rozenszajn 1. Role of T-Lymphocyte Colony Enhancing Factor, TLCEF, in the Induction of CFU -TL L.A. Rozenszajn, 1. Goldman, H. Poran, M.M. Werber, D. Shoham, and 1. Radnay ...

Locus-wide Studies Into the Transcriptional Regulation of Runx1 in Developmental Hematopoiesis Nov 12 2019 Developmental hematopoiesis sees the generation of the first blood cells and definitive blood during embryonic development. The founding cell of definitive hematopoiesis, the hematopoietic stem cell (HSC), gives rise to all adult blood :I:]] 1:: t '.1 '4 !..:. : 1 1 '.! . lineages throughout the the life span or an orgamism. It IS expected that future ex-vivo manipulation ofHSCs for therapeutic uses will benefit from a thorough understanding of the mechanisms, both cellular and genetic, that give rise to HSCs. One of the most critical regulators of HSC emergence in the embryo is the transcription factor (TF) Runxl. One aim of our lab is to decipher what controls the cis-regulation of Runxl to understand better how it exerts its function in the emergence of HSCs. In this thesis, chromatin assays were used to identify putative enhancers within the 1.3 Mb Runxl syntenic region. Seven novel enhancers were identified that mediate reporter gene expression in discrete patterns of Runx1-specific hematopoietic expression in transient transgenic embryos. Characterization of the cells marked by one of these enhancers, the + 11 0 enhancer in a transgenic mouse line, showed that it is active in clonogenic progenitors at Ell.5, but, interestingly, not HSCs. Finally, chromosome conformation capture (3C) assays showed physical interactions between the Runxl PI and P2 promoters and between the Runxl PI and P2 promoters and putative regulatory elements in the 1.3 Mb syntenic region. Together, these data increase our understanding of the complexity of Runxl cis-regulation during development and provide a starting point for characterizing what upstream trans-acting factors converge on Runxl to specify blood.

Immediate Early Genes and Proto-oncogenes as Positive and Negative Regulators of Hematopoietic Cell Differentiation Apr 17 2020

Towards the Identification of Cellular and Molecular Regulators of Hematopoietic Stem Cell Self-renewal Jun 12 2022 "This project will lead to a better understanding of the cellular basis regulating self-renewal of both normal and cancer stem cells and potentially to the future identification of new self-renewal determinants." --

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