ImmunoTools IT-Box-139 Award 2013

Daniel Puleston

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The Role of Autophagy in T cell responses and immune senescence

My PhD project is centred around the role of autophagy in T cells. Autophagy is a conserved intracellular pathway, concerned with the breakdown of organelles and large protein aggregates. I have shown in a mouse model, in which the essential autophagy gene Atg7 is deleted in all T cells, that autophagy is essential for T cell survival and function. Most interestingly, I have shown that autophagy-defieicnt T cells fail to generate long-lived memory cells when challenged with influenza and MCMV. I have also shown that loss of autophagy in T cells in mice leads to a failure to produce effective T cell reponses to influenza vaccination.

Other studies in the field of autophagy have now discerned a strong link between autophagy and ageing. The expression of many autophagy genes is found to be decreased in lower organs and in certain tissues in humans. Furthering these findings, I have shown that autophagy gene expression is diminshed in T cells from aged mice and humans. With age, humans gradually become less efficient at generating T cell memory and proper vaccine responses, leaving them exposed to a number of potentially fatal infections. This is highlighted in the case of influenza, where only one in three elderly individuals are protected following influenza vaccination. I hypothesise that impaired autophagy levels in T cells from elderly patients may correlate with poor memory and vaccine responses observed in these individuals. To do this, I will correlate the CD8 T cell response to influenza vaccination using tetramer technology with autophagy levels in the same cells.

The ImmunoTools *box award* would be of tremendous value in allowing us to phenotype influenza-specific T cells, checking for features such as activation and differentiation state, and to investigate whether impaired autophagy impacts on these features. We have a wealth of data in mice that indicates falling autophagy levels is a significant factor that drives immune senescence. Thus, I would also like to investigate whether impaired autophagy levels correlates with features of immune senescence in humans. These features include a reversed CD4:CD8 ratio, and an increase in $CD8^+$ $CD45RA^+$ $CD27^-$ $CD28^-$ terminally differentiated T cells. Data from my PhD also suggests that in mice, autophagy levels fall as T cells become more differentiated. I would like to repeat these findings in human T cells. The ImmunoTools *IT-box-139* would provide all the necessary antibodies, and more, to do this phenotypic assessment.

The work in my PhD thus far has mostly been centred around mouse work. The final half of my PhD will be aimed at seeing if these findings can be translated to humans. However, currently, we do not have human antibodies to begin these studies promptly. Thus, the ImmunoTools award would go a long way in kick-starting this part of my project and helping to discover if autophagy is implicated in human T cell responses and immune senescence.

ImmunoTools *IT-Box-139.3* for **Daniel Puleston** includes 100 antibodies

FITC - conjugated anti-human CD1a, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD9, CD11a, CD11b, CD14, CD15, CD16, CD18, CD19, CD21, CD25, CD29, CD36, CD41a, CD43, CD45, CD45RA, CD46, CD52, CD53, CD54, CD58, CD62p, CD63, CD69, CD71, CD80, CD86, CD95, CD235a, HLA-ABC, HLA-DR, IL-6, Control-IgG1, Control-IgG2a, Control-IgG2b, Annexin V

PE - conjugated anti-human CD2, CD3, CD4, CD8, CD11b, CD14, CD15, CD18, CD19, CD20, CD21, CD22, CD27, CD33, CD34, CD37, CD38, CD40, CD42b, CD45, CD45RB, CD50, CD72, CD95, CD105, CD147, CD177, Control-IgG1, Control-IgG2a, Control-IgG2b, Annexin V

PE/Dy647 -tandem conjugated anti-human CD45

APC -conjugated anti-human CD3, CD4, CD7, CD8, CD10, CD11c, CD14, CD16, CD19, CD27, CD37, CD40, CD44, CD56, CD59, CD61, CD62L, CD62P, CD69, IL-6, Control-IgG1, Control-IgG2a, Control-IgG2b, Annexin V DETAILS

plus CD45RA-PE, CD57-FITC