Research Highlights

Highlights from the latest articles in regenerative medicine

Targeting innate immunity to treat long-term Type 1 diabetes

Evaluation of: Faustman DL, Wang L, Okubo Y *et al.* Proof-of-concept, randomized, controlled clinical trial of bacillus-Calmette–Guerin for treatment of long-term Type 1 diabetes. *PLoS One* 7(8), e41756 (2012).

Selective destruction of autoimmune T lymphocytes (T cells) that target insulin-secreting β-cells could potentially provide a therapeutic avenue to treat Type 1 diabetes. Boosting the innate immunity through selective exposure to pathogens is a potential mechanism to achieve this goal. The administration of bacillus Calmette–Guerin (BCG), which is known to induce TNF expression through an innate immune response that selectively targets and destroys insulin-autoreactive T cells, is the underlying hypothesis driving this proof-of-principle study. In mice, BCG immunization-induced production of the cytokines TNF-α, INF-γ and IL-4 by splenocytes and increased expression of Fas, Fas ligand, and TNF receptors on T cells, which led to T-cell apoptosis [1]. Previous work by the Faustman laboratory had established that a subpopulation of $CD8^+$ cells in patient blood was vulnerable to TNF [2]. Adjuvent therapy, such as BCG, in humans was found to be effective in a small population of prediabetic patients; however, expanded clinical trials have cast doubt on the clinical efficacy of this approach. In the study by Faustman *et al.*, BCG was administered to patients with long-term Type 1 diabetes in a double-blind, placebo-controlled trial. Blood samples were monitored over 20 weeks for immune and pancreatic function. Patients treated with BCG, and one control patient diagnosed with acute Epstein–Barr virus infection (another trigger of innate immunity), had increased numbers of dead insulin-autoreactive T cells as measured by flow cytometry. Additionally, regulatory T-cell numbers increased in the BCG-treated

subjects. Antibody levels against glutamic acid decarboxylase, the tyrosine phosphatase IA–2A and the zinc transporter, ZnT8A, were measured in placebo and BCG-treated populations. In two out of the three BCG-treated subjects, glutamic acid decarboxylase levels sustainably changed, one increased and one decreased, but the third did not change from the baseline. For the other islet-specific autoantibodies, only ZnT8A decreased in one subject with statistical significance. C-peptide levels significantly and temporarily rose in two out of the six BCG-treated subjects as well as in the Epstein–Barr virus-infected placebo subject, which was suggestive of a brief functional improvement in β-cell function. Taken together, these results are consistent with BCG inducing a TNF expression that modulates the innate immune response, targets insulin-autoreactive T cells and transiently increases C-peptide levels. The results provide a foundation upon which expanded clinical trials will determine whether sustained increases in C-peptide levels can be reproducible in a larger population of patients with Type 1 diabetes.

References

1 Qin H, Chaturvedi P, Singh B. *In vivo* apoptosis of diabetogenic T cells in NOD mice by IFN-gamma/TNF-alpha. *Int. Immunol.* 16(12), 1723–1732 (2004).

2 Ban L, Zhang J, Wang L, Kuhtreiber W, Burger D, Faustman DL. Selective death of autoreactive T cells in human diabetes by TNF or TNF receptor 2 agonism. *Proc. Natl Acad. Sci. USA* 105(36), 13644–13649 (2008).

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