A powerful tool for the study of CD4 T cells in malaria

Although aimed at controlling invading pathogens, immune responses can sometimes be harmful to the host. Responses against the blood stage of malaria are an example of this: while B cells are activated and produce useful antibodies that kill parasites, killer $CD8^+$ T cells are also generated that inadvertently cause damage to the brain (a pathology called cerebral malaria), which may be lethal. $CD4^+$ T cells (or “helper” T cells) are key orchestrators of these immune responses, helping B cells make antibodies and activating another type of immune cell called a dendritic cell, which in turn stimulates killer T cell responses. Understanding the mechanisms by which $CD4^+$ T cells control immunity is therefore important for the design of strategies to enhance immunity and prevent malaria pathology.

An important difficulty when studying T cells is the fact that we (and mice) have tens of millions of them, with only a few (sometimes less than a hundred) recognising the same target (antigen). Thus, it is very hard for us to study the rare T cells specific for malaria during infection. T cell receptor-transgenic mice provide a solution for this, as all T cells in these mice are forced to express the same T cell receptor (TCR; the molecule that determines the antigen specificity of a T cell), so they all recognise the same antigen (for example, a malaria antigen). These cells usually carry a marker that enables us to distinguish them from the millions of normal T cells (mostly non-antigen specific) after we transfer them into a normal mouse. We made a $CD4^+$ T cell TCR-transgenic mouse line specific for malaria that we termed PbT-II. This mouse and its unique population of malaria-specific T cells enabled us to study in great detail the function of $CD4^+$ T cells during the course of malaria.

We first characterised our PbT-II cells and showed that they are reactive to multiple species of malaria parasites, even recognising *Plasmodium falciparum* parasites that normally infect humans. They also respond to malaria parasites that grow the liver, prior to blood stage infection. This means, PbT-II cells are a very versatile tool to study responses against malaria in multiple contexts.

For $CD4^+$ T cells to work as helpers, they need to get activated themselves. We sought to determine which cells were responsible for the activation of PbT-II cells during blood stage malaria – which we measured by quantifying PbT-II division in the presence or absence of certain antigen presenting cells. We established that dendritic cells (DC), and more specifically a subset called $CD8^+$ DC, were most efficient at inducing PbT-II cell proliferation. Moreover, $CD8^+$ DC promoted the differentiation of activated PbT-II cells into Th1 cells (a $CD4^+$ T cell subset that induces inflammation) and Tfh cells (follicular helper T cells; another subset specialised in stimulating antibody production).

Once activated, $CD4^+$ T cells interact with B cells and dendritic cells, enabling them to produce effective antibodies and to activate killer T cells against the invading pathogen. By using gene deficient mice, we demonstrated that PbT-II cells utilise the surface molecule CD40L, which binds

its receptor CD40 on B cells and dendritic cells, to carry out this function. While B cells activated in this way produced antibodies that eliminated the parasites from the blood, dendritic cells stimulated killer T cells that accelerated the onset of cerebral malaria.

In conclusion, we generated an important tool for the study of immune responses against malaria and used it to better understand $CD4^+$ T cell activation and the subsequent, dual role of activated $CD4^+$ T cells in immunity and pathology during blood stage malaria.

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