Editorial

Mechanisms of oral tolerance revisited

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Abstract

Oral tolerance induction is thought to depend on special antigen presenting cells in the gut. A new report in the previous issue of *Arthritis Research & Therapy* supports this idea by demonstrating that indoleamine 2,3-dioxygenase-expressing dendritic cells in Peyer's patches from orally tolerized mice suppress T-cell responses via the generation of $CD4^+CD25^+$ regulatory T cells. This finding provides novel input into the mechanisms of oral tolerance that could further facilitate its use for the treatment of autoimmunity and chronic inflammatory reactions.

Introduction

Oral tolerance refers to the immunological non-responsiveness to ingested protein antigens. Although the phenomenon of immunological hyporesponsiveness following oral administration of antigen has been known for more than 50 years, the mechanisms of oral tolerance induction have still not been elucidated fully. Nonetheless, it is generally accepted that specialized antigen-presenting cells located at strategic places in the gastrointestinal tract are responsible for oral tolerance induction. Especially, professional antigen-presenting cells in the gut-associated lymphoid tissues, comprising mesenteric lymph nodes, lamina propria, Peyer's patches and mucosal epithelium, are instrumental in tolerization to orally taken antigens by either 'anergy' induction, deletion of antigen-specific effector T cells, or by the induction of active immune regulation. In the latter case, local generation of regulatory T (Treg) cells is considered a plausible mechanism responsible for immune hyporesponsiveness to the orally administered antigens. Since oral administration of antigen can lead to systemic unresponsiveness, it represents potentially a powerful tool in the therapy of autoimmunity and chronic inflammatory reactions. Therefore, a better understanding of the mechanisms of oral tolerance induction could aid its use in the clinic, for example, in the treatment of patients with rheumatic diseases. The current work presented by Park and colleagues [1] provides further understanding on the mechanisms underlying oral tolerance induction by showing that indoleamine 2,3-dioxygenase (IDO)-expressing dendritic cells (DCs) located in the gut are involved in the inhibition of T-cell response and the generation of $CD4^+CD25^+$ Treg cells [1].

Treg cells are crucial regulators of peripheral self-tolerance. They can suppress the effector functions of many cell types, including T cells, B cells, and monocytes/macrophages in a cell-contact dependent manner as well as via secretion of soluble mediators, such as interleukin-10 and transforming growth factor-β [2]. Moreover, they have the capacity to inhibit arthritis, conceivably through the secretion of tumor necrosis factor receptor II [3,4]. Treg cells can be generated in the thymus upon confrontation with self-antigens presented by thymic epithelial cells, as well as in peripheral lymphoid tissues under specific conditions involving antigen presentation in the absence of co-stimulation [2,5]. The transcription factor forkhead box P3 (FOXP3) is essential for their development and function, and represents a specific marker for murine $CD4^+CD25^+$ Treg cells.

IDO in oral tolerance

IDO, an enzyme that degrades the essential amino acid tryptophan, can be synthesized by many cell types. IDO-expression is essential to maintain pregnancy as IDO-deficiency or pharmacological inhibition of IDO results in rapid T cell-induced rejection of allogeneic concepti, but is also involved in the control of many other immunological processes, such as tumor resistance, chronic infection, autoimmunity and allergic inflammation [6]. During an immune response, it can be expressed in response to, for example, interferon-γ, and thereby is thought to protect the host from collateral damage by suppressing T-cell responses [6]. The immune regulatory function of IDO has been attributed mainly to the reduction of local tryptophan concentration and the generation of tryptophan metabolites [6].

DC = dendritic cell; FOXP3 = forkhead box P3; IDO = indoleamine 2,3-dioxygenase; Treg = regulatory T.

The article by Park and colleagues now shows that IDO can also promote tolerance to orally administered collagen type II in mice [1]. $CD11c^+$ DCs in Peyer's patches from orally tolerized mice exhibit an immature phenotype and express higher levels of IDO compared to those from control mice. Functionally, they inhibit collagen type II-specific T cell proliferation and pro-inflammatory Th1 cytokine production, and more importantly, induce the generation of collagen type II-specific $CD4^+CD25^+FOXP3^+$ Treg cells from highly purified $CD4^+CD25^-$ T cells in an IDO-dependent manner. Notably, the generation of Treg cells is antigen specific, as IDO-expressing DCs without antigen have no effect [1]. These data are in line with recent findings showing that IDO-expressing DCs can also directly activate resting $CD4^+CD25^+FOXP3^+$ Treg cells for potent suppressor activity [7], and that cytotoxic T-lymphocyte antigen-4 and glucocorticoid-inducible tumor necrosis factor receptor-related protein, molecules highly expressed on $CD4^+CD25^+$ Treg cells, can induce IDO expression in DCs [8]. Together, these results indicate that IDO-producing DCs and $CD4^+CD25^+$ Treg cells may form a positive feedback loop in the induction of oral tolerance [1,7,8].

However, although the combined effects of tryptophan starvation and tryptophan catabolites may contribute to the induction of $CD4^+CD25^+$ Treg cells by IDO [9], the position of IDO in the induction of oral tolerance remains to be determined. Notably, recent reports showing that retinoic acid, a metabolite of vitamin A, produced by $CD103^+$ DCs in mesenteric lymph nodes promotes oral tolerance by enhancing the transforming growth factor-β-dependent conversion of naïve T cells into Treg cells [10] are of interest and pose the question whether different subtypes of DCs (CD103 positive versus negative) or DCs located at different places of the gut (mesenteric lymph nodes versus Peyer's patches) use different mechanisms (retinoic acid versus IDO) to induce Treg cells. Furthermore, the relative contribution of these two pathways in the induction of oral tolerance to defined antigens remains to be determined.

Concluding remarks

The identification of the role of IDO-expressing DCs opens another avenue to explore the possibility to treat human autoimmunity and chronic inflammatory conditions by 'preventive' vaccinations in an antigen-specific manner. However, caution should be taken as the knowledge obtained from mouse models can not be translated directly into human subjects. Because contradicting data on the immunoregulatory role of IDO-producing human DCs have been reported [11], further research is merited towards elucidating the role of IDO-positive human DCs in oral tolerance induction.

Competing interests

The authors declare that they have no competing interests.

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