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Cover story

Mechanism of cross-presentation of microencapsulated antigen

Treating diseases is important, and equally important, if not more, is to prevent the diseases. One of the most efficient ways of prevention is vaccination. Vaccines which are able to elicit potent T lymphocyte responses are urgently needed and the currently available systems leave ample room for improvement. One promising antigen delivery system is based on biodegradable poly(D,L-lactide-*co*-glycolide) microspheres (PLGA-MS) which can induce long lasting T helper as well as cytotoxic T lymphocyte responses in mice. PLGA-MS systems were able to protect mice from viral infection and tumor growth [1]. PLGA-MS containing peptides or proteins are readily taken up by macrophages and dendritic cells (DC) *in vitro* as well as *in vivo* leading to presentation on MHC class I and class II molecules. In particular, the cross-presentation on MHC class I molecules is remarkably efficient, and this poses a question about the intracellular fate of PLGA-MS in DC.

While some studies have shown by electron and fluorescence microscopy that PLGA-MS remain in endosomes after uptake [2], others have obtained evidence for release of MS, especially of nanoparticles, into the cytoplasm [3]. This important and controversial issue has been readdressed with the help of a new methodological approach in the study by Professor Groettrup and his team published in this issue [4]. In the beginning of their study, the authors realized that it was impossible to discriminate PLGA-MS in DC from other vesicles or droplets as their electron density is quite similar. Panyam and colleagues capsulated electron dense osmium tetroxide into PLGA nanoparticles to visualize them in cells by electron microscopy [3], but this substance is quite toxic and not ideal for the production of PLGA-MS by spray drying as performed by Professor Groettrup's group. The authors of the cover story in this issue used inorganic nanocrystals of lead sulfide which were included together with the PLGA polymer into the inorganic phase. These are electron dense and unambiguously label the MS in electron microscopy images of DC. Similarly, PLGA-MS labeled with strongly fluorescent cadmium selenide quantum dots were used to monitor the trafficking of MS within DC at different time points after uptake by confocal fluorescence microscopy. Using electron and fluorescence microscopy the authors were able to show that the MS remained encapsulated by a Lamp1$^+$ endosomal membrane in primary peritoneal macrophages and bone marrow derived dendritic cells of mice up to 48 hours after uptake. Since cross-presentation of a co-encapsulated model antigen was prominently detected already 16 hours after uptake, the data indicates that PLGA-MS encapsulated antigen must have been released into the endosome and transported into the cytoplasm for proteasome dependent processing and presentation on MHC class I molecules. Encapsulation of nanocrystals can even be exploited to magnetically sort phagocytic cells from non-phagocytes. This was achieved by feeding DC and fibroblasts with PLGA-MS charged with super-paramagnetic iron oxide nanoparticles (SPIONS); DCs which phagocytosed these particles could be easily separated from non-phagocytic fibroblasts on magnetic columns. The microencapsulation of nanocrystals into PLGA-MS turned out to be quite useful in several respects.

The work by Professor Groettrup and his group is highly important not only in vaccination but also drug delivery in general. The data presented in this issue indicates that the proteins loaded into PLGA-MS are released within the lysosomes and then cross the lysosomal membrane to result in cross-presentation of microencapsulated antigen. It remains to be seen whether other protein drugs can be released in the endosome to be effective, since protein drugs are rather different from vaccines in that the exact control of the concentration and stability of the latter is not that critical for efficacy. Nevertheless, understanding the exact process of release of the loaded proteins and immune responses allows design of better drug delivery systems for protein drugs in general.

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Kinam Park
Purdue University,
Departments of Biomedical Engineering and Pharmaceutics,
West Lafayette, Indiana, USA
E-mail address: kpark@purdue.edu.

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