Conference Scene

T-cell subset phenotype and function

Identifying T-cell subset phenotype and function in infections

10 March 2011, The Penridge Suite, London, UK

Organized by Euroscicon, this meeting focused on the complex and fast-paced research field of T-cell subset phenotype and function. During the past 20 years, this field has moved on from the simple Th1–Th2 paradigm to the discovery of a range of T-cell subsets, including Tregs and Th17 cells. The meeting brought together a variety of researchers currently exploring this field, to give insight into what we know, what we need to know and the potential implications of this research in the medical setting.

The meeting was opened by the chair, Marc Veldhoen (Babraham Institute, Cambridge, UK) (FIGURE 1), with an introduction of the six major subpopulations of CD4⁺ T helper (Th) cells in the immune system: Th1, Th2, Th3, Th9, Th17 and Tregs. Veldhoen's research has focused on the recently discovered Th17 cells, and he and his colleagues have found that these cells can convert to Th1 cells *in vivo*. Furthermore, they have shown that there are two types of Th1 cells: while Th1 cells derived from Th17 cells express the aryl hydrocarbon receptor and the IL-1 receptor 1, naive Th cells that differentiate into Th1 cells do not. Th17 cell plasticity is dependent on the *in vivo* inflammatory conditions, varying with acute and chronic inflammatory conditions.

Wild rodents as models

Janette Bradley (University of Nottingham, UK) discussed the use of wild rodents as a model system for studying the immune system, as human studies have ethical and practical constraints, and studies on laboratory mice are limited owing to controlled environmental conditions and a lack of exposure to a range of pathogens. Wild rodents are outbred and are infected by a community of parasites, in a similar way to humans in developing countries who are exposed to macro- and micro-parasites. Bradley's research aims to use T cells to determine the immune phenotype of individuals to understand the mammalian immune system under natural conditions and to study coinfection dynamics. By studying populations of wood mice (*Apodemus sylvaticus*) and field voles (*Microtus agrestis*), which are infected

with a range of parasites, it has been shown that microparasites are associated with an inflammatory immune response along the Th1–Th2 axis, whereas macroparasites are associated with regulatory and Th2 cell activity. Results so far indicate that production of the inflammatory cytokine TNF- α in wood mice increases with microparasite burden, while macroparasites such as lice dampen the inflammatory response. Current and future work aims to identify the causes and effects of these responses using longitudinal field data, and testing hypotheses in the field and laboratory environment.

Immunity to malaria

Eleanor Riley (London School of Hygiene and Tropical Medicine, UK) presented the malaria research that has been conducted in her laboratory over the past 10 years. Malaria infection leads to a strong pro-inflammatory, Th1 cell immune response. Riley discussed the effects of lethal and nonlethal strains of *Plasmodium yoelii* in C57BL/6 mice, and how the virulence of malaria infections is dependent on the cellular source of TGF- β and the timing of its production. During infection with the nonlethal malarial strain, the production of TGF- β leads to a rapid burst of IFN- γ resulting in clearance of the parasite and recovery. By contrast, TGF- β is produced within 24 h of infection of the lethal strain, delaying the production of IFN- γ and TNF- α , resulting in 100% mortality. As there was a comparable expansion and activation of classical Tregs in both lethal and nonlethal infections, Riley was keen to discover how the mice were clearing nonlethal infections. Her laboratory

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found that 60% of *IL-10* knockout (KO) mice were able to clear infections with the lethal strain, whereas infections with the nonlethal strain were cleared more easily in these KO mice than in wild-type (WT) mice. However, the lack of IL-10 production resulted in greater liver damage, suggesting that IL-10 protects the liver at the cost of clearing parasites. It was also shown that RAG mice, which lack T cells, had lower levels of IL-10 than WT mice, indicating CD4⁺ T cells are the major source of IL-10 during *P. yoelii* infection. Further work within Riley's research group has demonstrated that memory T cells are the primary source of IL-10.

Inflammatory bowel disease & *Helicobacter hepaticus*

Inflammatory bowel disease (IBD) affects 180,000 people in the UK and is on the rise in developed countries. With the focus on ulcerative colitis and Crohn's disease, Marika Kullberg (University of York, UK) discussed studies of the role of gut flora in disease pathogenesis in murine models of IBD. It has been found that *IL-10* KO mice housed in conventional animal facilities spontaneously develop enterocolitis, and

that disease is less severe when animals are housed under specific pathogen-free conditions. Therefore, Kullberg asked, "Can we induce colitis in specific pathogen-free *IL-10* KO mice using a single infectious agent." In this case, Kullberg's research group infected C57BL/10 KO mice with the Gram-negative bacterium *Helicobacter hepaticus*, which colonizes the cecum. While WT mice did not develop disease and showed an increase in IL-10 production, *IL-10* KO mice developed disease accompanied by an inflammatory Th1 immune response characterized by the production of IFN- γ and TNF- α . *H. hepaticus*-induced colitis is inhibited in *IL-10* KO mice during anti-IFN- γ or IL12p40 treatment, suggesting that IL-10 plays a protective role during *H. hepaticus* infection, steering the immune response away from a Th1 phenotype. *IL-10/IL12p40* KO mice do not develop colitis as a result of *H. hepaticus* infection, therefore Kullberg was interested to know which cytokines involved in colitis are critical: IL-12, which results in the expansion and maintenance of inflammatory Th1 cells; or IL-23, which leads to the expansion and maintenance of proinflammatory Th17 cells. By studying

Figure 1. Conference speakers. From left to right: Pranab Das (University of Amsterdam, The Netherlands), Marika Kullberg (University of York, UK), Janette Bradley (Nottingham, UK), Matthew Taylor (University of Edinburgh, UK), Werner Muller (University of Manchester, UK), Marc Veldhoen (Cambridge, UK) and Eleanor Riley (London School of Hygiene and Tropical Medicine, UK).

WT, *p40* KO and *p35* KO mice during anti-IL-10 receptor treatment, Kullberg found that IL-23 has a crucial role during *H. hepaticus*-induced colitis, with frequencies of both Th1 and Th17 cells being enhanced at the site of inflammation.

Conditional gene targeting

Conditional gene targeting is a method by which a gene of interest can be inactivated in either all cells or a given cell type. Research in the laboratory of Werner Muller (University of Manchester, UK) involves conditional gene targeting to inactivate cytokine and cytokine receptor genes in mice. Muller briefly highlighted the advantages and disadvantages of this technique, before discussing some of the results that his laboratory had obtained. Muller's work has focused on the cytokine IL-10. His research has demonstrated that knocking out the *IL-10* gene in T cells results in C57BL/6 mice exhibiting a Th1 immune response when infected with *Trichuris muris*, and that it is only T cell-specific IL-10 that controls the differentiation of T cells into Th1 or Th2 cells during *T. muris* infection. Furthermore, Muller generated conditional KO mice for the cytokine receptor, Gp130, which regulates Th17 and Treg cells *in vivo*. T cells lacking Gp130 were unable to drive the generation of Th17 cells, inducing a regulatory immune response via Tregs, resulting in resistance to *T. muris* infection.

Leprosy: balancing the T-cell response

Pranab Das (University of Amsterdam, The Netherlands) talked about leprosy and its potential as a human disease model to study aspects of immune dynamics due to changes in the host's immunity caused by the parasite *Mycobacterium leprae*. By establishing the cytokine profiles of T cells

cloned from skin lesions of patients, Das has shown that although a Th1 immune response sustains cell-mediated immunity to control the spread of intracellular infection it also leads to tissue damage. By developing clinical biomarkers to monitor the cytokine profiles of patients with leprosy, Das suggests that immune reactions could be prevented at an early stage of disease, reducing the risk of the nerve damage that leads to the disabilities caused by this disease.

Th2 cell quality versus quantity

The filarial parasite *Litomosoides sigmodontis* has been observed to cause chronic infection in susceptible BALB/c mice whereas C57BL/6 mice show resistance, eliminating the parasite within 30–60 days of infection despite both strains exhibiting a Th2 immune response. Matthew Taylor (University of Edinburgh, UK) discussed data from IL4-gfp (4get) mice to answer the question, "Why doesn't the Th2 response in susceptible mice kill the parasite?" His research group demonstrated that the number of Th2 cells increases during infection as the functional quality of effector cells decreases. Taylor highlights that this is important to keep in mind when performing assays to define the magnitude and type of T-cell responses.

Conclusion

The meeting highlighted the complexity of T-cell function during infections yet also showed how useful data can be gained from laboratory models and natural populations, as well as the limitations. It provided an opportunity for delegates to discuss the current research being undertaken within the T-cell field, as well as to explore how it may impact upon future decisions relating to treating diseases such as IBD and malaria.