

Preface

During vertebrate hematopoiesis many specialized cells types are formed with vastly different functions, such as B cells, T cells, granulocytes, macrophages, erythrocytes, and megakaryocytes. The complex blood cell system found in humans has evolved from a few simple cell types mainly involved in oxygen transport and phagocytosis to a highly efficient cell production facility, which constantly replenishes cells involved in oxygen transport, wound healing, the removal of cellular debris by phagocytosis, as well as providing a highly efficient innate and adaptive immune system designed to protect the body from infectious diseases, parasites, and tumor cells. To tightly control the enormous proliferative potential of developing blood cells, an intricately balanced signaling and transcription network has evolved that ensures that the different blood cell types are formed at the right time and in the right numbers. Finely tuned regulatory mechanisms ensure that blood cells function properly and have a determined life span. Moreover, in the adaptive immune system, long-lived memory cells have evolved that ensure that when pathogens have been seen once they will never cause a problem again.

All of these features of the hematopoietic system are under transcriptional and epigenetic control. Failures in this control cause incomplete differentiation, a dysfunctional immune system, problems with wound healing, as well as uncontrolled proliferation of blood cells and cancer. As the principles of differentiation control are similar in all multicellular organisms, the hematopoietic system has served as an excellent model system to study the principles of the epigenetic and transcriptional control of cell fate decisions in general. In this book we will therefore make a journey from first asking how very primitive organisms use the epigenetic regulatory machinery to balance growth with differentiation control, towards digging deep into what controls the function of specialized cells of the human immune system.

To introduce a general readership into the molecular basis of gene expression control in a chromatin context, Peter Cockerill and Constanze Bonifer will first introduce the general principles of chromatin structure and gene expression control. The next two chapters will then describe non-mammalian hematopoiesis and we will discover that flies make blood but exist without blood vessels, that fish make

blood cells in the kidney, and which precise genetic circuitries are required for these developmental pathways. The first by Paul Badenhorst introduces *Drosophila melanogaster* hematopoiesis and demonstrates why this model system is highly informative for mammalian blood cell development and human leukemia. The second by Xiaoxing Bai informs us about blood cell development in zebra fish as an important genetic model for vertebrate hematopoiesis and tells us why this model is important for drug screening.

The remainder of the book focuses primarily on mammalian hematopoiesis. We start with five chapters outlining general principles of gene regulation and development, beginning with Valerie Kouskoff and coworkers who describe the regulatory processes that drive the development of hematopoietic stem cells in the mammalian embryo. We then will make a detour into the realm of Polycomb complexes in the chapter written by Miguel Vidal which describes one of the most fundamental mechanisms used by all tissues in all animals to establish patterns of development and differentiation. Although this chapter will not focus on hematopoiesis, it will explain in comprehensive detail the general principles of the biochemical nature of Polycomb complexes and how they regulate gene expression and outline the breathtaking complexity of this system that we are only now beginning to understand. The following chapter by Vincent Van den Boom et al. then makes it abundantly why knowledge of the Polycomb system is essential for our understanding of normal blood cell development and it illustrates how aberrations in this pathway lead to abnormal blood cell development and contribute to diseases such as leukemia. To gain a more complete understanding of the regulatory network controlling development we next learn that the repressive activity of Polycomb proteins is counterbalanced by the Trithorax family of activating factors. This is the theme of the chapter written by Robert Slany. He introduces the MLL family of transcriptional activators, and he outlines why chromosomal translocations involving MLL disturb the balance between Polycomb and Trithorax activities at *HOX* genes and why such a disturbance causes leukemia. The final chapter on basic mechanisms is written by Grant Challen and Jenny Trowbridge and it explains the role of DNA methylation in reinforcing the decisions of stem cells to differentiate into all mature blood cell lineages and how this process is disturbed in malignant hematopoiesis.

The next major theme of the book focuses on mechanisms of hematopoietic differentiation and includes five articles describing how the development of the myeloid, erythroid/megakaryocytic, and lymphoid lineages is controlled. Peter Laslo and Thomas Stopka explain the control of myelopoiesis by transcription factors and epigenetic regulators and how mutation of their respective genes causes myeloid malignancies. Doug Vernimmen describes the network of transcription factors and the epigenetic regulators that control development and gene expression in the erythroid and megakaryocytic lineages. We then focus on the adaptive immune system and learn the fundamentals of how we acquire the ability to recognize millions of foreign antigens. We start with basic concepts of how the T-cell lineage develops from lymphoid progenitors in a chapter by Will Bailis and Warren Pear which describes the transcription factor networks and selection

processes controlling T-cell differentiation in the thymus. In this chapter we also learn that the mechanisms driving T-cell development can also be diverted to induce T-cell leukemia. To complete the story of T-cell development, Cristina Hernandez-Munain and coworkers describe the intricate mechanisms that lead to the huge diversity of T-cell antigen receptors (TCR) as a result of TCR gene rearrangements. This chapter is perfectly balanced by a parallel description by Kirkham et al. of the processes controlling immunoglobulin gene rearrangements in the B-cell lineage. This chapter also explores how B cells develop from lymphoid progenitors and informs of the ways how leukemia or immune deficiency arises as a result of defects in the gene rearrangement process.

The final two chapters will shed light on the molecular mechanisms that regulate immune cell function and describe processes that establish normal cells or lead to the development of cells with impaired function. Here we concentrate on two lineages: T cells and macrophages. First we learn from the group of Toshinori Nakayama of how we maintain adaptive immunity in T cells once an existing infection has been resolved. This introduces the concept of molecular memory in memory T cells which allows these cells to respond rapidly to subsequent exposure to the same pathogens. We also learn that T cells have the ability to differentiate along different pathways in response to intrinsic and extrinsic signals, allowing them to tailor their responses to different types of pathogens. The chapter by Poletti et al. describes the role of macrophages in regulating an inflammatory response, outlining in fine molecular detail recent genome-wide studies that shed light on how this response is controlled at the level of gene regulation.

At the end of this journey, we hope that the scientist/science student/health professional reader will understand general principles of cellular differentiation control at the molecular level and what is actually meant by epigenetic and transcriptional regulation. We also hope that this book will help readers to develop a clear picture of how gene regulatory processes function in a chromatin context and how their deregulation causes blood cell development to go astray.

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