Non-steady-state hematopoiesis regulated by the C/EBPβ transcription factor

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Key words
Cancer, C/EBPβ, emergency, hematological malignancy, steady-state

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Funding Information
Ministry of Education, Culture, Sports, Science and Technology of Japan; Ministry of Health, Labor and Welfare of Japan; National Cancer Center Research and Development Fund; Takeda Science Foundation; Princess Takamatsu Cancer Research Fund; Kobayashi Foundation for Cancer Research.

Received March 23, 2015; Revised April 26, 2015; Accepted April 27, 2015

Cancer Sci 106 (2015) 797–802
doi: 10.1111/cas.12690

Transcription Factor CCAAT/Enhancer Binding Protein β

CCAAT/Enhancer Binding Protein β (C/EBPβ) belongs to the C/EBP leucine zipper domain-containing family of transcription factors (Fig. 1).\(^1\),\(^2\) This intronless gene product binds to certain genomic regulatory regions either as a homodimer or as a heterodimer with other molecules, including other members of the C/EBP family. In addition to direct DNA binding, C/EBPβ cooperates with the switch/sucrose non-fermentable complex to regulate gene expression through chromatin remodeling.\(^3\) It induces or represses the expression of target genes and, ultimately, regulates the proliferation, differentiation, metabolism, and survival of many different cell types.\(^1\)

The expression and function of C/EBPβ are regulated in a complex way during transcription, translation, post-translational modification, and protein–protein interactions.\(^4\)–\(^8\) Notably, alternative translation through the use of different initiation codons generates three different isoforms of C/EBPβ: liver-enriched activating protein* (LAP* or full-length), liver-enriched activating protein (LAP), and liver-enriched inhibitory protein (LIP) (Fig. 1).\(^6\) Both LAP* and LAP are transcriptional activators, whereas LIP (which is the shortest isoform and lacks transactivation domains but retains DNA binding and dimerization domains) acts as a repressor or a dominant negative inhibitor of other C/EBP family transcription factors.\(^9\) The ratio of these isoforms is regulated by different signaling events and has a significant impact on the overall function of C/EBPβ.\(^10\)–\(^11\)

Within the hematopoietic system, C/EBPβ is expressed at high levels by monocytes and macrophages, and regulates genes involved in immune and inflammatory responses.\(^12\)–\(^16\) In addition, we found that C/EBPβ plays a crucial role in hematopoiesis, especially under stress conditions.\(^17\)–\(^19\) Here, we discuss the role of this transcription factor in non-steady-state hematopoiesis, including the emergency response to infection and cancer, and in hematological malignancies.

Modes of Hematopoiesis

Hematopoiesis is a continuous process that supplies an organism with all blood cells over its lifetime. To avoid either an excess or lack of any specific type of blood cell, hematopoiesis must be tightly regulated according to demand. During steady-state conditions, the constant production of mature blood cells is maintained by fine-tuning the proliferation and differentiation of hematopoietic precursors in both a cell-intrinsic and a cell-extrinsic manner. By contrast, in emergency situations such as infection or bleeding, large numbers
clear boundaries between steady-state and emergency hematopoiesis, including cancer and autoimmune diseases. Stress can be elicited by various kinds of pro-inflammatory addition to responses to infection or bleeding, hematopoietic stimuli and are resolved when the activating signals cease. In logical non-steady-state responses are triggered by external stimuli, including infection and cancer. Hematopoietic stem cells give rise to mature granulocytes through successive intermediates, such as common myeloid progenitors and granulocyte–macrophage progenitors. Granulocytes have an extremely short half-life; therefore, they must be produced continuously in the bone marrow, stored, and supplied to the periphery. As is the cases with other hematopoietic lineages, either an excess or a lack of granulocytes is harmful to the host; therefore, granulopoiesis must be tightly regulated according to demand. It is well known that C/EBPα plays critical roles in granulopoiesis. In Cebpa-deficient mice, transition from common myeloid progenitors to granulocyte–macrophage progenitors is completely abrogated and no granulocytes are present under steady-state conditions.

Overexpression of C/EBPα represses the proliferation of leukemic cells and induces their differentiation into granulocytes. Collectively, these findings suggest that C/EBPα is the master regulator of steady-state granulopoiesis.

While searching for the regulatory mechanisms involved in emergency granulopoiesis, we found that granulopoiesis can be induced by cytokines in the absence of C/EBPα. This suggests the existence of a C/EBPα-independent pathway of granulopoiesis under emergency conditions. Interestingly, all members of the C/EBP family, except C/EBPβ, were downregulated in response to cytokine stimulation. Cytokine or infection-induced enhancement of granulopoiesis is impaired in Cebpb knockout mice, and the C/EBPβ-dependent pathway of granulopoiesis is significantly attenuated by inhibiting C/EBPβ. By contrast, C/EBPβ is not necessary for steady-state granulopoiesis. These results clearly suggest that C/EBPβ is required for stress-induced granulopoiesis; indeed, this requirement has been verified in other mouse models and in a zebrafish model. Both C/EBPβ and C/EBPα share many common target molecules, including genes associated with granulocytic differentiation. By contrast, they show a differing ability to regulate the cell cycle. C/EBPα strongly inhibits the cell cycle through direct or indirect interactions with cell cycle regulators, whereas C/EBPβ has a less inhibitory effect. These differences might be the reason for the selective requirement of C/EBPα and C/EBPβ for steady-state and emergency granulopoiesis, respectively. As the transition from steady-state to emergency granulopoiesis (or vice versa) is a continuous process, C/EBPα or C/EBPβ might collaborate with each other to ensure an adequate supply of granulocytes by fine-tuning the proliferation and differentiation of granulocyte precursors (Fig. 3). Furthermore, we also found that CEBPβ is required by early granulocyte precursors under emergency conditions; we are currently investigating the role of CEBPβ in regulating hematopoietic stem cells.
Role of C/EBPs in the Pathophysiology of Severe Congenital Neutropenia

Severe congenital neutropenia (SCN) is an inherited condition characterized by severe neutropenia in the peripheral blood (<500/µL) and by arrest of myeloid precursor maturation at the promyelocyte/myelocyte stage in the bone marrow, resulting in increased vulnerability to bacterial and fungal infections. The majority of patients with SCN respond to treatment with recombinant granulocyte-colony stimulating factor, which increases the neutrophil count and reduces both the frequency and severity of infections. Patients with SCN harbor mutations in diverse genes. These heterogeneous genetic alterations reflect the complex mechanisms governing the homeostasis of neutrophils. Establishing induced pluripotent stem cells from SCN cells in combination with an in vitro differentiation system will further our understanding of both the pathogenesis of this disease and the physiological regulation of granulopoiesis.

Cancer-associated Myelopoiesis

Cancer progression, including tumor growth, invasion, and metastasis, cannot be achieved by tumor cells alone; it requires the appropriate microenvironment. Accumulating evidence suggests that myeloid cells are major components of the cancer microenvironment. Indeed, there is a strong association between increased numbers of macrophages or neutrophils in cancer tissues and poor patient survival. Thus, these myeloid cells can be good candidate therapeutic targets. Tumor cells, or other stromal cells, in the microenvironment produce a variety of growth factors and chemokines, which then recruit myeloid cells from the bone marrow or reservoir tissues. Therefore, the mode of hematopoiesis is altered in the presence of cancer, and hematopoietic systems release a variety of myeloid cells into the cancer microenvironment. Such cells include monocytes, macrophages (tumor-associated macrophages), dendritic cells, neutrophils (tumor-associated neutrophils), and eosinophils. Recent studies by ourselves and others identified fibrocytes as important constituents of the cancer microenvironment.

Role of CEBPβ in Chronic Myeloid Leukemia

Chronic phase chronic myeloid leukemia (CP-CML) is characterized by a massive expansion of myeloid cells. In sharp contrast to acute myeloid leukemia (AML) with leukemic hiatus, both myeloid progenitors and mature granulocytes accumulate in the bone marrow, peripheral blood, and spleen in CP-CML. The myeloid expansion in CP-CML is attributed to the BCR–ABL fusion protein, which arises from a translocation between chromosomes 9 and 22. The leukocytosis observed in patients with infections, severe burns, or cancer is sometimes referred to as a “leukemoid” reaction because of the marked increase in the number of myeloid cells with a “left shift” in the shape of the nucleus. The resemblance between leukemoid reactions and CP-CML prompted us to examine whether BCR–ABL might use the emergency-specific pathway of granulopoiesis. Therefore, we investigated the role of C/EBPβ in CP-CML. BCR–ABL upregulates C/EBPβ, at least in part, by activating signal transducer and activator of transcription 5 (Myeloid differentiation and proliferation (induced by BCR–ABL) are significantly impaired in Cebpb-deficient bone marrow cells both in vitro and in vivo. Interestingly, higher numbers of Cebpb-deficient leukemic stem cells were maintained after serial transplantation than wild-type leukemic stem cells in this mouse model. These results sug-
in some hematological malignancies, resulting in maintenance or progression of cell-extrinsic stress, including infections and cancer, activate myeloid expansion and leukemic stem cell exhaustion might lead to novel therapeutic strategies for eradicating CML stem cells.

Role of C/EBPβ in other Hematological Malignancies

Hematological malignancies are the consequence of dysregulated differentiation and/or proliferation; therefore, they can be regarded as a form of pathologically induced non-steady-state hematopoiesis. Because C/EBPβ promotes neutrophilic differentiation and inhibits the cell cycle, many cases of AML are associated with recurrent mutations in, or dysregulation of, C/EBPβ.(62–64) By contrast, no recurrent mutations in C/EBPβ have been identified in AML, possibly reflecting the fact that this transcription factor is required for emergency-specific responses. However, C/EBPβ plays a role in the pathogenesis of many hematological malignancies. In AML, LIP (the shortest isoform of C/EBPβ) collaborates with a proto-oncogene, Evi1, to induce leukemia in a mouse bone marrow transplantation model.(66) The same isoform is induced by signaling downstream of internal tandem duplication of fms-like tyrosine kinase 3, thereby supporting the proliferation of blasts.(67) These findings suggest that regulating the amount or the ratio of C/EBPβ isoforms might be a common pathway that is abrogated during the development of AML.

Acute promyelocytic leukemia (APL) is a subtype of AML characterized by a promyelocytic leukemia-retinoic acid receptor α(PML-RARα)-mediated differentiation block at the promyelocytic stage, which occurs (at least in part) through an impairment in C/EBPβ function.(68) This block is reversed by all-trans retinoic acid (ATRA), which is used as frontline therapy for APL.(69) After the start of ATRA treatment, mature neutrophil-like cells originate from leukemic promyelocytes and their numbers increase in the bone marrow and peripheral blood of responder APL cases. During this process of differentiation-inducing therapy, C/EBPβ is upregulated in the presence of PML-RARα and increases the number of neutrophils derived from APL cells by promoting their proliferation and differentiation.

It is clear that C/EBPβ regulates not only myeloid hematopoiesis, but also bone marrow B lymphopoiesis, in both a cell-intrinsic and cell-extrinsic manner.(71,72) One study examined the contribution of C/EBPβ to the development of lymphoid neoplasias in cases with acute B-cell precursor leukemia and identified recurrent translocations in C/EBPβ, which resulted in the upregulation of C/EBPβ.(73)

Anaplastic large cell lymphoma (ALCL) is a subset of non-Hodgkin’s lymphoma characterized by unique cell morphology and expression of CD30.(74) In ALCL cells, the anaplastic lymphoma kinase (ALK) gene is frequently fused to the nucleophosmin (NPM) gene, and the resulting ALK activity is the central driver for the survival of ALCL cells. Recently, C/EBPβ was identified as a downstream target of ALK-mediated signaling (74) C/EBPβ is upregulated in the presence of activated ALK through signal transducer and activator of transcription 3(74,75) or by post-transcriptional regulation,(76) whereupon it contributes to the transformation and survival of ALCL cells.(77) The pathogenesis of multiple myeloma remains unclear and, at present, this plasma cell disorder is incurable. A recent report shows that C/EBPβ is overexpressed in myeloma cells.
and is involved in regulating several transcription factors, including IRF4, XBP1, and BLIMP1, all of which are critical for the differentiation and survival of myeloma cells.\(^{78}\) Inhibiting C/EBPβ translation in myeloma cells using immunomodulatory derivatives of thalidomide has been proposed as a novel therapeutic strategy for multiple myeloma.\(^{79}\)

**Conclusions**

The expression and/or function of C/EBPβ are upregulated in the hematopoietic system in response to various kinds of cell-extrinsic stress, including infections and cancer. This upregulation increases the supply of myeloid cells. Dysregulation of C/EBPβ is observed in several hematological malignancies, resulting in the maintenance or progression of disease. Although the roles of C/EBPβ in hematopoiesis have not been fully elucidated, it appears to play a key role in non-steady-state hematopoiesis, including hematological malignancies, and hematopoiesis in host with cancers in addition to hematopoietic responses against infections (Fig. 5). Even though direct targeting of this transcription factor might be technically difficult, identifying the upstream and downstream networks involving C/EBPβ will lead to a better understanding of the pathogenesis and pathophysiology of diseases mediated by non-steady-state hematopoiesis.

**Acknowledgments**

This work was supported by a Grant-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) (to H.H., A.Y., and T.M.), a grant from the Project for Development of Innovative Research on Cancer Therapeutics from MEXT (to H.H. and T.M.), a Grant-in-Aid from the Ministry of Health, Labour and Welfare in Japan (to T.M.), the National Cancer Center Research and Development Fund (to T.M.), the Takeda Science Foundation (to H.H.), a research grant from the Princess Takamatsu Cancer Research Fund (to T.M.), and the Kobayashi Foundation for Cancer Research (to T.M.).

**Disclosure Statement**

The authors have no conflict of interest.

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