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Sommario/riassunto

The term allorecognition refers to the series of mechanisms used by an individual's immune system to distinguish its own cells and tissues from those of another individual belonging to the same species. During evolution, different cells and molecules of both innate and adaptive immune systems have been selected to recognize and respond to antigens expressed by allogeneic cells, but not autologous cells (alloantigens). This research topic focuses on allorecognition by lymphocytes of the adaptive immune system and its involvement in rejection or tolerance of allogeneic transplants. T and B cells recognizing alloantigens via specific receptors become activated and undergo proliferation and differentiation into different types of effector and memory cells. Allorecognition by lymphocytes occurs regularly during pregnancy upon trafficking of both maternal and fetal cells. In this setting, allorecognition triggers an alloresponse that is protective towards the fetus thus preventing abortion. Protective alloimmunity is mediated through cooperation between different lymphocytes and antigen presenting cells (APCs), as well as regulatory mediators and receptors. Likewise, certain transplants placed in organs and tissues called immune-privileged sites such as the eye, the central nervous system and the testis elicit protective rather than destructive adaptive immune responses. Therefore, under certain circumstances, allorecognition by regulatory lymphocytes (Tregs and Bregs) can lead to tolerance of alloantigens. In contrast, allorecognition by T cells in non-

immune privileged sites and under inflammatory conditions leads to a destructive immune response. Indeed, after transplantation of most allogeneic organs and tissues, activation of pro-inflammatory T cells (TH1 and TH17), which recognize donor MHC proteins (direct pathway) or peptides derived from donor MHC and minor antigens (indirect pathway), leads to graft rejection. This inflammatory response leads to the differentiation of allospecific cytotoxic T cells as well as production of donor specific antibodies by B cells, both of which contribute to the destruction of the transplant. In this Research Topic, we describe the different pathways of allorecognition by T cells involved in allograft rejection, as well as the role of different antigen presenting cells and graft-derived microvesicles (exosomes) involved in this process. Another aspect of this Research Topic addresses the essential role of alloreactive memory T cells in allograft rejection and resistance to transplant tolerance induction in laboratory rodents, as well as non-human primates and patients. Indeed, it has become evident that laboratory mice display very few memory alloreactive T cells pre-transplantation, essentially due to the fact that they are raised in pathogen-free facilities. In contrast, primates display high frequencies of alloreactive memory T cells, either generated through prior exposure to allogeneic MHC molecules or via cross-reactivity with microbial antigens. We and others have provided ample evidence showing that this feature accounts for differences in terms of tolerance susceptibility between laboratory rodents and patients. This implies that further investigation of tolerance protocols in laboratory mice should be performed using "dirty mice" i.e., mice raised in non-sterile conditions. In summary, this Research Topic addresses key aspects of allorecognition by lymphocytes and alloantigen presentation by dendritic cells, and specifically how these processes shape our immune system and govern the rejection or tolerance of allogeneic tissues and organs.