CHAPTER 3

CtBP and Hematopoietic Transcriptional Regulators

Alexis Verger,* Jose Perdomo and Merlin Crossley

Abstract

The C-terminal binding proteins (CtBPs) are ubiquitous corepressors that recruit histone-modifying enzymes to a variety of sequence specific DNA-binding proteins and other transcriptional regulators. CtBPs appear to play an important role in mediating repression and transforming activities of a variety of hematopoietic transcription factors such as Basic Krüppel-like Factor/Krüppel-like Factor 3 (BKLF/KLF3), Friend of GATA (FOG), Evi-1 and members of the Ikaros family. Mice lacking CtBPs die during embryonic development and exhibit defects in a wide range of developmental processes, including aberrant heart formation and absence of blood vessels in the yolk sac. The ongoing identification of repressed target genes and interacting transcriptional partners will help to unravel the contributions of CtBP proteins to hematopoiesis.

Introduction

Hematopoiesis is the process through which the various blood lineages (erythrocytic, lymphocytic, monocytic/myelocytic, granulocytic and thrombocytic) develop from self-renewing, pluripotent stem cells.[1] This process is tightly regulated by the action of growth factors that signal to lineage restricted or widely expressed transcription factors and their associated coregulators (Figs. 1, 2). These factors then orchestrate lineage commitment by activating and repressing defined sets of target genes. For example, the zinc finger protein GATA-1 and its cofactor FOG are involved in coordinating the expression of genes that drive erythrocytic and megakaryocytic development.[2,3]

Understanding the transcriptional networks that coordinate such programs of gene expression is an important focus in the study of cell differentiation. Accumulating evidence suggests that the corepressor C-terminal binding protein (CtBP) is an important regulator of hematopoietic homeostasis by virtue of its physical interaction with hematopoietic transcription factors such as BKLF, Evi-1, FOG and Ikaros. This chapter addresses the mechanisms of transcriptional repression and the role of CtBP in development, hematopoiesis and leukemogenesis.

CtBP Proteins during Development

CtBP1 is the founding member of the CtBP family of corepressors. It was first identified as an E1A interacting protein that negatively modulates the oncogenic transformation activity of E1A.[4] Subsequently, highly homologous human and mouse proteins termed CtBP2 were

*Corresponding Author: Alexis Verger—School of Molecular and Microbial Biosciences, University of Sydney, 2006 New South Wales, Australia. Email: a.verger@mmb.usyd.edu.au

CtBP Family Proteins, edited by G. Chinnadurai.

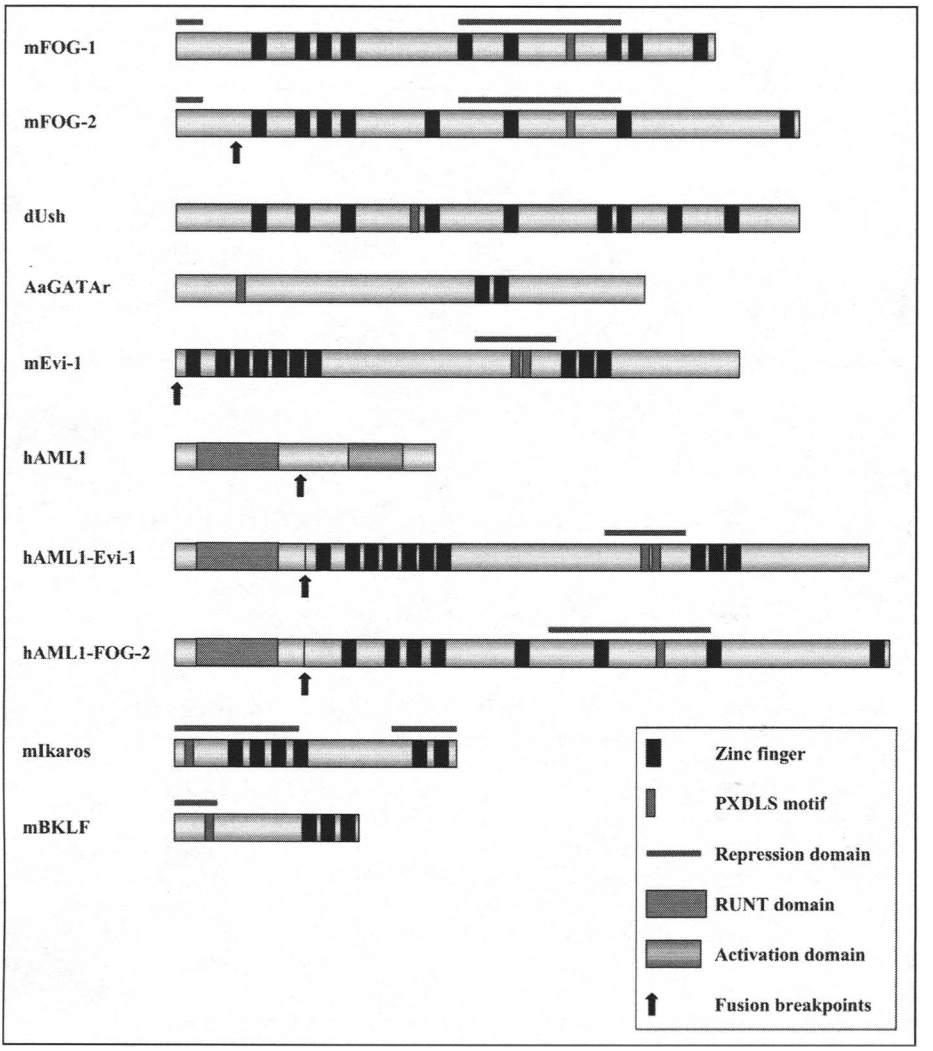

Figure 1. Schematic representation of CtBP partners discussed in this chapter. Structures of mFOG-1, mFOG-2, dU-shaped, AaGATAr, mEvi-1, hAML1, hAML1/Evi-1, hAML1/FOG-2, mIkaros and mBKLF are shown. Zinc fingers are represented as vertical solid bars, the PXDLS CtBP binding motif is indicated as red vertical bars. Blue overlining indicates the repression domains containing the CtBP binding motif. A color version of this figure can be viewed at http://www.Eurekah.com.

identified by analysis of EST data bank sequences and in a yeast two-hybrid screen against the erythroid transcription factor BKLF.[5,6]

CtBP1 and CtBP2 are widely expressed and are often coexpressed. Knockout studies have revealed that *CtBP1*-null mice are viable while *CtBP2*-null embryos die by E10.5.[7] Thus the functions of CtBP2 cannot be assumed by CtBP1. Further evidence for distinct functions comes from an examination of expression patterns. CtBP1 is expressed in the thymus and peripheral blood leukocytes, whereas CtBP2 is not readily detected.[8,9] In human cancer lines, differences in expression are common with high expression of CtBP1 in chronic myelogenous leukemia K-562 and lymphoblastic leukemia MOLT-4 cell lines.[9] Conversely, CtBP2 is readily