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Background Information • Background Information •

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Background of the research of Tim Mosmann on T cell subsets

The immune system is critical for resisting a multitude of different infectious agents, and may also be harnessed to fight cancer. Sometimes it may seem that the infections are dominant, but the constant infections faced by people with immunodeficiencies show us how many diseases we successfully resist. Because of the strength of the immune system, it can also cause severe problems when it over-reacts, leading to autoimmunity, allergies or asthma.

There is enormous interest in products that modify the immune system, either to increase its effectiveness against infectious diseases and cancer, or to prevent autoimmunity and allergy. In the early 1980's, Alex Zaffaroni established DNAX Research Institute, a small company focused on putting together immunology with the powerful techniques of molecular biology. Our goal was to understand the mechanisms of the immune system, in the belief that valuable therapeutics could be designed on the basis of the knowledge that we gathered.

What we discovered

Our initial target was to understand the structure and function of cytokines, small proteins produced by cells in the immune system. Our focus at DNAX was on the cytokines produced by T cells, which regulate many of the functions of the immune system. We set up techniques that allowed us to collect large amounts of data, and as a result could see patterns in that data that led us to discover that there were two different types of T cell, based on their ability to make two different groups of cytokines. When we looked at the functions of these cytokines, we realized that the two types of T cell could explain the separation of some immune functions that had been recognized by previous researchers.

The cells that we called Th1 cells make cytokines that cause inflammatory responses that help to eliminate many infectious agents that live inside cells, whereas the cytokines produced by Th2 cells are important for defeating infections by parasitic worms. Both of these subsets can also cause problems if they over-react; for example Th1 cells are involved in some types of autoimmunity, and Th2 cells contribute to allergy and asthma. Since our initial discovery of these two types of cell, and their cytokine patterns, many groups around the world have identified the contributions of these subsets and others to different infectious and immunological diseases.

The two T cell subsets that we described were just the beginnings of understanding the complexity of T cell and cytokine responses. Many other research groups have now

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discovered additional cytokines and T cell types, building up a very diverse set of molecules and cell types involved in different types of immunity. We are only beginning to understand the complexity of the interactions between all of these components.

Where this could lead

The immune response is very delicately balanced. In any infection, the danger of under-reacting and allowing the pathogen to spread has to be balanced against the danger of over-reacting and causing too much tissue damage. The immune system needs a knife-edge balance to quickly attack all infections, without making mistakes and attacking host tissues (autoimmunity) or reacting too strongly against harmless substances in the environment such as pollen or food substances (allergy).

To help the immune system to achieve this balance, we need to know how the system is regulated. There has been a great deal of progress over the last few decades in understanding this regulation by T cell subsets as well as other major cell types in the immune system such as dendritic cells, macrophages, B cells and others.

Vaccines are an extremely important area in which to apply this knowledge. Many vaccines have reduced or eliminated serious infectious diseases, often by inducing an antibody response. However, there are still many serious infections for which we do not have effective vaccines, and for at least some of this diseases we may need different types of immunity, not just antibodies. This is where we hope that the detailed information on immune regulation will help to design vaccines that induce exactly the right type of immunity for each infectious agent.

Hand-in-hand with this increasing knowledge of the regulation of types of immunity, we must learn more about each major infectious disease, and what immune mechanisms have the best chance of defeating them. Although we have made remarkably progress in understanding different infectious agents, and equally remarkable progress in understanding the mechanisms and regulation of the immune system, it is very sobering to realize that we still do not have vaccines or immune therapies for such important diseases as HIV/AIDS, tuberculosis, malaria, leishmaniasis and many others.

In addition to vaccines, our increased knowledge of immune regulation is also helping to design therapies for diseases such as rheumatoid arthritis and allergies. We hope that the information that we identified on the T cell subsets and their cytokines will contribute to designing vaccines and therapies that are increasingly focused on inducing exactly the right type of response to eliminate infections, yet prevent the undesirable effects of immunity such as autoimmunity and allergies.

Additional Information

http://www.urmc.rochester.edu/GEBS/faculty/Tim_Mosmann.htm

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