What initiated your interest in Fas ligand-positive (FasL+) killer B cells?

My doctoral dissertation focused on mechanisms of T helper (Th) cell death in the schistosome worm infection model in mice. The ability of B cells to express Fas ligand was unknown to me and most other immunologists at the time, yet we found that the B cells in the model were highly FasL+ and very effective at killing Th cells. Another really surprising finding was that a small subset of B cells in the spleens of uninfected mice expressed Fas ligand. This fundamentally changed my perspective on the normal functions of B cells in the immune system, and led to a shift in my interests towards whether killer B cells play a role in suppressing allergies or autoimmune diseases.

How have your priorities shifted over the course of your career?

During my postdoctoral fellowships, I went on to find that killer B cells in the lungs regulated Th cells in an allergic asthma model and that severity of autoimmune arthritis was linked to poor functioning of killer B cells. This fundamentally changed my perspective on the normal functions of B cells in the immune system, and led to a shift in my interests towards whether killer B cells play a role in suppressing allergies or autoimmune diseases.

What specific diseases do your current projects focus on?

One of our biggest challenges has been to decide which diseases or conditions to target with our research. We believe that killer B cell functions are important in regulating many (if not all) types of autoimmunity and allergic responses. They are also likely to be involved in the protection of the foetus from the mother’s immune system and may play a pathogenic role in cancer by inhibiting the immune responses toward tumours.

Currently our killer B cell work is focused primarily on allergic asthma and type 1 diabetes – two important and prevalent diseases of childhood for which there is some direct evidence that FasL+ B cells can regulate the pathology. Interestingly, the incidence of these diseases is very low in areas where schistosome infections are common, suggesting that nature may already be applying the principles we are advocating.

How do you see your research developing in the future?

We are very excited by our recently reported discovery that human B cells that are transformed into rapidly growing tumour cells by EBV are able to produce FasL+ vesicles called exosomes. These exosomes were effective at killing human Th cells in much the same way as we have shown for mouse killer B cells. This was a very consistent finding using B cells isolated from many individuals, suggesting that EBV-transformed B cells from any patient could be used as factories to produce potentially therapeutic exosomes. The strain of virus we used does not replicate, which we hope will greatly reduce the risk of causing harm to recipients of the exosomes. FasL+ exosomes may have many properties that are superior to killer B cells, and the nature of the system that we have discovered is likely to overcome many obstacles in the way of translating our research into human therapies. We still have a long way to go in proving that manipulation of killer B cells or their exosomes will be effective and produce safe treatments for human diseases, but this will continue to be our goal for the foreseeable future.
Fas ligand findings

A University of Michigan laboratory is conducting pioneering work aimed at developing novel treatments for a variety of autoimmune and inflammatory diseases by targeting antigen-specific T helper cells with killer B cells.

THE FAS LIGAND is expressed by many cells including T helper (Th) cells. This ligand is well known for its role in inducing cell death (apoptosis) when it binds with the Fas receptor – an interaction that plays an important part in immune system regulation and cancer progression. At the University of Michigan, Dr Steven K Lundy and his team are aiming to utilise this mechanism in order to develop novel treatments for autoimmune and inflammatory diseases, by harnessing Fas ligand expression by Fas ligand-positive (FasL+) killer B cells. “My lab studies the ability of B cells to kill Th cells through Fas ligand signalling,” Lundy summarises.

One subset of Th cells the team aims to target are those that are self-reactive, as these are associated with autoimmune diseases in people who, for genetic and/or environmental reasons, are unable to control self-reactive T cells effectively. By stimulating natural Th, cell control mechanisms such as Fas ligand/receptor interactions, it is possible that these harmful cells may be destroyed and Th cell-mediated disease risk reduced in a therapeutic setting. However, if such outcomes are to be achieved, a more detailed understanding of the basic biology involved is first required.

ASTHMA AND DIABETES

The Lundy Lab posits that using killer B cells to target Th cells could have applications in a wide variety of associated diseases, including food allergy, asthma, type 1 diabetes, multiple sclerosis and rheumatoid arthritis. At present, he is focusing his lab’s research efforts predominantly on allergic asthma and type 1 diabetes. This decision was driven both by the fact that these are two very serious, prevalent conditions and as a result of the wealth of pre-existing and ongoing research in these areas, which the Lundy Lab can utilise to enhance their research goals. “Drawing upon progress made within the larger research community will make our hypotheses much easier to test and hopefully lead to quicker translation of our work into humans,” Lundy expands. Of course, progress made in studying these conditions is likely to have significant applications to devising novel treatments for a range of other diseases.

Lundy and his colleagues are currently working to answer a number of fundamental questions surrounding Fas ligand B cell expression and how it impacts Th cells. It is not yet known, for example, how Fas ligand expression is regulated in B cells; exactly which B cell subsets express Fas ligand in humans; or whether patients affected by autoimmune disease or allergies have defective killer B cell function. Questions also remain as to whether boosting killer B cell numbers or activity levels may be used to treat – or even prevent – Th cell-mediated diseases. Furthermore, it is unclear how killer B cells relate to other immune regulatory functions, and whether the Th cells targeted by the researchers may be able to develop a resistance to killer B cell-mediated apoptosis.

Investigations aimed at answering these questions are underway within the Lundy Lab. For example, current research efforts are examining how Fas ligand expression is regulated in B cells, with the ultimate goal being to identify ways in which this might be targeted immune-mediated diseases

By studying the mechanisms of immune regulation, Lundy is advancing new and innovative ways to treat immune-mediated diseases such as:

- Rheumatoid arthritis
- Type 1 diabetes
- Grave’s thyroiditis
- Autoimmune retinopathy
- Allergic asthma
The team is aiming to utilise this mechanism in order to develop novel treatments for autoimmune and inflammatory diseases.