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News & views

Drug delivery

Lipid nanoparticles target pancreas using proteins

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A two-pronged strategy directs drug-delivering nanoparticles to the pancreas — and shows promise in animal models of serious pancreatic diseases.

The clinical use of lipid nanoparticles (LNPs) for drug delivery is currently limited by their tendency to accumulate in the liver. Tuning their biodistribution to reach other tissues and to target specific cell types in an organ remains a major challenge[1,2]. Writing in *Nature*, Lei *et al.*[3] report their approach for engineering LNPs that specifically deliver therapeutic RNA to the pancreas — successfully targeting cell populations that were previously beyond the reach of LNPs, and unlocking avenues of research towards therapies that combat currently incurable pancreatic diseases.

It is well established that the physical and chemical properties of LNPs, such as their particle size and surface charge, decisively influence where these particles accumulate in the body[4]. Moreover, LNPs interact with the body's proteins, some of which can form a layer on the particle surface (a protein corona) that also affects the biodistribution of the particles[5]. Researchers have therefore used a process called passive targeting — optimizing LNP formulations to modulate their properties and the formation of protein coronas — to achieve organ localization and cell specificity. However, much of the current research in this area relies on empirical formulation screening and observational biodistribution data, hindering the establishment of general design principles for targeting LNPs to organs other than the liver[6,7].

An alternative approach called active targeting enhances cell specificity by decorating nanoparticle surfaces with ligand molecules — such as antibodies, peptides, sugars, oligonucleotides and small molecules — that bind to specific cellular receptors. However, this strategy often requires unique ligands for each targeted cell population and rarely improves the overall accumulation or retention of LNPs in specific organs. So, although active cellular targeting dictates which cells internalize LNPs, it has little influence over where the particles are distributed in the body[8].

Lei and colleagues' study illustrates how a deeper mechanistic understanding of the factors that control the uptake of LNPs by specific organs can move the field beyond trial-and-error formulation screening towards knowledge-driven LNP design for specific therapeutic goals. The authors show how passive targeting can be leveraged to achieve retention of LNPs in the pancreas in combination with selective uptake by specific cell populations through receptor-mediated processes.

The researchers examined two aspects of LNPs that might affect their uptake by the pancreas, the first of which was particle size. Most organs in the abdomen are encased in a protective 'capsule' of connective tissue. Lei *et al.* proposed that the thinner the capsule is that surrounds an organ, the larger the particles would be that can infiltrate it. Given that the capsule around the pancreas is thinner than those of other organs, the authors speculated that larger nanoparticles would selectively permeate the pancreas.

Sure enough, when the authors injected nanoparticles of different sizes into the abdominal cavity of mice, the largest particles (about 300 nanometres in diameter) preferentially accumulated in the pancreas. This preferential accumulation occurred regardless of the nanoparticles' composition — that is, independently of whether they were made up of lipids, polymers or inorganic molecules. However, when Lei *et al.* tested whether LNPs of around 300 nm are effective agents for delivering messenger RNA, they observed limited expression of the mRNA in the pancreas, despite the fact that the nanoparticles were selectively taken up by that organ.

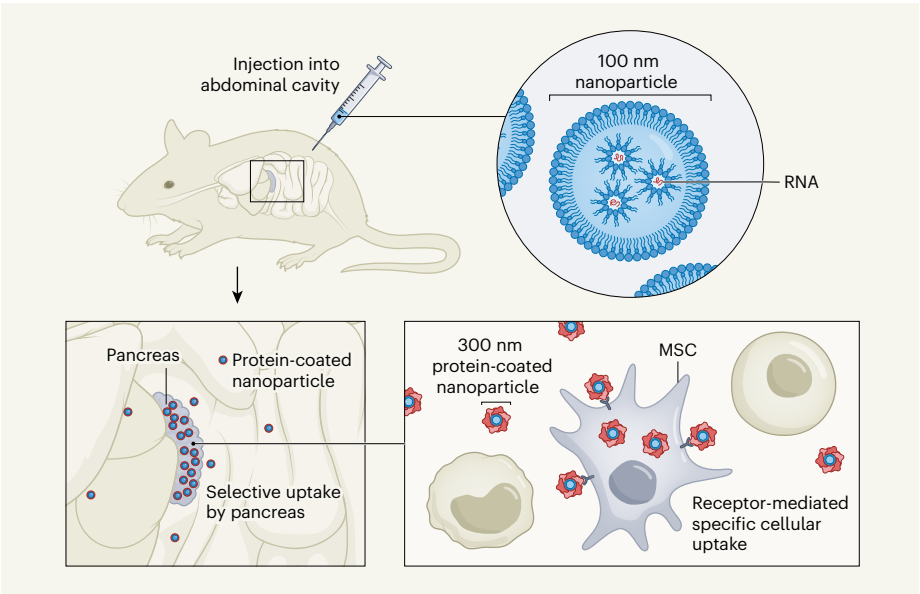

Figure 1 | Modified lipids form nanoparticles that deliver RNA to the pancreas. Lei *et al.*[3] studied the biodistribution in animals (including mice, shown) of nanoparticles formed from lipids that have a pair of amino acids (arginine–histidine) attached. The particles are initially about 100 nanometres in diameter, but form a coat of proteins (a protein corona) when injected into the abdominal cavity. The protein-coated nanoparticles have a diameter of about 300 nm; the authors' experiments show that nanoparticles of this size accumulate in the pancreas, rather than in other organs. Moreover, the proteins in the corona cause the nanoparticles to be specifically taken up by mesenchymal stromal cells (MSCs) through receptors on the cell surface.

Previous studies have shown that mRNA delivered by smaller LNPs (about 100 nm in diameter) is expressed effectively in cells[9]. This prompted the authors to develop a creative approach to overcome the limited expression observed with their pancreas-selective nanoparticles. They prepared LNPs of around 100 nm using ionizable lipid molecules that have an arginine amino acid attached, which drives the formation of a corona when the nanoparticles encounter proteins from the abdominal cavity. The resulting LNP–protein complexes had a diameter of about 300 nm. The authors' strategy bridges the requirement to use smaller LNPs to enable mRNA expression with the need to use larger LNPs to target the pancreas.

The second aspect of LNPs investigated by the authors was the composition of the protein corona, which is profoundly influenced by which amino acid (or combination of amino acids) is attached to the ionizable lipid molecules. The attachment of an arginine–histidine dipeptide (Arg–His) to lipids preserved the localization of the resulting LNPs in the pancreas (Fig. 1), and significantly increased pancreatic expression of mRNA carried by the nanoparticles. Lei and colleagues' thorough analysis revealed that the corona of Arg–His-LNPs was distinctly enriched with lipid-binding proteins found in very-low-density lipoproteins (VLDLs; molecular assemblies that transport lipids through fluids in the body), compared with the corona of LNPs made from lipids that have no amino acids attached.

Remarkably, these lipid-binding proteins mediated cellular uptake of the nanoparticles through the VLDL receptor (VLDLR), which is highly expressed in the pancreas, particularly on mesenchymal stromal cells (MSCs, which support tissue repair and regeneration). This finding shows that corona composition can result in cell-type-specific LNP delivery, and explains why mRNA delivered by Arg–His-LNPs was preferentially expressed in MSCs in Lei and colleagues' *in vivo* experiments in mice.

The new study also highlights the importance of aligning the LNP delivery strategy with the condition the therapeutic is intended to treat (the therapeutic indication). In this case, nanoparticles were injected into the abdominal cavity to take advantage of their size-dependent infiltration into the organs in that part of the body, enabling access to the pancreas while minimizing uptake by the liver. The findings underscore the fact that distribution of LNPs in the body is not determined solely by nanoparticle design, but emerges from the interplay between the particles' physical and chemical properties, anatomical context and route of administration.

By precisely controlling this interplay, the authors used LNPs to deliver two therapies for aggressive pancreatic cancer specifically to the affected organ in mice. When used in combination with other therapies, the LNP treatment showed promising results in these animals by shrinking tumours or inhibiting tumour growth.

Questions remain regarding the contributions made by each design element of the LNPs. For example, although enrichment of VLDL lipid-binding proteins in the corona is strongly associated with the uptake of Arg–His-LNPs by MSCs, it is unclear whether other factors also contribute to this cell specificity. Experiments in which LNPs that do not target MSCs are pre-incubated with purified lipid-binding proteins before administration could help to disentangle the relative roles of corona composition, particle-size enlargement and lipid chemistry in the VLDLR-mediated uptake pathway and strengthen the causal links between cell-type specificity and protein adsorption to LNPs.

Nevertheless, Lei and colleagues' impressive findings open up avenues of research for developing therapies for pancreatic diseases. More broadly, the authors have created a blueprint for a knowledge-based approach for engineering LNPs that precisely target the specific tissues and cells needed for a particular indication. Researchers now need to establish systematic discovery pipelines and general guidelines for designing LNPs that achieve organ- and cell-type-specific delivery of therapeutics, thereby overcoming a major bottleneck in the field. Readily deployable approaches for profiling LNP protein coronas, together with modular methods for attaching ligands that target biological targets to the surface of LNPs, could accelerate the translation of LNPs to the clinic for a range of therapeutic indications.

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