Correlation Between In Vitro and In Vivo Release of Radiolabeled Antigen from PLGA Microspheres Using SPECT/CT Imaging

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Typically, for inactivated subunit vaccines, multiple doses have to be administered to generate a protective response: an initial priming injection followed by one or more booster shots. To improve patient compliance with such vaccination schedules, drug delivery systems have been developed to release antigen over a tightly controlled series of burst and lag phases from a single injection. Biodegradable poly(lactide-co-glycolic acid) (PLGA) have received considerable attention for this application due to their peculiar ‘prime-lag-boost’ release profile. Although the release of antigens from PLGA microspheres is well characterized on the bench in buffers and physiological media, the in vivo performance of these particles remains largely unknown.

To shed a light on the latter, the model antigen ovalbumin (OVA) was radiolabeled with the long-lived gamma-emitter 111In and encapsulated into PLGA microspheres using a W/O/W emulsion technique; these particles are termed 111In-msOVA. The morphology of the particles was assessed using scanning electron microscopy (SEM) and dynamic light scattering (DLS; Z-Ave 4.6 ± 0.9 µm). Benchtop release curves were obtained in 1x PBS and diluted mouse serum using a gamma counter over a period of 3.5 weeks. The same microspheres were also injected into the subcutaneous fat of healthy female C57Bl/6 mice, and using a preclinical SPECT/CT imager, the activity remaining at the site of administration was measured over a 2 week period. A prime phase of release was observed both in vitro and in vivo, consisting of ~30-40% of the antigen load over the first 24 hours. However, while the in vitro microspheres entered a prolonged lag phase for the next 2 weeks, antigen was continually released from the in vivo injection site. No apparent boost phase was observed for the in vivo microspheres either. However, 111In-msOVA did prolong antigen retention compared to free OVA. The timing of antigen administration is crucial in producing the desired immune response from a vaccine. Our data shows that the in vitro release profile of antigen from PLGA microspheres does not always reflect what occurs in the body. In order to design and develop better vaccine delivery systems, a particularly important topic in the time of the COVID-19 pandemic, more attention needs to be addressed to their pharmacokinetics.