

Novel bioengineered immune therapeutics to control autoimmunity in type 1 diabetes

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Type 1 diabetes is an autoimmune disease associated with hyperglycemia. Increased glucose flux enhances the hexosamine biosynthetic pathway and intracellular posttranslational modification of proteins by the sugar N-acetyl glucosamine (GlcNAc) in a process called O-GlcNAcylation. We discovered that hyperglycemia increases the O-GlcNAcylation of the transcription factor, nuclear factor kappaB (NF- κ B) c-Rel at serine 350. O-GlcNAcylation of c-Rel activates c-Rel-dependent transcription of proautoimmune cytokines in T cells. Hence, blocking the function of O-GlcNAcylated c-Rel will have benefits in controlling autoimmune diabetes by diminishing the T cell-mediated autoimmunity. We developed a novel peptoid, called peptoid3, by molecular modeling and de novo synthesis, which specifically blocks the function of O-GlcNAcylated c-Rel. We found that peptoid3 treatment significantly decreased T cell receptor-induced, O-GlcNAcylation-dependent expression of proautoimmune cytokines. Peptoid3 treatment selectively affected autoimmunity-associated genes and did not exhibit toxicity on survival or proliferation of T cells. Broad inhibition of hexosamine biosynthetic pathway or NF- κ B will cause many side effects due to their ubiquitous importance in multiple biological functions. Therefore, inhibitors of O-GlcNAcylated NF- κ B c-Rel function may prove long-sought-after specific molecular therapeutic to diminish autoimmunity in type 1 diabetes.