PREFACE

The process of developing the diverse blood cell repertoire from stem and progenitor cells termed hematopoiesis has been subject to considerable investigation. However, key steps in the complex process of hematopoiesis, including hematopoietic stem cell generation during embryogenesis, hematopoietic stem, and progenitor cell expansion to accommodate physiological and pathological requirements, and mechanisms that ensure hematopoietic stem and progenitor cell phenotypic integrity remain incompletely understood. Elucidating these mechanisms will yield concepts that can be extrapolated to diverse biological realms, and given the vital importance of the hematopoietic system, future efforts will invariably lead to medical breakthroughs that advance human health.

This issue of *Current Topics in Developmental Biology* reviews cutting-edge research on mechanistic and biological aspects of hematopoiesis. The initial chapters lay the groundwork for understanding the cellular origin of hematopoietic stem cells (Dzierzak and de Pater) and the pivotal role of the microenvironment or "niche" in non-cell-autonomously regulating hematopoietic stem cell genesis and function (Yu and Scadden). The next series of chapters probe into molecular mechanisms governing the development of hematopoietic stem and progenitor cells and for maintaining their unique phenotypes. Whereas a plethora of studies have used loss-of-function approaches to delineate proteins with activities essential for hematopoiesis, Hewitt et al. describe a new strategy aimed at discovering noncoding DNA sequences or *cis*-regulatory elements with nonredundant activities to control hematopoiesis. Editing specific *cis*-regulatory elements out of the mouse genome disrupts specific steps of hematopoiesis, yields instructive animal models, and provides unique systems for decoding the global *cis*-regulatory element network governing hematopoietic stem/progenitor cell transitions termed a "Hematopoietic Stem/Progenitor Cell Cistrome." Upstream of GATA-2, the generation and identity of endothelial cells with the unique capacity to form hematopoietic stem cells (hemogenic endothelial cells) requires an intriguing ETS transcription factor termed ETV2/ER71/Etsrp. Sumanas and Choi describe foundational studies on this critical protein, provide a unique perspective on how ETV2 functionally interfaces with a cohort of other ETS factors, and highlight the promise of forging ETV2-dependent regenerative medicine strategies. Having emerged from studies

on mechanisms underlying leukemogenesis, the transcription factor Runx1, previously deemed Acute Myeloid Leukemia protein 1, has multiple crucial roles in the hematopoietic hierarchy. Tober et al. describe its activities to control hematopoietic stem and progenitor cell transitions and its relationship to a host of other components implicated in specific steps in hematopoiesis. A huge challenge is to assemble and decipher the complex protein networks governing hematopoiesis, and the basic helix-loop-helix protein Stem Cell Leukemia (SCL)/T-cell Acute Lymphocytic Leukemia Protein 1 (TAL1) is integral to such networks. SCL/TAL1 commonly colocalizes with GATA factors on chromatin and functions at multiple levels of the hematopoietic hierarchy. Hoang et al. provide a comprehensive perspective of how SCL/TAL1 controls normal hematopoiesis and is deregulated in leukemia. Moreover, they highlight how the mechanistic insights have illuminated new avenues to reprogram cellular phenotypes. Transcription factors commonly engage non-DNA binding coregulators that mediate activation or repression through enzymatic or nonenzymatic biochemical mechanisms. In certain cases, the same coregulator mediates activation and repression, often through elusive context-dependent mechanisms. DeVilbiss et al. describe concepts related to how GATA-1 negotiates coregulator ensembles to control the development and function of specific blood cell types. They highlight the concept of a "coregulator matrix," which, in effect, constitutes a code for how a given transcription factor functions in a specific environment—a code that exhibits fluidity dictated by the overall regulatory milieu. Progress on the role of noncoding regulatory RNAs in biological regulation has exploded in recent years, and this area is ripe for making discoveries to understand and modulate hematopoiesis. Jeong and Goodell provide an insightful overview of noncoding RNAs implicated in hematopoiesis and discuss prospective mechanisms. Noncoding RNA-dependent mechanisms are expected to function at all levels of the hematopoietic hierarchy and to converge upon the mechanisms involving ETV2, GATA-2, RUNX1, SCL/TAL1, and GATA-1 discussed in this volume. For the most part, integrating noncoding regulatory RNA mechanisms with the emerging factor-dependent pathways remains virgin territory.

In aggregate, this series of chapters highlights compelling mechanistic and biological advances, and the progress to date has emphasized the need to increase the depth of investigation into these problems—to get beyond limitations of dissecting complex mechanisms in cell populations, rather than in individual cells, to develop definitive insights as to whether murine mechanisms can be seamlessly extrapolated to humans, and to devise novel

strategies for dissecting mechanisms within microenvironments impacted by diverse non-cell-autonomous regulatory inputs. It will be particularly instructive to determine how the respective mechanisms react to dynamic alterations in the microenvironment and systemic changes associated with pathologies and aging. The resulting knowledge will yield a veritable Pandora's box of scholarly insights that fill mechanistic/biological voids and transform existing concepts. Future mechanistic leveraging will yield desperately needed new strategies for treating nonmalignant (eg, anemia) and malignant hematopoietic disorders (eg, leukemia) and has potential to yield economically viable pipelines for engineering therapeutic blood products.

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