THE ROLE OF FOXO TRANSCRIPTION FACTORS IN B CELL DEVELOPMENT AND ACTIVATION

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A functional immune system depends on a diverse, self tolerant B cell repertoire. Mature B cells distributed throughout secondary lymphoid organs respond to antigenic stimuli by dividing and differentiating into plasma cells and other effector cell types. Signaling from the B cell receptor (BCR) plays a critical role at several points during this developmental process. Cell survival, proliferation, differentiation, death, anergy, and receptor editing may occur in response to BCR stimulation. A variety of factors, including signal strength and duration, cytokine presence, and co-stimulation determine the ultimate B cell fate.

In this thesis, the roles Foxo transcription factors play in maintaining B cell homeostasis will be explored. Foxo1, Foxo3, and Foxo4 have both anti-mitogenic and pro-apoptotic properties. The transcription factors are posttranslationally controlled via Akt. When a mature B lymphocyte is stimulated through the BCR, Akt-mediated phosphorylation of Foxos results in their exclusion from the nucleus. In the absence of Foxo nuclear activity, the B cell progresses into the cell cycle.

We have discovered a second PI3K-dependent means of control for Foxos, at the level of mRNA expression. Downstream of the BCR, this means of control is unique and functionally relevant. Mature B cells proliferating in response to anti-IgM downregulate Foxo mRNA expression. This is via activation of the PI3K/Btk/BLNK/PLC-gamma2 pathway. Conversely, Foxo mRNA expression is upregulated in immature B cells, both when the tonic/basal signal through the BCR is disrupted and when the BCR is engaged with anti-IgM. Overexpression of Foxo3 mRNA in an immature B cell line promotes anti- IgM induced apoptosis. Primary immature B cells from Foxo3-/- mice have decreased apoptotic response to BCR crosslinking. Thus, at the immature stage of development our work has revealed a potential role for Foxo3 in promoting clonal deletion. Foxo3-/- mice also have reduced frequencies of pre-B and mature recirculating B cells in the blood and bone marrow. The mice demonstrate increased basal levels of IgG2a, IgG3, and IgA.

Thus, Foxo3 deficiency affects numerous aspects of B cell development.