DRUG DELIVERY

Transferrin' the load

With an increasing number of therapeutic proteins and peptides on the market, patients still have to accept drug delivery via the needle. Needle-less protein delivery is an attractive goal, and a number of strategies are in clinical research, such as pulmonary delivery of insulin. Now, in the *Proceedings of the National Academy of Sciences,* Wei-Chiang Shen and colleagues at the University of Southern California School of Pharmacy demonstrate that oral delivery of a pharmacologically active form of the cytokine granulocyte colony-stimulating factor (G-CSF) is possible using the protein transferrin (Tf) as a carrier.

Tf is a natural transport protein that binds and delivers iron to endosomal compartments of cells. Tf receptors are expressed along the blood–brain barrier (BBB) and on tumour cells, and Tf has therefore been considered as a carrier for drugs crossing the BBB and for targeting certain cancers. The Tf receptor is also abundantly expressed in the human gastrointestinal epithelium and, because Tf is relatively resistant to gastrointestinal digestion, it has potential as an oral drug carrier.

The authors generated and expressed functionally active G-CSF as a recombinant fusion protein with Tf to explore the possibility of using Tf as a carrier for oral delivery of proteins. G-CSF increases the production of neutrophils within the bone marrow. Recombinant G-CSF is important for accelerating recovery of neutrophil counts in patients following a variety of chemotherapies. The authors first established that subcutaneous administration of their human Tf fusion protein to BDF1 mice generated a similar increase in neutrophil count to that of commercial human G-CSF. When delivered orally to the mice, the Tf fusion protein produced a significant increase in neutrophil count, but oral delivery of G-CSF had no effect, indicating that the Tf moiety of the fusion protein not only provides protection from proteolysis, but also increases the transport across the gastrointestinal epithelium. Co-administration of free Tf with the fusion protein abolished the increase in neutrophil count seen with the fusion protein alone, indicating that the fusion protein is taken up by a Tf receptor-mediated process.

These results show that a Tf-based recombinant fusion protein technology is a promising approach for future development of orally active protein and peptide drugs. Further work is underway to produce an insulin–Tf fusion protein. On the basis of the authors' previous results from the study of oral delivery of an insulin–transferrin chemical conjugate it is very likely that an orally active insulin fusion protein can be obtained.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Bai, Y., Ann, D. K. & Shen, W.-C. Recombinant granulocyte colony-stimulating factor–transferrin fusion protein as an oral myelopoietic agent. *Proc. Natl Acad. Sci. USA* **102**, 7292–7296 (2005)

FURTHER READING Rosen, H. & Abribat, T. The rise and rise of drug delivery. *Nature Rev. Drug Discov.* **4**, 381–385 (2005) | Goldberg, M. & Gomez-Orellana, I. Challenges for the oral delivery of macromolecules. *Nature Rev. Drug Discov.* **2**, 289–295 (2003)