ABSTRACT

Neutrophils, known primarily as key players in defense against invading pathogens, represent an essential component of both the innate and adaptive immunity. Continuous production of large quantities of neutrophils is ensured by a complex process termed granulopoiesis. In order to maintain a stable neutrophilic population, granulopoiesis requires to be tightly regulated. Moreover, impaired granulopoiesis may lead to aberrant bone marrow function and, ultimately, give rise to acute myeloid leukemia (AML). Despite decades of research, the mechanisms regulating granulopoiesis are still unclear. In particular, the CCAAT/enhancer binding protein (C/EBP) family of transcription factors plays a critical role in this process. C/EBPα acts as a master regulator of granulopoiesis mainly by orchestrating expression of its target genes, which will mediate granulocytic differentiation. Thus, characterization of novel C/EBPα target genes is critical for a better understanding of the molecular mechanisms that regulate granulopoiesis. Previously, we showed that another C/EBP member, CEBPG, is a direct target of C/EBPα. In the first part of the present work, we addressed the unknown role of C/EBPγ in granulopoiesis. We observed that Cebpg conditional knockout (KO) mice, which have the Cebpg gene ablated specifically in the hematopoietic system, are viable and present no signs of disease. Consistently, we showed that production of mature blood cells as well as function of hematopoietic stem and progenitor cells remains unaffected upon Cebpg deletion. Surprisingly, several models of stress granulopoiesis induced by administration of LPS, G-CSF or Candida albicans showed that Cebpg KO mice respond to these stimuli similarly as control mice. Taken together, these findings led to the unexpected conclusion that the transcription factor C/EBPγ, although being expressed at high levels in all hematopoietic cells, is dispensable for steady-state and emergency granulopoiesis. In the second part of this thesis we focused our research on another C/EBPα target gene, EVI2B. Detailed study of this transmembrane protein demonstrated that EVI2B is involved in regulation of neutrophilic differentiation and functionality of hematopoietic progenitors. In the third part of this thesis, we studied the regulation of neutrophilic differentiation by a different type of molecules – microRNAs. Our data showed that miR-143 accelerates neutrophilic differentiation partially through posttranscriptional control of its direct target, the transcription factor ERK5. Finally, we identified miR-143 as potential prognostic marker in AML. Altogether, data described in this thesis not only contribute to improve our understanding of normal granulopoiesis but also provide new insights into the processes altered in leukemogenesis.