

Vasoactive Intestinal Peptide-mediated Gene Therapy for Diabetes

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All patients with type 1 Diabetes (T1DM) and most patients with type 2 Diabetes (T2DM) become insulin dependent due to the progressive nature of the disease, eventually leading to beta-cell loss. The increase in apoptosis, but not the decrease in new islet formation or beta-cell replication, is blamed for the loss of beta-cell mass observed in patients with T2DM. Thus, therapeutic approaches that either interfere with apoptosis of beta cells and/or increase beta-cell mass have the potential not only for managing hyperglycemia but also for reversing disease progression. Vasoactive intestinal peptide (VIP) is a neuropeptide of the secretin family just like GLP1 and PACAP with equipotent insulinotropic effects. More importantly, it is an effective anti-inflammatory agent involved in suppression of Th1 immune response and activation of regulatory T cells for inducing immune tolerance. For this reason, VIP is now considered to be an emerging therapeutic agent for autoimmune diseases such as rheumatoid arthritis, ulcerative colitis, multiple sclerosis, and T1DM. Despite all these advantages, VIP is extremely sensitive to peptidases (DPP-4) present in most tissues. Thus, multiple injections of VIP at high doses are required to observe any therapeutic effect. Contrary to using peptide forms of therapeutic agents, some gene therapy vectors can provide long-term and stable gene expression. Thus, viral and non-viral VIP gene delivery methods have been under development. Despite the successful results obtained from these studies, especially against autoimmune diseases, some limitations of using gene therapy vectors were revealed in recent studies. For example, the clinical efficacy of plasmid DNA transfer is low. Adenoviral vectors only provide transient gene expression due to the antigenic character of adenoviral epitopes. AAV has limited cargo capacity and low transduction efficiency. Compared with other gene therapy vectors, lentiviral vectors appear to be the vector of choice when considering long-term gene expression, transduction efficacy, and safety. Consequently, the testing of the efficacy of lentivirus-mediated VIP gene delivery against diabetes became an essential issue to discuss in experimental animal model of diabetes.
