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POSTER ABSTRACTS

501.HEMATOPOIETIC STEM AND PROGENITOR CELLS AND HEMATOPOIESIS: BASIC AND TRANSLATIONAL

Dynamic Expression of *Erg* Controls Fetal-to-Adult Maturation of the Hematopoietic System

Mayuri Tanaka-Yano, PhD[1], *Dahai Wang, PhD*[2], *Diana Chen*[3], *Biju Isaac, PhD*[4], *Tianxin Scarlett Liu, PhD*[2,5,6], *Liang Sun, PhD*[4], *Edroaldo Lummertz da Rocha, PhD*[7], *Berkley Gryder, PhD*[3], *Stuart H Orkin, MD*[6,5,8,9,1], *Robert Grant Rowe*[1,2,10,6,5]

[1] Department of Hematology/Oncology, Harvard Medical School/Boston Children's Hospital, Boston, MA
[2] Pediatric Hematology-Oncology, Boston Children's Hospital, Boston, MA
[3] Genetics & Genome Sciences, Case Western Reserve University, Cleveland, OH
[4] Research Computing, Boston Children's Hospital, Boston, MA
[5] Harvard Medical School, Boston, MA
[6] Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston, MA
[7] Graduate Program of Pharmacology, Federal University of Santa Catarina, Florianopolis, Brazil
[8] Dana-Farber Cancer Institute, Inc., Boston, MA
[9] Howard Hughes Medical Institute, Boston
[10] Stem Cell Transplantation Program, Boston Children's Hospital, Boston, MA

Many blood diseases are biased in their age of onset toward infancy, childhood, or mature adulthood. This occurs in concert with underlying changes in the properties of hematopoietic stem and progenitor cells (HSPCs) over the course of development, maturation, and aging that tailor the output of effector blood cells to age-specific physiology. Understanding how blood formation changes over the course of a lifetime would form a foundation upon which to investigate age-related determinants of manifestations of blood diseases. A growing body of work has shown that the heterochronic Lin28b/ *let-7* switch defines fetal versus adult definitive HSPC states. In previous work, we found that the Polycomb repressive complex 1 component Cbx2 is a downstream target of *let-7* that functions to specify the temporal maturation state of the hematopoietic system.

In our current study, we find that Cbx2 represses the master hematopoietic stem cell (HSC) transcription factor (TF) Erg in fetal HSPCs, providing a mechanism by which the Lin28b/ *let-7* axis integrates with the core HSC TF circuitry. During developmental maturation, Erg is upregulated during the fetal-to-adult HSC transition in humans (5.5-fold), mice (3.8-fold), and zebrafish (4.9-fold). Moreover, by analyzing existing ATAC-seq datasets, we find that Erg motifs are highly enriched in chromatin regions specifically active in adult relative to fetal HSPCs ($P < 0.0001$). Together, these findings suggest age-biased role(s) for Erg in hematopoiesis. We therefore hypothesized that since *Erg* is a key regulator of self-renewal and lineage output in HSCs, Erg likely serves stage-specific roles in HSCs.

To test this, we either suppressed *Erg* expression in adult HSPCs or ectopically activated *Erg* in fetal HSPCs to determine consequences on HSPC function. We found that ectopic expression of Erg in HSPCs reprogrammed to the fetal state by expression of LIN28B resulted in blunting of fetal-like lineage biases. In adult mice, loss of a gene dose of *Erg* resulted in persistence of hallmarks of the fetal HSC state among blood effector cells and fetal-like HSPC distributions into maturity. During the normal process of fetal-to-adult maturation, HSCs transition from a highly proliferative to a quiescent state. We find that early postnatal *Erg* $^{+/-}$ HSCs do not effectively transition to quiescence and maintain active fetal-like self-renewal, which is leads to impairment in HSC function and susceptibility to replicative exhaustion later in adulthood.

Mechanistically, we find that adult *Erg* $^{+/-}$ HSPCs ectopically maintain fetal-like gene expression profiles and patterns of promoter-enhancer looping. This is associated with failure to repress self-renewal promoting TFs that are normally expressed only in fetal HSPCs. Together, these findings demonstrate that master hematopoietic TFs and their associated networks are tightly titrated to implement age-appropriate rates self-renewal and mature cell output in HSPCs. Our results confirm heterochronic roles for Erg in defining age-tailored hematopoiesis on schedule with normal development and maturation and form a basis for applying this understanding of temporal hematopoietic maturation to disease models.

Disclosures No relevant conflicts of interest to declare.

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