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Comment on Huang et al, page 1012

The polyphony of BACH2

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In this issue of *Blood*, Huang and colleagues examine the role of BACH2, a transcription factor known to be expressed highly in germinal center B cells.[1-3]

B cells undergo very striking changes as they differentiate from stem cells to become the effector cells of humoral immunity. This process requires that B cells undergo the germinal center reaction where B cells migrate through lymph nodes and interact with other immune cells including dendritic cells and helper T cells. In germinal centers, these B cells proliferate rapidly as they undergo somatic hypermutation and class-switch recombination—2 mechanisms through which B cells develop affinity for antigens. Indeed, these normal B cells have a doubling time of 6 hours, that is, more rapid than most tumors. B cells with affinity for antigen further differentiate into memory B cells and plasma cells, which are the effector cells of humoral immunity.

BCL6 is well known as a major regulator of germinal center differentiation. Mice lacking BCL6 expression are unable to form germinal centers. BCL6 promotes the rapid proliferation of B cells and blocks the DNA damage response that accompanies somatic hypermutation. Not surprisingly, this process is fraught with the potential for oncogenic transformation. Indeed, most B-cell tumors arise from either germinal center or post–germinal center B-cell stages. Thus, it appears likely that there are other genes beyond BCL6 that aid in closely regulating this important process.

Huang and colleagues generated transgenic mice that expressed BCL6 and BACH2 variably. They demonstrate convincingly that the mice that are deficient in both BCL6 and BACH2 show profoundly decreased formation of germinal center B cells and a predisposition toward increased plasma cells.[4] They further demonstrate through genome-wide DNA-binding experiments that these transcription factors bind overlapping sites in the genome. They also demonstrate biochemically that BCL6 stabilizes BACH2 protein expression. Taken together, these experiments shed new light on the role of this important transcription factor in this important process.

The role of BACH2 has recently been described in the function of T cells[5] and alveolar macrophages.[6] In early B cells, BACH2 regulates the tumor suppressor role of p53, which suggests it has a more extensive role in cancers. BACH2 mutations occur in about 5% of diffuse large B-cell lymphomas,[7] as well as other cancers,[8] although their specific role is unknown. Future work will be needed to define the role of BACH2 in cancer and the potential role of other collaborating transcription factors and genes in B-cell differentiation.

Although much of the study of biology has focused on the role of individual genes, it is becoming increasingly apparent that most important biological processes are governed by multiple genes working in concerted fashion.

The multifaceted actions of BACH2 in different contexts are reminiscent of a polyphonic composition with intertwining melodies carried by different sections of the orchestra. The Baroque era composer J. S. Bach (1685-1750) was one of the foremost composers in this style and his work remains widely performed to this day. Although the full name BTB and CNC homology 1, basic leucine zipper transcription factor 2 is difficult to remember, recalling the polyphonic work of Bach can remind us of the gene BACH2 and its many functions.

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