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COMMENT

Two kinds of macrophage memory: innate and adaptive immune-like macrophage memory

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It is believed that the adaptive immune system responds to nonself entities with its specificity and memory properties. In contrast, the innate immune system lacks adaptive characteristics. Whether innate immune cells can generate adaptive immune features has always been an unanswered question. However, an increasing number of studies have shown that innate immune cells exhibit antigen specificity and memory characteristics similar to those of adaptive immune cells after first-time stimulation. Studies of natural killer cells (NK cells) with immune memory were reported as early as 2006 [1]. O'Leary et al. found that mouse NK cells can trigger hapten-specific contact hypersensitivity with memory properties [1]. Subsequently, memory NK cells could be detected in mice infected with mouse cytomegalovirus, further strengthening the conclusion that NK cells have immune memory. Subsequently, additional studies have shown that NK cells have immune memory for various viruses, such as cytomegalovirus, vaccinia virus, and influenza virus [2–4].

Whether macrophages also have immune memory is an unanswered question. In 2012, Liu et al. reported that macrophages primed with allogeneic cells recognized and rejected them in a second challenge [5]. Since then, studies have also shown that macrophages can exhibit short-lived nonspecific memory after bacterial infection. In 2018, Yao et al. reported that mouse alveolar macrophages could be induced to become memory alveolar macrophages after adenovirus infection. As a result, they become more efficient in protecting mice from a subsequent viral infection [6]. Published in the March 2020 issue of Cellular & Molecular Immunology, Chu et al. [7] showed that macrophages could independently mediate acute allogeneic skin graft rejection with some degree of antigen specificity after the adoptive transfer of allogeneic antigen-primed macrophages of immunocompetent mice into MHC-matched immunodeficient SCID mice (Fig. 1). In this study, the authors established a unique mouse transplantation model in which immunodeficient recipient mice were

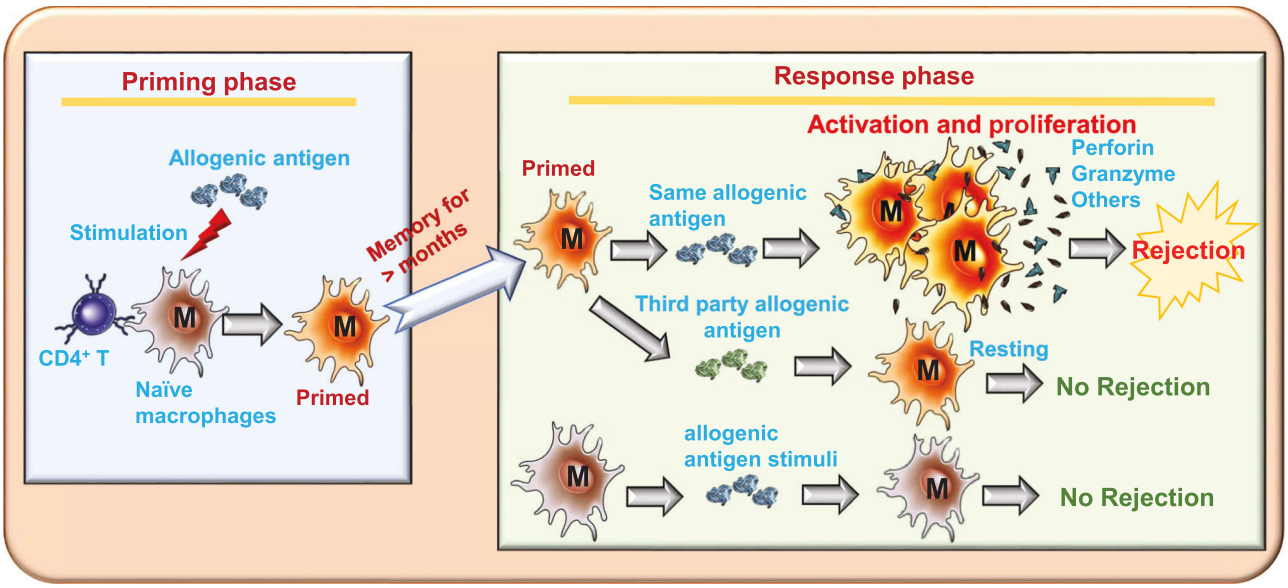

Fig. 1 Macrophages directly mediate acute allogeneic graft rejection as effector cells. Macrophages gain the potential ability to reject allogeneic grafts in the priming phase, in which macrophages are primed with allogeneic antigens with the help of $CD4^+$ T cells. These primed macrophages become activated, proliferate, and migrate to allogeneic grafts to reject grafts in an antigen-specific manner

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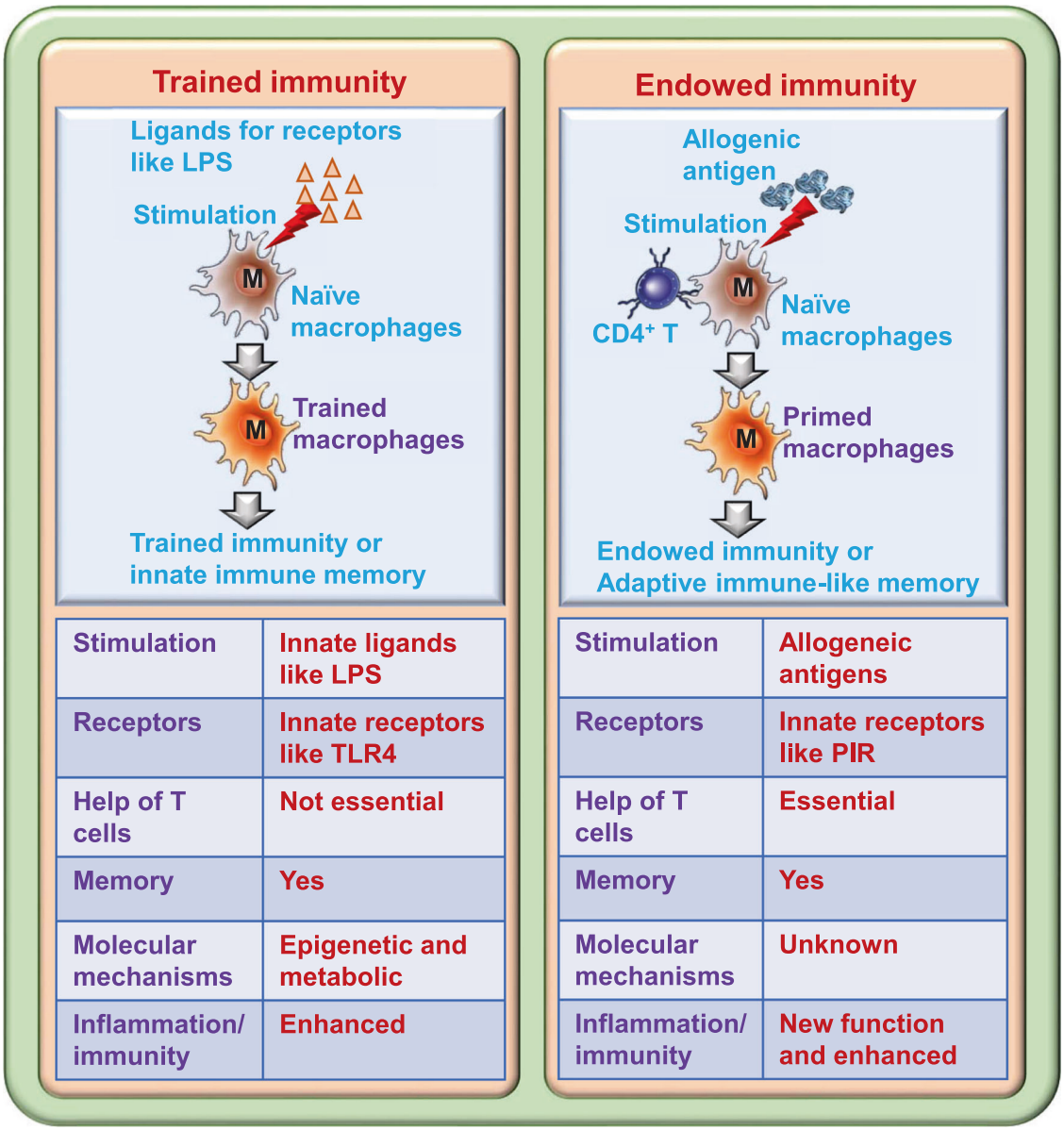

Stimulation	Innate ligands like LPS
Receptors	Innate receptors like TLR4
Help of T cells	Not essential
Memory	Yes
Molecular mechanisms	Epigenetic and metabolic
Inflammation/ immunity	Enhanced

Stimulation	Allogeneic antigens
Receptors	Innate receptors like PIR
Help of T cells	Essential
Memory	Yes
Molecular mechanisms	Unknown
Inflammation/ immunity	New function and enhanced

Fig. 2 Two types of macrophage immune memory. There may be two types of immune memory for once-activated macrophages. The innate immune memory of macrophages represents the enhanced (or decreased) inflammatory response intensity of macrophages in subsequent rechallenge stimulations. In contrast, the adaptive immune-like memory of macrophages represents the gained antigen-specific immunity function of macrophages during the first immune response in the presence of $CD4^+$ T cells, which is apparent in the following challenge

adoptively transferred with MHC-matched or syngeneic primed macrophages. Macrophages were sorted from immunocompetent mice preimmunized with allogeneic splenocytes or skin before allogeneic skin grafting. Under such conditions, the primed macrophages greatly expanded, migrated into the allogeneic skin graft, and rapidly rejected the corresponding allogeneic skin grafts without the interference of host T and B cells. Notably, upon rechallenge, these immunodeficient mice rejected allogeneic skin grafts from the same donors of the immunizing splenocytes or skin tissues more efficiently than the third-party allogeneic skin grafts. The effect of the primed macrophages in the rejection of allogeneic skin was partially dependent on the perforin pathway. In follow-up studies, Chu et al. found that the ability of the primed macrophages to reject allografts and long-term memory lasted for at least four months (the end of the experiment) [8].

Similarly, Dai et al. also showed that monocytes and macrophages primed with alloantigen acquired a specific memory for that antigen and were able to rapidly promote the rejection of allogeneic grafts [9]. They identified that paired immunoglobulin-like receptor-A, an MHC-I receptor, was necessary for the primed macrophage-mediated memory response in mice [9]. Further studies have shown that the acquired so-called adaptive immune ability of primed macrophages requires the help of $CD4^+$ T cells during the priming phase [5, 7]. In another experimental model, the generation of antigen-specific memory in mouse alveolar macrophages after adenovirus infection required the support role of $CD8^+$ T cells and their secreted IFN-γ, as reported by Yao et al. [6]. The generation of macrophage antigen-specific memory in different disease models may require the assistance of various types of T cells. The requirements for $CD4^+$ or $CD8^+$ T cells to promote memory macrophage formation in different conditions must be clarified. Nevertheless, these studies clearly demonstrated that activated macrophages, with the help of $CD4^+$ T cells, can gain the ability to reject allogeneic grafts with a certain memory

and specificity in the subsequent immune response. This observation provides a new fundamental basis for challenging the dogma that macrophages solely have innate features in animals with an adaptive immune system.

In the process of allogeneic graft rejection, macrophages generally act as inflammatory and antigen-presenting cells to capture, process, and transmit antigens to T cells through MHC molecules to activate adaptive immunity. In addition, macrophages provide costimulatory signals to promote T-cell activation. Moreover, macrophages infiltrating grafts trigger inflammatory responses in the grafts by secreting inflammatory and other effector factors to induce graft necrosis. In the study by Chu et al., memory macrophages mediated allograft rejection partially through the perforin pathway. Perforin is mainly expressed in cytotoxic T lymphocytes and NK cells and is an essential protein that induces target cell death. Perforin is associated with a variety of autoimmune diseases [10] and immune responses to viral infections and tumors [11, 12]. Chu et al. demonstrated that once-activated macrophages could also directly act as effector cells through the perforin pathway to mediate acute allograft rejection. These studies enriched our knowledge of the roles and effector mechanisms of macrophages in transplant rejection, which should cause more caution regarding the role of macrophages in allograft rejection.

The concept of trained immunity points out that macrophages can acquire immune memory characteristics after transient stimulation of innate immune cells. This phenomenon, termed trained immunity or innate immune memory, is orchestrated by different epigenetic reprogramming and metabolic mechanisms (reviewed in ref. [13]). We must recognize the conceptual difference between these two different memory properties of the once-activated macrophages (Fig. 2). Trained immunity of macrophages refers to the enhanced (or decreased in a tolerance induction state) inflammatory response of macrophages in a following stimulation after the first activation. The adaptive immune-like memory of macrophages results in specific immune response ability after macrophages are activated in the presence of $CD4^+$ T cells. These diverse memory properties of the once-activated macrophages also signify that macrophages might have distinctive inflammatory and immune response characteristics in animals that do or do not have adaptive immune cells. Macrophages may gain some unique defense ability with the presence of T cells and the crosstalk between macrophages and T cells in hosts, in addition to their innate immunity capabilities. This potential ability of macrophages in mammals or some vertebrates may be established through the coevolution of innate and adaptive immune cells during the evolution from lower to higher animals.

Overall, the studies by Chu et al. greatly enriched our understanding of the immune memory properties of activated macrophages and have a considerable impact on our knowledge of the role of innate immune cells in allogeneic graft rejection. The discovery that macrophages specifically mediate acute allograft rejection provides a new research field and potential therapeutic approaches to treat acute allogeneic graft rejection. Obviously, there are still many critical unanswered questions, such as how once-activated macrophages gain and maintain antigen-specific memory, that need to be addressed. Elucidating the detailed molecular mechanisms for macrophage memory formation would significantly advance our understanding of macrophage biology.

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AUTHOR CONTRIBUTIONS

YZ conceived of this commentary. CW and YZ wrote the manuscript. YX revised the manuscript. All authors contributed to the article and approved the submitted version.

COMPETING INTERESTS

The authors declare no competing interests

ADDITIONAL INFORMATION

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