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Cover story

Mast cells for cell-mediated therapy

Cell penetrating peptides (CPPs) are proven vehicles for the delivery of bioactive moieties across the relatively impermeable plasma membrane of eukaryotic cells. The majority of CPPs are relatively short sequences, with less than 30 amino acids, that bear a net positive charge contributed by the side chains of cationic residues of which arginine is often the predominant species [1]. Both direct membrane translocation and a plethora of energy-dependent endocytotic mechanisms are known to internalize CPPs and their cargoes, which vary from small drug molecules to peptides, proteins, and oligonucleotides. Cargoes can be covalently attached to a monomeric CPP or delivered as a non-covalent complex; the latter strategy being particularly amenable to the intracellular transport of larger negatively-charged oligonucleotides. The pharmacokinetic disadvantages of peptides as drugs and drug-delivery vectors are, nevertheless, readily apparent. Most peptides are rapidly metabolized by both circulating and membrane-bound enzymes, and so their therapeutic applications usually require undesirable routes of administration. One other major caveat, more-specifically associated with polycationic peptides, is the undesirable acute activation of circulating mast cells. Within the cardiovascular system and other compartments of the human body, the exposure of mast cells to polycationic CPPs could promote the regulated secretion of inflammatory mediators by a mechanism which may involve the receptor-independent activation of heterotrimeric G proteins [2].

The paper by Professor John Howl and Dr. Sarah Jones in this issue [3] addresses fundamental questions relating to the potential applications of mast cells as a cell-mediated therapy. By screening a range of chemically diverse sequences, two CPPs, Tat and C105Y, were identified as efficient vectors for the delivery of cargoes into RBL-2H3 cells in the absence of exocytosis. The arginine-rich Tat CPP (GRKKRRQRRRPPQ) effectively delivered the TAMRA chromophore, as a covalent chimera, and the much larger protein avidin as a non-covalent complex. Intriguingly, confocal microscopy revealed that Tat transduction resulted in a cytoplasmic distribution of fluorescent avidin, whilst TAMRA-Tat accumulated within secretory lysosomes. Both TAMRA-Tat and avidin can be released by treating cells with mastoparan, a wasp venom secretagogue, and by the physiological mechanism of antigen-induced aggregation of high affinity IgE receptors. These findings provide an evidence for at least two pools of secretory mediators in RBL-2H3 cells that can be accessed by CPPs. More significantly, these observations indicate a strategy that can exploit mast cells to direct the delivery of bioactive agents to disease sites as an alternative cell-mediated therapy.

The study by Howl and Jones provides interesting pointers towards the exploitation of human mast cells as a novel cell-mediated therapeutic approach. Achieving this outcome, however, requires replicating the results of RBL-2H3 cells in cells of human origin. Human mast cells might well display a different sensitivity to polycationic peptide-mediated secretion. Moreover, the different ultrastructure of human mast cells, marked by the presence of much larger mature secretory granules, may require a CPP other than Tat to affect the delivery of bioactive cargoes into an "exocytosis-competent" pool. Currently, such studies are inhibited by relatively high costs and practical difficulties associated with the isolation, maintenance and expansion of primary human mast cell cultures. Should such hurdles be overcome, then CPP technologies could be further exploited to load human mast cells with a therapeutic payload prior to their transfusion. As an alternative strategy, it should also be possible to load mast cells with CPPs that exhibit defined bioactivities, termed "bioportides" by the authors. If bioportides can also be stored and released by exocytosis from human mast cells, this approach will negate the requirement to conjugate a therapeutically useful payload to a CPP vector.

It will almost certainly be some time before any cell-mediated therapy becomes clinically practical. Quite often, we place too much optimism and expectation upon an unproven technology simply because it is new, as is the case with nanoparticle-based targeted drug delivery. It is important to continue research on cell-mediated therapies but without false expectations either to revolutionize the future of medicine or to become its next pillar. This is simply because genuine advances in science, not to mention medical science, are both difficult to achieve and usually time consuming. The idea of using mast cells for such application, however, opens up a new avenue of exploring various approaches in a hope to find cures for difficult diseases. The work by the Howl team provides a tool to study cell mediated therapy that can be combined with other drug delivery technologies.

References

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