論 文 要 旨

Safe and low-dose but therapeutically effective adenovirus-mediated hepatocyte growth factor gene therapy for type 1 diabetes in mice

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Hepatocyte growth factor (HGF) is a multifunctional cytokine that plays important roles in pancreatic physiology. Approvals of gene therapy drugs have highlighted gene therapy as an innovative new drug modality, but the very recent reports of deaths in clinical trials have provided a warning that high-dose gene therapy can cause dangerous liver toxicity. Here, we describe adenovirus-mediated HGF gene therapy for streptozotocin-induced type 1 diabetes (T1D) in mice; the doses are low enough to be safe but still therapeutically effective. A single intravenous injection of a low dose (3×10^8 plaque forming units) of adenoviral vector that expresses the HGF gene under the transcriptional control of a strong promoter, *i.e.*, the cytomegalovirus immediate-early enhancer and a modified chicken β-actin promoter (Ad.CA-HGF), significantly attenuated the elevation of blood glucose concentrations at the acute phase of T1D, which continued for several weeks. Temporal upregulation of plasma insulin at the acute phase was maintained at a normal level in Ad.CA-HGF-treated mice, suggesting that the therapeutic mechanism may involve protection of the remaining β-cells by HGF. Liver enzymes in plasma were not elevated in any of the mice, including the Ad.CA-HGF-treated animals, all of which looked healthy, suggesting the absence of lethal adverse effects observed in patients receiving high intravenous doses of viral vectors. Taken together, these findings indicate that intravenous injection of a low dose of Ad.CA-HGF represents a safe but therapeutically effective strategy against T1D.