Stephen D Miller, J Neurol Disord 2016, 4:9(Suppl)
http://dx.doi.org/10.4172/2329-6895.C1.013

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Translation of a novel tolerance therapy employing antigen-encapsulated PLG nanoparticles for the treatment of autoimmune disease and allergy

Ag-specific tolerance is the desired therapy for immune-mediated diseases. Our recent phase I clinical trial showed that infusion of myelin peptide-coupled autologous apoptotic PBMCs induces dose-dependent regulation of myelin-specific T cell responses in MS patients. Antigen-coupled apoptotic leukocytes accumulate in the splenic marginal zone (MZ) and are engulfed by F4/80$^+$ MZ macrophages and CD8$^+$ DCs inducing up-regulation of PD-L1 in an IL-10-dependent manner. Tolerance results from the combined effects of PD-L1/PD-1-dependent T cell anergy and activation of Tregs recapitulating how tolerance is normally maintained in the hematopoietic compartment in response to uptake of senescing blood cells. To further advance clinical translation of tolerogenic therapies, we have shown that long-lasting tolerance is inducible by i.v. administration of (auto)antigens covalently linked to or encapsulated within 500 nm carboxylated poly(lactide-co-glycolide) (PLG) nanoparticles (Ag-NP) abrogating development of Th1/Th17-mediated autoimmune diseases (EAE, T1D and celiac disease) and Th2-mediated allergic airway disease when used prophylactically and ameliorating progression of established disease when administered therapeutically. Ag-NP-induced tolerance is mediated by the combined effects of cell-intrinsic anergy and Treg activation and is dependent on route of administration, particle size and charge, uptake by MZ and live APCs via the MARCO scavenger receptor. As with tolerance induced by Ag-coupled apoptotic PBMCs, Ag-NP tolerance is induced and maintained by the combined effects of PD-L1/PD-1-dependent T cell anergy and activation of both Foxp3$^+$ iTregs and Tr1 regulatory cells. These findings demonstrate the utility of Ag-NP as a novel, safe and cost-effective means for inducing antigen-specific tolerance for (auto) immune-mediated diseases using an FDA-approved biomaterial easily manufactured under GMP conditions.

Biography

Stephen D Miller is the Judy Gugenheim Research Professor of Microbiology-Immunology at Northwestern University Feinberg School of Medicine and Director of the Northwestern Interdepartmental Immunobiology Center. He is internationally recognized for his research on pathogenesis and regulation of autoimmune diseases. He has published over 370 journal articles, reviews and book chapters and has trained multiple generations of scientists. His work has significantly enhanced understanding of immune inflammatory processes underlying chronic autoimmune diseases focusing on translation of tolerance therapies induced by antigen-linked biodegradable PLG nanoparticles for the treatment of autoimmunity, allergy and tissue/organ transplantation.

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