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Specific immune tolerance of antigen-presenting cells: Hypothesis and significance

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Summary Antigen-presenting cells (APCs) play a crucial role in both innate and adaptive immunity. The mechanisms for APCs to distinguish self and nonself have not been uncovered. In the present manuscript, we hypothesized the balance between the activating and inhibiting receptors on APCs will control the state of APCs. In general, they keep balanced by the endogenous ligands so that APCs are in a non-activating state in the naïve bodies. However, foreign antigens or altered self cells will trigger the activating/inhibiting receptors positively or negatively, so these receptor-mediated signals into APCs will be in tendency to be unbalanced. As long as the activating signals are over the inhibiting receptors, APCs will then be activated to function. This hypothesis will help us to explain how APCs can distinguish self and nonself antigens as well as their close relationships with the occurrence of autoimmune diseases. The activated state of APCs in the early stage of autoimmune diseases may be due to imbalance of the activating/inhibiting receptors on APCs triggered by host endogenous ligands. On the other hand, the poor immunity against tumor cells in the late stage of tumor patients may be partially due to the so-called ''tolerance'' state of APCs in hosts. We believe that, with the proving by the coming evidences, the impacts of the present hypothesis on basic and clinical immunology would be significant.

Background

Antigen-presenting cells (APCs), including but not limiting to macrophages and dendritic cells (DCs), were the critical first-line defense against invading microorganisms and foreign substances. They were presently believed to be part of a nonspecific immune response characterized by engulfment and digestion of microorganisms and invading foreign substances. However, accumulated evidence has suggested that considerable specificity and memory may exist in innate immunity in general [1–4]. Although the reactions of the innate system protect the host from invasion by pathogens, they may also initiate the development of autoimmunity in some cases [5,6]. It has been reported that activation of APCs including macrophages may break self tolerance and induce autoimmune diseases [7]. Therefore innate immunity must be under tight control to keep host immunity self-tolerant. However, it is far not clear about the mechanisms for the self-tolerance of APCs until now.

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Presentation of the hypothesis

We here in proposed a hypothesis as follows (Fig. 1). APCs including macrophages and DCs express a list of activating/inhibiting receptors on their surface. In general, they keep balanced by the endogenous ligands and APCs are in a non-activating state in the naïve bodies. However, so called exogenous ligands including foreign antigens or changed self cells will trigger the activating/inhibiting receptors positively or negatively, so these receptor-mediated signals into APCs will be in tendency to be unbalanced. As long as the activating signals are over the inhibiting receptors, APCs will then be activated to function such as phagocytosis, cytokine production, up-regulation of co-molecules and antigen presentation. This hypothesis will help to explain how APCs themselves can keep self-tolerant and can distinguish self and nonself antigens.

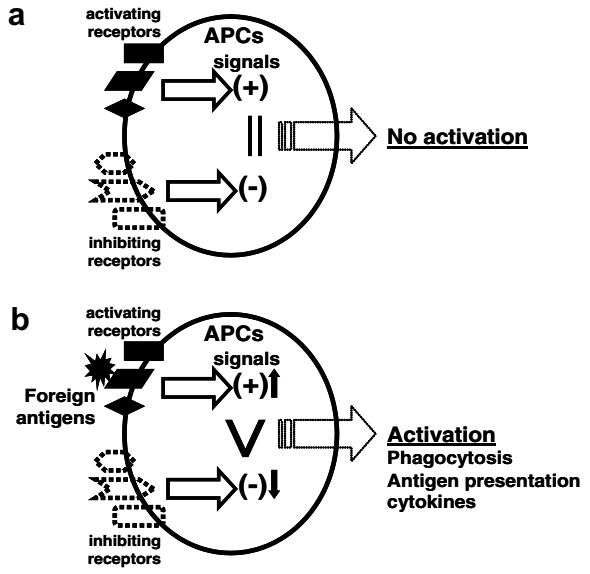

Figure 1 The states of APCs were controlled by the balance between activating and inhibiting receptors. It is proposed that APCs (macrophages or DCs) express both activating and inhibiting receptors which can recognize endogenous and exogenous antigens. The activating and inhibiting receptor-mediated signals to APCs are usually in balance so APCs display a non-activated state. Whenever the activating receptor-mediated signals are stronger than the inhibiting receptor-mediated signals due to the altered ''self'' or invading pathogens, APCs will be activated to function. (a) represents the naïve state of APCs showing the balanced signals by activating and inhibiting receptors. (b) represents the activated state of APCs when activating signals enhanced and/or inhibiting signals decreased by their ligands (antigens). This model emphasizes the balance between activating and inhibiting receptors on APCs.

Evidence supporting the hypothesis and the coming studies

The following evidences strongly support the hypothesis: (A) It has been demonstrated that APCs such as macrophages and DCs express a diverse receptors that recognize antigens. These receptors include toll-like receptors (TLRs), carcinoembryonic antigen-related cell adhesion molecule 3 (CEACAM3, also known as CD66d), nucleotide-binding oligomerization domain (NOD), dectin-1, mannose receptors, DEC-205, and so on. (B) The heterogeneous sub populations of macrophages or DCs in their phenotypes, functions or activations have be identified [8,9]. (C) It has been reported that the innate immune processes including granulocytes and macrophages, are involved in the rejection of allografts and xenografts [10]. The principle that the induction of mixed hematopoietic chimerism can lead to transplantation tolerance (including immune tolerance of T, B and NK cells) to another organ from the same donor has been verified in rodents and large animals including non-human primates [11]. However, if host macrophages or other APCs are not tolerant to donor antigens, they will continue to clean the live donor cells so that the donor cells will decline gradually in the mixed chimeras. The fact was not the case, the levels of donor cells in mixed chimeras kept stable for long term. Therefore, host macrophages should be modified to avoid killing donor cells in mixed chimeras.

Although there are a lot of antigen-recognizing receptors expressing on APCs, the diversity of these receptors has not been determined so far. The coming studies should include: (1) determining the diversity of receptors on macrophages and DCs, (2) identifying the inhibiting receptors on macrophages and DCs, and (3) identify the endogenous ligands for the receptors of APCs.

Here, we should point out that the mechanisms for antigen specific recognition by APCs is distinctly different from that by T cells. Innate immune recognition relies on a limited number of germline-encoded receptors. Whereas T cells use a much diverse profile of T cell receptors to recognize antigens through the gene rearrangement. Thus, the degree of antigen-recognizing specificity by APCs or T cells may be different.

Implications of the hypothesis

Understanding how APCs recognize nonself while keeping self-tolerance is a fundamental question in basic and clinical immunology. The present

hypothesis will significantly help us to understand the critical role of APCs in triggering immune response to foreign antigens while keeping host immunity self-tolerant. It can explain how the defaults of APCs are closely related to the occurrence of autoimmune diseases. The activated state of APCs in the early stage of autoimmune diseases may be due to imbalance of the activating/inhibiting receptors on APCs which are triggered by host endogenous ligands. Thus, the initial role of APCs in autoimmune immunity should be emphasized. On the other hand, for the patients with tumors, the poor immunity against tumor cells in the late stage may be, at least partially, due to the so-called ''tolerance'' state of APCs in hosts. Importantly, it will change our traditional thoughts on innate immunity and adaptive immunity so that the antigen-recognizing specificity and tolerance mechanisms will be recognized. We believe that, with the coming evidences, the impacts of the present hypothesis on basic and clinical immunology would be of great significance.

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