

Disguising insulin as an antibody: a Trojan horse for type 1 diabetes prevention

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The first signs of autoimmune activation leading to beta-cell destruction in type 1 diabetes (T1D) appear during the first months of life. Thus, the perinatal period offers a suitable time window for disease prevention. Moreover, thymic selection of autoreactive T cells is most active during this period, providing a therapeutic opportunity not exploited to date. We therefore devised a strategy by which the T1D-triggering antigen preproinsulin fused with the immunoglobulin (Ig)G Fc fragment (PPI-Fc) is delivered to fetuses through the neonatal Fc receptor (FcRn) pathway, which physiologically transfers maternal IgGs through the placenta. PPI-Fc administered to pregnant PPI T-cell receptor–transgenic mice efficiently accumulated in fetuses through the placental FcRn and protected them from subsequent diabetes development. Protection relied on ferrying of PPI-Fc to the thymus by migratory dendritic cells and resulted in a rise in thymic-derived CD4⁺ regulatory T cells and in effector CD8⁺ T cells displaying impaired cytotoxicity. Moreover, polyclonal splenocytes from nonobese diabetic (NOD) mice transplacentally treated with PPI-Fc were less diabetogenic upon transfer into NOD.scid recipients. Transplacental antigen vaccination provides a novel strategy for early T1D prevention and, further, is applicable to other immune-mediated conditions.