Chapter 11

Memory T-Cell Subsets in Parasitic Infections

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Abstract

Parasitic infections remain a major health problem throughout the world and unlike many viral or bacterial diseases, there are no vaccines to help control parasitic diseases. While several important advances have been made that will contribute to the development of parasite vaccines, such as cloning of dominant parasite antigens and a better understanding of the effector T-cell subsets needed for immunity, fundamental questions remain about how to induce long-term immunologic memory in vaccines. Here we examine a few of the experimental models that have been used to elucidate the nature of the memory T cells that are generated during parasitic infections. Although significant hurdles remain in the development of parasite vaccines, studies with both protozoa and gastrointestinal nematodes suggest that long-term immunity induced by vaccination is a realistic goal for control of parasitic infections.

Introduction

The ability to induce immunologic memory is the key to the development of successful vaccines, which have been pivotal in controlling infectious diseases that have plagued humans and animals for centuries. The most famous example is the eradication of smallpox in the 20th century, which inspired a global campaign to control several other important infectious diseases (e.g., measles, polio) by large-scale vaccination programs. The success of those campaigns begs the question why vaccines for all infectious diseases have not been developed; it is particularly notable that there are no vaccines for any of the parasitic diseases that cause tremendous morbidity and mortality in large parts of the world. In short, the answer is that we do not have a good understanding of how immunologic memory is established or maintained, a deficit that is particularly evident when it comes to T-cell memory. Without a framework for understanding memory, the development of vaccines continues to rely on a trial and error approach. This has clearly not been successful for developing parasite vaccines.

Fortunately, over the last decade a renewed interest in understanding the cellular and molecular basis of memory has generated a substantial amount of new information about immunologic memory. New tools, including the ability to monitor specific T cells with tetramers, adoptive transfer of TCR transgenic cells and intravital imaging techniques, have helped define the in vivo life history and biology of T cells during infection or following immunization. Based upon the results of these studies several models have been proposed that attempt to explain memory cell development and maintenance. In this chapter we will explore some of the advances in our understanding of immunologic memory in parasitic infections, specifically...
focusing on recent studies that tell us about the memory T-cell subsets that mediate immunity to parasitic infections.

The future of vaccines for parasites looked particularly bright in the 1980’s and 90’s. The molecular revolution led to the identification and large-scale production of parasite antigens that previously were impossible to obtain in any reasonable quantity. At that time, the strategy for vaccine design was quite simple: identify the dominant antigens recognized by the immune system, clone those antigens and use them to induce a protective immune response. However, this approach turned out to be less successful than anticipated. The most notable failure was in the field of malaria vaccine development. It was known from pioneering studies in the 1960s that irradiated sporozoites could provide protection against malaria and it was later shown that this immunity was directed against the major surface antigen of the sporozoites, known as the circumsporozoite protein. Cloning the circumsporozoite protein from malaria was prematurely heralded as the first step in what was thought to be the rapid development of a malaria vaccine. Unfortunately, there is still no malaria vaccine. However, while the malaria vaccine was not immediately forthcoming, the ability to clone this parasite molecule and subsequently many other malaria proteins, was a key advance on the pathway to a vaccine.

The other important advance that occurred in the 1980’s was the discovery that CD4+ T cells could be separated into subsets, termed Th1 and Th2 and that these subsets performed distinct immunologic functions. Studies of the immune responses to parasites played a key role in elucidating the factors that control T-cell development. Notably, the differential development of Th1 and Th2 cells following infections with the protozoan parasite Leishmania major demonstrated the key role these subsets played in the development of immunity. As it became clear that cytokines associated with the innate immune response could preferentially direct the development of T-cell subsets, there was a greater focus on understanding the role of adjuvants as inducers of innate cells that could influence the response to a vaccine. This led to many important advances in our understanding of how microbial products—what Janeway once referred to as the “immunologists dirty little secret”—influence the immune response. This led to the notion that if the appropriate immune response was stimulated by modulating the cytokine milieu, then a vaccine would be successful. In the case of leishmaniasis, it was found that inclusion of IL-12 in a vaccine could successful induce a protective immune response. However, the duration of the immunity induced was limited and thus, simply inducing the appropriate response did not lead to long-term immunity. While understanding the different subsets of T cells will be important in vaccine development, these results demonstrate that there is more to immunologic memory than simply inducing an appropriate effector response.

The failure to develop vaccines for several of the most important pathogens causing disease today, in spite of our ability to clone and produce critical antigens and our increased understanding of effector T-cell subsets, has led to a re-evaluation of what is required for immunologic memory. The simple notion that memory T cells represent the few cells left after an effector response has dissipated has been replaced by more complicated models of memory T-cell development. It is now apparent that the memory T-cell pool is heterogeneous and contains several types of memory T-cell subsets. One subset has the characteristics of effector cells, while another has been proposed to act as a reservoir of antigen-specific T cells that can expand upon rechallenge, differentiate into effector T cells and replenish the effector cell population (see Fig. 1). These latter cells, termed “T central memory cells” by Lanzavecchia, express the adhesion molecule CD62L (L-selectin) and the chemokine receptor CCR7, which target the cells to the lymph nodes. The former subset, termed “T effector memory cells”, develops from effector T cells, produces effector cytokines (such as IFN-γ or IL-4) and migrates through the tissues. Thus, effector memory T cells have the ability to immediately respond to a challenge infection, while central memory T cells proliferate in the lymph nodes and can replenish the T effector pool. Memory T cells would be expected to express the IL-7R, since IL-7 provides survival signals to T cells. On the other hand, effector cells would be expected to be short-lived. Understanding how these memory T cells develop and are maintained will be critical in the development of vaccines for parasitic infections.