

## Editor's Note: T Cell Response to Live Antigenic Cells

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The role of T cells in the resolution or exacerbation of COVID-19, as well as their potential to provide long-term protection from reinfection with SARS-CoV-2, remains debated. Nevertheless, recent studies have highlighted various aspects of T cell responses to SARS-CoV-2 infection that are starting to enable some general concepts to emerge. A T cell is a type of lymphocyte. T cells are one of the important white blood cells of the immune system and play a central role in the adaptive immune response. T cells can be easily distinguished from other lymphocytes by the presence of a T-cell receptor (TCR) on their cell surface. T cells are born from hematopoietic stem cells,[1] found in the bone marrow. Then, developing T cells migrate to the thymus gland to mature. T cells derive their name from this organ where they develop (or mature).[2] After migration to the thymus, the precursor cells mature into several distinct types of T cells. T cell differentiation also continues after they have left the thymus. Groups of specific, differentiated T cell subtypes have a variety of important functions in controlling and shaping the immune response.

The immune system protects the body from possibly harmful substances by recognizing and responding to antigens. Antigens are substances (usually proteins) on the surface of cells, viruses, fungi, or bacteria. Non living substances such as toxins, chemicals, drugs, and foreign particles (such as a splinter) can also be antigens. The immune system recognizes and destroys, or tries to destroy, substances that contain antigens. Your body's cells have proteins that are antigens. These include a group of antigens called HLA antigens. Your immune system learns to see these antigens as normal and usually does not react against them. Inflammation occurs because these molecules attract immune system cells to the affected tissue. To help get these cells to the tissue, the body sends more blood to the tissue. To carry more blood to the tissue, blood vessels expand and become more porous, allowing more fluids and cells to leave blood vessels and enter the tissue. Inflammation thus tends to cause redness, warmth, and swelling. The purpose of inflammation is to contain the infection so that it does not spread. Then other substances produced by the immune system help the inflammation resolve and damaged tissues heal. Although inflammation may be bothersome, it

indicates that the immune system is doing its job. However, excessive or long-term (chronic) inflammation can be harmful. A complex pattern of T cell response to SARS-CoV-2 infection has been demonstrated, but inferences regarding population level immunity are hampered by significant methodological limitations and heterogeneity between studies, as well as a striking lack of research in asymptomatic or pauci-symptomatic individuals. In contrast to antibody responses, population-level surveillance of the T cell response is unlikely to be feasible in the near term. Focused evaluation in specific sub-groups, including vaccine recipients, should be prioritised.

Current estimates of population immunity rely solely on seroprevalence studies, however in the context of evidence for cellular responses in seronegative exposed individuals, and the potential waning of antibody responses over time, current surveillance methods are likely to be underestimating both exposure and immunity. A more developed understanding of the role of T cells in long-term protection will be helpful to policy makers in terms of modelling where population-level immunity lies and informing long-term surveillance and immunisation strategies. However, by contrast with antibody testing—a mainstay of immune surveillance for many communicable diseases—existing T cell assays are difficult to standardise and hard to scale, therefore unlikely to be deliverable at population level within the timeframe of the SARS-CoV-2 pandemic. In the short-term, emphasis may need to be placed on determining the utility of T cell assays to guide clinical and public health actions at the individual level, particularly in patients with immunosuppression, or those at the extremes of age. In parallel, adequately-powered and controlled studies providing deep immune phenotyping of T cells, B cells, and comprehensive characterisation of immune responses in mild or asymptomatic cases, and in vaccine recipients, will yield insights about the interdependence and relative importance of cellular and humoral responses. Over the long-term, development of scalable T cell assays may help to strengthen population immune surveillance systems. T-cell responses are induced by antigen-presenting cells (APCs) that present alloantigens. There are two forms of alloantigen recognition—direct and indirect (Fig. 48-1). Direct allore cognition

denotes recognition of donor antigens on donor APCs provided by the graft. The extraordinarily high frequency of T cells with alloreactivity is caused by direct recognition of allogeneic MHC. Indirect recognition is the recognition of donor antigens that are picked up and presented on recipient MHC molecules on recipient APCs. The indirect response is more similar to "normal" T-cell responses, in which professional APCs present peptide antigens to T cells that are present at relatively low frequency in the naïve repertoire.

Direct allo reactivity is particularly important in the early post-transplantation period, when APCs within the transplanted organ are still present; many of these cells migrate to the lymphoid tissues, where they initiate the allo response. However, the APC supply that comes with the donor graft is not renewable; therefore, if the direct response is not maintained by the recognition of donor antigens on endothelial cells or other cells in the graft, it recedes in importance. The indirect response, in contrast, can be maintained by the constantly renewed pool of recipient APCs. The indirect response is of particular importance in inducing antibody responses. T cells are activated to produce armed effector T cells the first time they encounter their specific

antigen in the form of a peptide: MHC complex on the surface of an activated antigen-presenting cell (APC). The most important antigen-presenting cells are the highly specialized dendritic cells, whose only known function is to ingest and present antigen. Tissue dendritic cells ingest antigen at sites of infection and are activated as part of the innate immune response. This induces their migration to local lymphoid tissue and their maturation into cells that are highly effective at presenting antigen to recirculating T cells. These mature dendritic cells are distinguished by surface molecules, known as co-stimulatory molecules, that synergize with antigen in the activation of naive T cells. Macrophages, as phagocytic cells that provide a first line of defence against infection, can also be activated to express co-stimulatory and MHC class II molecules. This enables them to act as antigen-presenting cells, although they are less powerful than dendritic cells at activating naive T cells. B cells can also serve as antigen-presenting cells in some circumstances. Once a T-cell response has been initiated, macrophages and B cells that have taken up specific antigen also become targets for armed effector T cells. Dendritic cells, macrophages, and B cells are often known as professional antigen-presenting cells.