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A POSSIBLE APPROACH FOR ORAL DRUG DELIVERY OF NANOPARTICLES

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Advances in biotechnology have led to numerous discoveries and development of proteins and other macromolecules as pharmaceutical drugs.[2] The production of macromolecules as therapeutics has improved treatment options in many areas in medicine. However, delivery of these macromolecule drugs has mostly been restricted to parenteral methods of administration. The development of a more convenient oral delivery system still faces many challenges.

Many macromolecule drugs are vulnerable to the pH variation and enzymatic degradation in the gastrointestinal tract.[2] One way to protect the drugs from degradation is by encapsulation.[4] In particular, encapsulation of drugs in nanoparticles (NPs) has received considerable attention. Nanoparticles are microscopic particles that have at least one dimension measuring 100 nm or less.[1] At the nanoscale, the properties of many conventional materials change.[2] Unlike bulk materials, which are larger than one micrometer and have constant physical properties regardless of their size, nanoparticles exhibit special properties. These special properties include surface effects and quantum effects and result from the very small size of nanoparticles and the significant percentage of atoms at the surface of the nanoparticles relative to the total atom number.[2] These special properties are the reason why nanoparticles have a wide variety of potential applications in various fields such as medicine, energy and electronics industries. Thus, the development of an oral delivery system using nanoparticles is advantageous. If successful, the method could be combined with other techniques, such as a nanoparticle-based chemotherapy free of the debilitating side-effects,[7,9] to further improve available treatment options.

There have been several attempts to develop a method for oral drug delivery using nanoparticles,[2] but these attempts have mostly had undesirable drawbacks. The extent to which a protein drug is absorbed into the bloodstream after administration, or the bioavailability of the drug, still remain a major challenge for oral delivery of macromolecules. Normally, most clinically used drugs are absorbed through epithelial cells by transcellular passive diffusion.[2] However, the largely hydrophilic nature of macromolecules prevents their crossing through the phospholipid bilayer of cell membranes.[4] One approach to overcome this barrier made use of the ability of nanoparticles to target M-cells of Peyer's patches in the small intestine and the consequent absorption of the nanoparticles by transcytosis.[15]

While successful to an extent, Peyer's patches only make up a specific portion of the intestine, thus limiting the surface area for absorption. Another approach sought to increase the permeability of the intestinal epithelium by using permeation enhancers to target the tight junctions in between adjacent cells.[13] This method, however, risks transport of not only drugs into the bloodstream, but potentially harmful substances as well. Hence, these drawbacks prompt further exploration into different approaches to develop an oral drug delivery system for nanoparticles.

In a paper recently published in Science Translational Medicine, Pridgen *et al.* described a method that could pave the way for a more convenient oral administration of nanomedicine.[10] The authors exploited the ability to easily manipulate the surface of nanoparticles. The surface of nanoparticles is crucial to determining their properties such as stability, solubility and cell type specific uptake.[14] Taking advantage of this property, Pridgen *et al.* decided to conjugate immunoglobulin G (IgG) Fc fragments to the surface of nanoparticles. Based on previous evidence of the neonatal receptor (FcRn) mediating the transcytosis of nanoparticles across a monolayer of epithelial cells,[6,16] the authors hypothesised that Fc-conjugated nanoparticles (NP-Fc) would be targeted to the FcRn and be transported across the intestine epithelium.

FcRn is a neonatal receptor that is important during postnatal development by mediating the intestinal uptake of IgG from breast milk by the offspring. Of note, FcRn is also expressed at similar levels in adults.[5] FcRn binds to the Fc portion of IgG with high affinity in acidic (pH < 6.5) but not physiological environments (pH ~ 7.4).[11] Thus, in the intestine, NP-Fc would bind to FcRn on the apical surface and be taken up by endocytosis.[12] During intracellular trafficking, the acidic endosome would ensure the continued interaction between NP-Fc and FcRn.[3] Upon reaching the basolateral side, however, exocytosis and exposure to a neutral pH would cause the release of the NP-Fc,[8] which will then enter systemic circulation.

Using fluorescently labelled nanoparticles, the authors demonstrated that Fc-conjugated nanoparticles were able to cross the intestinal epithelium. When labelled NP-Fc were orally administered to wild-type mice, fluorescence was observed inside the villi on the basolateral side of intestinal epithelial cells. However, no fluorescence on the basolateral side was observed with non-targeted nanoparticles. This suggests that conjugating Fc fragments to nanoparticles could be a viable approach for oral delivery of nanomedicine.

The authors also quantified their observations by radiolabelling the nanoparticles with ^{14}C. The biodistribution measured in the spleen, kidneys, liver, heart and lungs showed that orally administered NP-Fc successfully entered the systemic circulation and were able to reach several organs known to express FcRn. Notably, the accumulation of ^{14}C measured in the organs was transient; the nanoparticle accumulation peaked at 2.5 h after delivery before the nanoparticles were cleared from the organs. The basis for this pharmacodynamic profile warrants further attention. The absorption efficiency calculated from the biodistribution data showed that Fc-conjugated nanoparticles have a higher absorption efficiency than non-targeted nanoparticles by 11.5 fold. It is worth mentioning that not all organs expressing FcRn were measured in the experiment, and ^{14}C-labelled nanoparticles may also be freely circulating in the blood. Thus, the absorption efficiency may actually be higher than what was calculated. However, for this method of delivery to be on par or as effective as intravenous administration, which boasts 100% bioavailability, further studies may be required to improve the absorption efficiency.

Having demonstrated that oral delivery is successful by modifying the nanoparticle surface with Fc fragments, Pridgen *et al.* then showed that this method remains viable when drugs are encapsulated within the modified nanoparticles. Nanoparticles encapsulating insulin (insNPs) were developed and the observed insulin release profile *in vitro* showed that all the insulin was released before 10 h. Since nanoparticles have been shown to be cleared from our system after 10 h,[10] the insulin release profile observed is favourable as it would mean that all the insulin would be delivered before complete clearance. Furthermore, when the insulin released *in vitro* was injected into the tail vein of mice, a hypoglycemic response was elicited. After confirming the function of the insNPs, the authors showed that, consistent with their previous results, insNPs targeted to FcRn (insNP-Fc) were able to generate a significant hypoglycemic response upon oral administration. In comparison, non-targeted insNP produced a response similar to that of the negative controls, which were orally

administered free insulin and NP-Fc without insulin. These results suggest that targeting nanoparticles to FcRn is a feasible approach to oral drug delivery.

There are a number of additional aspects that makes the FcRn receptor targeted nanoparticle approach stand out. For instance, the authors reported that the dose of insulin encapsulating NP-Fc required to generate the hypoglycemic response was markedly lower than other nanoparticle-based oral insulin delivery systems.[2] Furthermore, the oral insNP-Fc was shown to produce a prolonged hypoglycemic response of 15 h compared to 1.5 h with injected insulin.

The idea that any molecule, when encapsulated in nanoparticles, could be trafficked across the epithelial barrier has many positive implications in medicine. The results by Pridgen *et al.* demonstrate that the FcRn-mediated drug delivery approach is successful with monolayers of Caco-2 cells, a human epithelial colorectal adenocarcinoma cell line known to endogenously express human, as well as *in vivo* using a mouse model. The effectiveness of FcRn-mediated oral drug delivery in humans still awaits verification. However, before the FcRn based delivery method could be tested in humans, there are a number of aspects that require further study. For instance, potential immunological responses to the conjugated Fc fragments need to be investigated. More studies may also be needed to determine why a considerable percentage of the Fc-conjugated nanoparticles failed to enter systemic circulation. Furthermore, FcRn is expressed in many tissues. While this may prove useful to expand the method of delivery to other organs, for instance by enabling the delivery of drugs through the blood-brain barrier, there is also a possibility of off-target effects. One possible future direction would be to use directed evolution of the IgG Fc fragment to optimize the pH dependency of the binding and release kinetics of Np-Fc and FcRn.

The method of delivery described by Pridgen *et al.* has the potential to improve the treatment of various diseases by enabling oral administration of nanoparticle-based therapies. If combined with other technologies currently being developed, such as the ability to target specific tissues or cell types, even more possibilities for treatment can be envisioned in the future.

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