Do Tregitopes have the potential to impact the current treatment landscape of autoimmune diseases?


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Tregitopes are regulatory T-cell epitope sequences contained in IgG that were discovered by the team of De Groot and Martin in the course of searching for T effector (Teff) epitopes in monoclonal antibody (mAb) therapeutics [1,2]. These highly conserved (in IgG), promiscuous Treg epitopes have been shown to trigger the expansion of Tregs in vitro. A retrospective review of the T-cell epitope (and Tregitope) content of therapeutic mAbs, published in 2009 [3], revealed a close correlation between the presence of Tregitopes and the absence of HLA-binding Teff epitopes, with the lack of mAb immunogenicity in clinical use.

Taking this observation one step further, the presence of Treg epitopes in IgG might explain why immunoglobulins, which are produced by B cells that undergo somatic hypermutation in the periphery, do not generally elicit the expected immune response against the new ‘foreign’ hypervariable (complementarity determining regions, or CDR) sequences. Recognition of the importance of Tregitopes in mAb therapeutics led to the incorporation of Tregitope-specific adjustments in certain immunogenicity predictions, improving the accuracy of the results [4,5].

Tregitopes may also explain, in part, the tolerance-inducing effect of intravenous immunoglobulin (IVIg) therapy [6]. This theory is supported by reports that IVIg-induced expansion of Tregs in vitro and in vivo, [7–9], and IVIg experts generally agree that Treg epitopes such as Tregitopes may be contributing to the tolerizing effects of IVIg [10,11]. Although it is only approved for use in a handful of diseases [12], IVIg is used off-label for hundreds of conditions [13–19].

Recently published in vivo studies of Tregitopes in mouse models of human autoimmune diseases have further validated the Tregitope discovery [20]. Additional publications demonstrate that co-administration of Tregitopes with target antigens in vivo and in vitro leads to the induction of antigen-specific tolerance [21] and suppression of both humoral [22] and cellular immune responses, including antigen-specific CD8+ T-cell response [6,23]. ‘Control’ peptides have been compared in vitro...
The proposed Tregitope mechanism of action is distinct from some IVIg mechanisms of action but similar to ease, providing independent confirmation of Tregitope studies. In another recent publication, cross-conservation (at the T-cell receptor surface) with other highly conserved T-cell epitopes in autologous proteins is identified as a potential distinguishing feature of Treg epitopes (such as Tregitopes) but not from Teff epitopes [25]. Other groups have reported that specific IgG-derived peptides subsequently identified as Tregitopes [26–28] induce tolerance in animal and human autoimmune disease, providing independent confirmation of Tregitope studies.

The discovery of Tregitopes naturally led to the concept of actively integrating Tregitopes into biologics. Tolerization of immune responses to protein therapeutics (by introduction of Tregitopes) could be considered to be an alternative to humanization of mAbs, and it might also be applied to non-mAb biologic products [20]. Tolerization across the breadth of HLA alleles expressed in the general human population would involve inclusion of the complete repertoire of Tregitopes present in each IgG that is developed for clinical applications. Studies that support the effectiveness of this approach have been carried out by De Groot and Couzens et al. [6,20,21] and are currently underway in the laboratories of a number of other research groups [22,23].

The origin of Tregitope-specific T cells is as yet undetermined. They may be natural Tregs, induced Tregs or both. Regardless of the origin or mechanism of action of Tregitopes, the potential for these peptides and epitope presentation is likely to occur when the IgG recycling protein, FcRN, is overwhelmed (as it may be when high doses of IgG, as in IVIg, are given).

Tregitopes may also be useful for their IVIg-like effects in conditions such as allergy, where Treg induction is considered to be important but IVIg was considered to be too dangerous (and expensive) to use as therapy. Tregitopes could be combined with the target of autoimmunity, where the target is known, such as glutamic acid decarboxylase (GAD 65) protein in diabetes. For example, early studies in autoimmune disease models clearly demonstrated that Tregitopes have promise as a standalone treatment for autoimmune disease [6,20]. Where the antigen is unknown, Tregitope immunotherapy might be given during a flare, when autoimmune antigens are being presented to the immune system by activated antigen-presenting cells. Whether used on their own, or co-administered with a specific autoimmune disease antigen, Tregitope-based immunotherapy has the potential to augment future therapeutic options for autoimmune disease.
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The author is founder and majority owner of EpiVax, Inc., a biotechnology company that provides immunogenicity screening services and access to the Tregitope technology on a fee-for-service basis. Due to this relationship with EpiVax, the author acknowledges that there is a potential conflict of interest inherent in the publication of this manuscript, and asserts that she made an effort to reduce or eliminate that conflict where possible. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No external writing assistance was utilized in the production of this manuscript.

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