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Magnetite-filled micelles as a versatile delivery vehicle for a TLR4 mediated cancer nanovaccine

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Toll-like receptors (TLRs) are important components of the innate immune system, and increasingly for therapeutic targeting in a wide set of diseases and autoimmune disorders. Among TLRs, TLR4 is involved in recognition of lipopolysaccharide and many other modulators. However one of the limiting factors to their use as vaccine adjuvants is the systemic cytokine production, which can cause severe side effects and even death. For this reason, there is considerable interest in studying new TLR4 modulators and how changes in their delivery can fine-tune the immune response. Here, we have loaded a TLR4 agonist derived from Xanthomonas campestris into magnetite-containing micelles composed of PEG-phospholipids, obtaining a new biocompatible delivery system showing a uniform size distribution of ca. 40 nm. The nanoparticle-based system was used for targeted delivery of the TLR4 agonist, co-delivery of a model antigen ovalbumin (OVA) and multimodal imaging tracking of cargo delivery to the target receptor and tissue. To attach the antigen we have applied a fast and chemoselective bisaryl-hydrazone linkage strategy, which afforded a high yield (>95%) of conjugation. Administration of these systems to J774A.1 mouse macrophages showed that the micelles reduced the toxicity of the ligands and retained their immune stimulating activity. We have studied the efficacy of these systems to mediate anti-tumour immunity in the syngeneic B16-F10 (OVA) mouse melanoma model in C57BL/6 mice. The results showed that magnetite-containing micelles significantly improve the prophylicatic vaccine efficacy. Moreover, when administered in combination with an immune checkpoint blockade strategy for the immunosuppressive programmed death-ligand 1 PD-L1, the anticancer effects are significantly enhanced. The possibility of in vivo tracking coming from the iron oxide nanospheres combined with the use of FDA approved anti-PD-L1 antibodiesoffer new possibilities for the use of this system in cancer immunotherapy.

Recent Publications:

1. O'Neill, et al. (2009) Therapeutic Targeting of Toll-Like Receptors for Infectious and Inflammatory Diseases and Cancer. Pharmacol. Rev. 61(2):177–197.
2. Baxevanis, et al. (2013) Toll-like Receptor Agonists: Current Status and Future Perspective on Their Utility as Adjuvants in Improving Anticancer Vaccination Strategies. Immunotherapy 5(5):497–511.
3. Brito, et al. (2014) Designing and building the next generation of improved vaccine adjuvants. J. Control. Release 190:563-579.
4. Cobaleda- Siles, et al. (2014) An Iron Oxide Nanocarrier for dsRNA to Target Lymph Nodes and Strongly Activate Cells of the Immune System. Small 10(24):5054–5067.
5. Ruiz-de-Angulo, et al. (2016) Microdosed Lipid-Coated (67) Ga-Magnetite Enhances Antigen-Specific Immunity by Image Tracked Delivery of Antigen and CpG to Lymph Nodes. ACS Nano 10(1):1602–1618.

Biography

Giordano Traini has received both his Bachelor's and Master's degrees in Chemistry at the University of Camerino (Le Marche, Italy). During his Master's degree he has spent five months in Grenoble (France) at the European Synchrotron Radiation Facility as part of a research project granted and financed by the COST actions. In 2015 he joined the group of Theranostic Nanomedicine lead by Prof. Juan Mareque in CIC biomaGUNE (San Sebastián, Spain) as an early stage researcher enrolled in "TOLLerant", a project funded by the European Union's Horizon 2020 Research and Development Program and focusing on the interaction of toll-like receptor four with both small molecules and nanoparticles.

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