ImmunoTools IT-Box-Cy55M-Award 2013

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Regulation of the transcription factor E4BP4; a central player in NK cell development

Natural killer (NK) cells are large granular lymphocytes that sit at the interface between innate and adaptive immunity, where they coordinate tumour immunosurveillance and immune responses to invading pathogens. NK cells have the innate ability to kill transformed cells and so there is continued interest in the potential use of these cells for cell-based immunotherapy against cancer (1). However, before such therapies can reach the clinic a greater understanding is required of how these cells develop so that the production of large numbers of NK cells can become possible.

The genetic pathway that leads to the differentiation and function of NK cells is being resolved and numerous transcription factors that control this process have been identified. One of the key regulators of NK cell development is the basic leucine zipper transcription factor E4BP4, which is essential for the commitment of progenitor cells to the NK cell lineage. *E4bp4*$^{-/-}$ mice specifically lack NK cells, whilst having normal numbers of B cells, T cells and NKT cells (2). The development of NK cells in the bone marrow of *E4bp4*$^{-/-}$ mice is interrupted at the earliest stages and *E4bp4*$^{-/-}$ hematopoietic progenitor cells (HPCs) fail to develop into NK cells *in vitro* even in the presence of IL-15 (2).

In addition to its role in NK cell development, E4BP4 is also essential for the development of CD8α^{+} dendritic cells; heavy chain class switching in B cells and the production of various pro-inflammatory cytokines by different T cell subsets (3). As E4BP4 is central to such a broad range of processes, its functions are likely to be tightly regulated. However, very little is known about how E4BP4 functions on a molecular level or how its activities are controlled. The aim of my project is to analyse the post translational modifications of E4BP4 and determine how these regulate its function.

We have established that E4BP4 has numerous post translational modifications and some of these directly influence its function in promoting NK cell development. We would now like to determine what signals effect the post translational modifications of E4BP4 and ultimately could influence the development of NK cells. Using the ImmunoTools cytokines we would be able to screen how a wide range of cytokines influence the post translational modifications of E4BP4. Some cytokines, such as IL-15, are well known to influence NK cell development, but how it affects the functions

of E4BP4 are yet to be explored. Ultimately this work will lead to a greater understanding of how NK cell development is controlled and potentially how it can be manipulated to result in the production of larger numbers of NK cells.

References:

1. Shook, D.R. and D. Campana, Natural killer cell engineering for cellular therapy of cancer. Tissue Antigens, 2011. 78(6): p. 409-15.

2. Gascoyne, D.M., et al., The basic leucine zipper transcription factor E4BP4 is essential for natural killer cell development. Nat Immunol, 2009. 10(10): p. 1118-24.

3. Male, V., et al., E4BP4: an unexpected player in the immune response. Trends Immunol, 2012. 33(2): p. 98-102.

ImmunoTools *IT-Box-Cy55M* for **Tomasz Kostrzewski**
includes 55 recombinant mouse cytokines

rm EGF, rm Eotaxin / CCL11, rm FGF-a / FGF-1, rm FGF-b / FGF-2, rm FGF-8, rm Flt3L / CD135, rm G-CSF, rm GM-CSF, rm GRO-a / CXCL1, rm GRO-b / CXCL2, rm IFNgamma, rm IL-1alpha, rm IL-1beta, rm IL-2, rmIL-3, rm IL-4, rm IL-5, rm IL-6, rm IL-7, rm IL-9, rm IL-10, rm IL-11, rm IL-13, rm IL-15, rm IL-16, rm IL-17A, rm IL-17C, rm IL-17F, rm IL-19, rm IL-20, rm IL-21, rm IL-22, rm IL-25 / IL-17E, rm IL-27, rm IL-31, rm IL-33, rm IP-10 / CXCL10, rm LIF, rm MCP1 / CCL2, rm M-CSF, rm MIP-1α/ CCL3, rm MIP-1β / CCL4, rm MIP3α / CCL20, rm MIP3β / CCL19, rm NGF-beta, rm PDGF-AA, rm PDGF-BB, rm RANTES / CCL5, rm sCD40L / CD154, rm SCF, rm SDF-1α / CXCL12a, rm SDF-1β / CXCL12b, rm TNFα, rm TPO, rm VEGF DETAILS.