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In vivo reprogramming of immune cells: Technologies for induction of antigen-specific tolerance☆

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ABSTRACT

Technologies that induce antigen-specific immune tolerance by mimicking naturally occurring mechanisms have the potential to revolutionize the treatment of many immune-mediated pathologies such as autoimmunity, allograft rejection, and allergy. The immune system intrinsically has central and peripheral tolerance pathways for eliminating or modulating antigen-specific responses, which are being exploited through emerging technologies. Antigen-specific tolerogenic responses have been achieved through the functional reprogramming of antigen-presenting cells or lymphocytes. Alternatively, immune privileged sites have been mimicked using biomaterial scaffolds to locally suppress immune responses and promote long-term allograft survival. This review describes natural mechanisms of peripheral tolerance induction and the various technologies being developed to achieve antigen-specific immune tolerance *in vivo*. As currently approved therapies are non-specific and carry significant associated risks, these therapies offer significant progress towards replacing systemic immune suppression with antigen-specific therapies to curb aberrant immune responses.

Contents

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1. Introduction

Induction of antigen (Ag)-specific immune tolerance is a complex process that requires the collaboration of multiple immunological pathways. Aberrant activation of T cells *in vivo* results in cellular damage against specific tissues and is responsible for the development of autoimmune diseases. To minimize the occurrence of undesirable immune responses to self-Ags, most self-reactive lymphocytes are eliminated in the thymus and bone marrow by a mechanism known as central tolerance. Unfortunately, this process is only 60–75% effective and potentially harmful Ag-specific cells with possible effector activity are released into the blood and tissues [1,2]. To suppress potentially autoreactive cells that have avoided elimination by central tolerance, peripheral tolerance mechanisms exist. Intrinsic peripheral tolerance mechanisms are sometimes insufficient to curb inappropriate immune activation, necessitating therapeutic intervention to enable the body to limit responses to "self." Common therapies used to subdue abnormal immune activation are not Ag-specific and involve systemic immune suppression or immunodepletion therapies that target the T cell receptor (TCR), co-signaling molecules, cytokines, or inhibit leukocyte trafficking, among other mechanisms [3,4]. However, administration of these non-specific treatments over a prolonged period of time is associated with numerous adverse effects, including increased patient susceptibility to opportunistic infections [5], viral reactivation [6], and neoplasia [7].

Ag-specific tolerance approaches are needed to restore immune homeostasis in the cases of autoimmune disease as indicated above, and can be extended to establish selective Ag tolerance in the cases of allogeneic transplant and allergy. In Ag-specific tolerance, undesired immune activation is suppressed while the activity of the remaining immune system is maintained. Thus, the desirability of therapies to address these conditions has gained significant traction over several decades as the incidence of immune-mediated diseases has steadily risen [8,9]. T cell-mediated autoimmune diseases are driven by the continued presentation of self-Ag by Ag-presenting cells (APCs) to autoreactive T cells. Conversely, allograft rejection involves a combination of allorecognition by T cells and alloantibody production by B cells [10]. Allergic reactions involve the activation of granulocytes such as mast cells, basophils, and eosinophils by allergen binding to antibodies [11]. Important immune elements of these diseases are the development of Ag-specific effector T-helper type 1 (Th1) and Th17, or Th2 responses that are associated with the clinical features of disease progression [12]. The acquired phenotype of a T cell that differentiates from a naïve T cell is determined by its type of interaction with an APC as well as other factors that include the microenvironment, co-signaling molecule expression, type and load of Ag, and the intramolecular signals transduced [12]. A thorough discussion of the molecular mechanisms of these conditions is beyond the scope of this review and readers are directed towards several excellent reviews [10,13–18].

Peripheral tolerance can be induced *in vivo* using a variety of technologies (Fig. 1). For Ag-specific tolerance, the Ag is presented by APCs in the presence of low levels of co-stimulatory molecule expression and in the absence of other activating stimuli (*i.e.* absence of inflammation, infectious agents, and other pathologies) [3,19]. These specific interactions aid in driving Ag-specific effector T cells towards an unreactive state (anergy or deletion) or induce regulatory T cells (Tregs) that can modify the activity of other T cells [4]. To drive immune responses towards tolerance, the Ag must be delivered to the

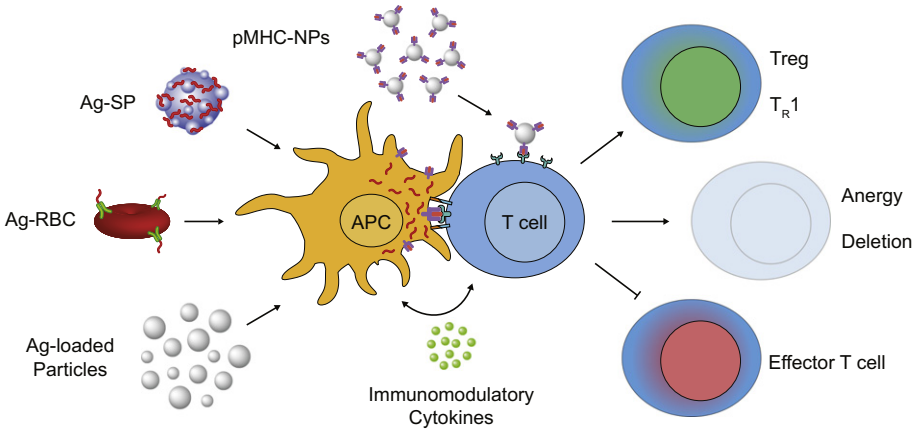

Fig. 1. Highlighted approaches of technologies implemented for antigen-specific tolerance induction. Most antigen-specific tolerance strategies result in reprogramming lymphocytes through antigen presenting cells (APCs), however, there are platforms that target T cells and specifically recognize their autoreactive T cell receptors. Inspired by the natural clearance of apoptotic cells which results in peripheral tolerance maintenance, antigen has been delivered by various platforms including antigen-coupled splenocytes (Ag-SP), erythrocyte-targeted peptides (Ag-RBC), and antigen-loaded synthetic particles. These carriers are internalized, processed by APCs, and induce tolerogenic costimulation and soluble signaling pathways that direct T cell phenotypes away from immunogenic effector T cell activation and towards regulatory T cells (Tregs), anergy, or deletion. Direct interaction of particle-bound peptide-major histocompatibility complexes (pMHC-NPs) with antigen-experienced T cells can induce a tolerogenic regulatory-like T_R1 phenotype that can mitigate immune-mediated disease progression.