Immunomodulation of Type 1 Diabetes: Raising the Bar

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In the past several months I've written a few pieces about immunomodulation of type 1 diabetes, or attempts to suppress the immune attack on insulin-producing beta cells. These studies have involved compounds that rein in the immune system in a more or less specific way, and all have been tested on mice with a tendency to develop type 1 diabetes. Now, a new study published in the journal *Lancet* raises the bar just a bit further, because the tests were performed in human beings with type 1 diabetes and not rodents.

The study, a collaboration between academic groups and an Israeli company called Peptor, was built upon the observation that treating diabetic mice with a fragment of a protein called heat shock protein 60 (hsp60) could subdue the autoimmune attack on their beta cells. This effect could be seen even after the onset of frank diabetes.

Heat shock proteins are induced in cells in times of stress, and are known to modulate the immune response in very specific ways. This is extremely important, because general immunosuppression leads to an increased risk of infection, a serious problem that has held the field of immunomodulation up for decades. Hsp60 reduces the activity of immune cells called T helper 1 (Th1) which are pro-inflammatory, and boosts the activity of anti-inflammatory Th2 cells.

This is all well and good for mice, but the Israeli group took the leap and asked whether injections of hsp60 (actually, a piece of the hsp60 molecule called DiaPep277) could improve type 1 diabetes in humans. They set up a randomized, double-blinded trial in 35 men who had been recently diagnosed with type 1 diabetes. Although phase 1 safety studies had shown no toxic effects of DiaPep277, women were excluded to avoid the possibility that a patient could become pregnant while taking the drug. Patients were given a total of three injections over a six-month period.

The trial was a success, but success in immunomodulation of type 1 diabetes has to be carefully defined. First, no one had any toxic effects of the DiaPep227, confirming the earlier Phase 1 results. Those patients receiving DiaPep227 showed more beta cell survival at ten months, and also required less insulin than did patients who received placebo. To be clear, no one was "cured" of his diabetes, and in fact this was not expected. Even the mice are not cured of their diabetes with DiaPep227, or any other similar therapy. Still, these results are promising enough to warrant a larger trial with many more patients.

Clearly, the ultimate hope for immunomodulatory therapy is to identify people at the

highest risk for type 1 diabetes *who do not yet have the disease*. Whereas DiaPep227 seems to be of limited effectiveness in full-blown diabetes, the possibility remains open that such treatment might delay or even prevent the onset of the condition. There is another group of patients who may benefit from therapies like DiaPep227 even sooner; those who have received either a whole pancreas or islet cell transplant for type 1 diabetes. One of the problems with these procedures is the need to take a harsh regimen of immunosuppressives to prevent rejection. Newer regimens are being developed, and I'm intrigued by the possibility of including a drug like DiaPep227 to block the patient's immune system from attacking their new beta cells.

I don't think that a complete cure is around the corner, but the mere fact that studies of immunomodulation are being performed in humans with type 1 diabetes shows just how rapidly this field is progressing. That there appears to be a beneficial, albeit modest, effect of these treatments, is enormously encouraging as well, and I suspect we will start seeing some form of this therapy in the clinic before very long.

Reference:

Beta-cell function in new-onset type 1 diabetes and immunomodulation with a heat-shock protein peptide (DiaPep277): a randomised, double-blind, phase II trial. Itamar Raz, Dana Elias, Ann Avron, Merana Tamir, Muriel Metzger, Irun R Cohen. *Lancet* 2001; **358:** 1749-53