ImmunoTools *special* Award 2014

Mark Sims, PhD student

Supervisor: Dr. Adrien Kissenpfennig

Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, 97 Lisburn Road, Belfast, BT9 7AE

The role of Interleukin-34 in the inflammatory response

Interleukin-34 (IL-34) is a recently discovered cytokine, the functions of which remain poorly characterised. This cytokine shares a receptor with M-CSF, namely CSF1R, and displays overlapping functions with M-CSF despite no significant homology between the two cytokines. One such function is the ability of IL-34 and M-CSF to trigger differentiation of macrophages from monocytes. The binding of each ligand seems to result in different downstream intracellular signalling events, resulting in different gene expression profiles.

It is now established that the contribution of various factors in the process of macrophage differentiation can produce cells with markedly different phenotypes. One scheme of macrophage nomenclature refers to such populations as M1 and M2. These subsets function in opposition to each other, displaying pro-inflammatory and anti-inflammatory phenotypes respectively. It is relatively well established that M-CSF contributes to alternative activation of macrophages, inducing an M2 phenotype. The role of IL-34 in this process, however, requires further scrutiny. The role of macrophage polarization is now widely researched, both as an aetiological process, as well as a potential therapeutic target. This is an exciting field of research, as techniques for modulation of innate immunity could be applied to a very wide range of diseases. Investigating the role of IL-34 in macrophage polarization could open up a new avenue of research in this field.

Some work has been carried out to characterise the effect of IL-34 on the phenotype of microglia. It has been shown that IL-34 induces these cells towards a more phagocytic phenotype in a model of Alzheimer's disease, demonstrating an enhanced ability to clear amyloid-β plaque. This, therefore, demonstrates the role of IL-34 as a potential therapeutic. If taken together with the data suggesting that IL-34 induces M2-like macrophages, it could be hypothesised that IL-34 may generate macrophages with an anti-inflammatory, yet more phagocytic phenotype. This could be explored as a possible treatment for sepsis, whereby IL-34 may increase bacterial clearance by macrophages, as well as helping to dampen down excessive inflammation. Any research which attempts to contribute to our understanding of

sepsis is of value, as this devastating clinical syndrome is a major cause of morbidity and mortality in our society.

Studies to date have mostly focused on the role of IL-34 on the development and maintenance of immune cell populations in the steady state. For example, IL-34$^{-/-}$ mice show reduced numbers of microglia and Langerhan's cells. At present, there are very few published studies which attempt to describe a role for IL-34 in response to infection. Such an investigation could yield surprising and novel results, providing the field of immunology with a wealth of knowledge on the functions of this newly-discovered cytokine. Considering that antibiotic resistance is becoming a very real problem in modern medicine, it is vital that academic research continues to deepen our understanding of the body's response to pathogens, in an attempt to develop new treatments.

Given that so little is known about the biological effects of IL-34, research on this cytokine can be challenging. One of the major obstacles is the need for wide experimental screens, in order to more fully determine the effects of this signalling molecule. The nature of this work requires a broad range of reagents, in an attempt to carry out a more complete characterisation of the role of IL-34 in the inflammatory response.