Multifunctional neonatal Fc receptor targeted nanomedicines for the oral delivery of antidiabetic peptides

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Diabetes mellitus is a metabolic disorder characterized by the inability of the body to produce or respond to insulin, leading to hyperglycemia. The treatment embraces non-pharmacological actions (e.g., diet and exercise) and the exogenous administration of antidiabetic drugs, such as insulin (Type 1 Diabetes) or glucagon-like peptide-1 (GLP-1) analogs (Type 2 Diabetes).
However, most of antidiabetic peptides are administered via invasive routes, which is associated to poor patient compliance. Attempts to develop no-invasive insulin delivery limited success. Semaglutide is the first GLP-1 analog approved for oral administration, but its modest bioavailability (< 1 %) is still a limitation.
FcRn is a heterodimeric glycoprotein that plays a key role in mediating the transcellular transport of albumin and immunoglobulin G (IgG) through polarized epithelial cells, such as the enterocytes. Ligand-receptor interaction is pH-dependent, meaning that the binding is favored at pH 6.0 and release occurs at pH 7.4. In the gut, the interaction occurs at the slightly acidic pH of intestinal lumen and afterwards, the complex is transported through the enterocytes inside acidic endosomes. When the complex encounters the basolateral side of the enterocytes, it is exposed to the physiological pH of the lamina propria, where albumin and IgG are released.
In this talk, our recent data on functionalized nanoparticles towards intestinal FcRn will be discussed. We showed that nanomedicines surface-modified with albumin or Fc domain of IgG were able to target the human FcRn (hFcRn) receptor in intestinal epithelial cells, which improved their intestinal transcytosis over non-targeted nanomedicines. A novel class of mucodiffusive PLGA-PEG nanoparticles, with insulin loading over 10 % were decorated with an engineered human albumin variant with improved human FcRn binding, which enhanced transcytosis in 2-fold across polarized epithelia compared with WT albumin decorated NPs. When tested for oral delivery in human FcRn Type 1 Diabetic transgenic mice, induced with diabetes, nanoparticles were able to reduce glycemia up to 40 % after 1 h and enhance pharmacologic availability.
Also, semaglutide-loaded nanoparticles surface-functionalized with peptide FcBP and affibody Z_{FcRn} exhibit a high and strong interaction with intestinal cells and a 3D *in vitro* intestinal model (human intestinal organoids) expressing hFcRn compared to non-targeted NPs. The oral administration of FcRn-targeted semaglutide-loaded nanoparticles to diabetic mice improved glucose-lowering effect over the oral free semaglutide in solution, after 8 h of a single oral administration (reduction of 30% of blood glucose levels) and after 4 days of daily oral administrations (reduction of 40% of blood glucose levels). In addition, the loading of semaglutide into FcRn-targeted nanoparticles increased the production of insulin from pancreatic β cells over non-targeted NPs and oral free semaglutide.
Therefore, FcRn-nanoparticles revealed a strong potential to improve the pharmacological effect of antidiabetic peptides when orally administered.

References

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