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CENTER FOR COOPERATIVE RESEARCH IN BIOMATERIALS

seminar

Friday, 12th July, 12.00 pm, Seminar Room

Host: Dr. Jordi Llop

Nanoparticle-filled micelles as versatile delivery vehicles for TLR4 mediated cancer immunotherapy

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Despite the tremendous potential of Toll-like receptor (TLR) 4 agonists in cancer immunotherapy, only some lipopolysaccharides (LPS) isolated from particular bacterial strains or synthetic structures like monophosphoryl lipid A (MPLA) are able to avoid toxic overactivation of the immune system while retaining adequate immunogenicity to act as vaccine adjuvants[1] . For cancer immunotherapy applications, the delivery of TLR4 agonists and their immunostimulatory activity modulation can be improved using nanoparticles. Moreover, combination of vaccines with immune checkpoint blockade (CPB) strategies could overcome the intrinsic weaknesses of vaccines and CPB monotherapies[2]. Here, we developed a nanovaccine by incorporating different LPS-related structures into nanoparticle-filled phospholipid micelles (mNPs) through a self-assembly process, exploiting the amphipathic structures of the adjuvants creating a nano-adjuvant for efficient vaccine delivery and potent cancer immunotherapy. The structurally unique LOS of the plant pathogen Xcc was incorporated into phospholipid micelles encapsulating oleic acid-coated 6 nm iron oxide nanoparticles (mIONPsp-Xcc LOS), producing stable pathogen-mimicking mNPs with ideal size, charge and hydrophobicity for targeting antigen presenting cells in the lymph nodes. The antigen OVA was attached to mIONPsp via a hydrazone bond (mIONPsp-HyNic-OVA) creating a NP-based antigen delivery vehicle and enabling rapid, easy-to-monitor and high yield antigen ligation at low concentrations[3] . The protective effect of mIONPsp-HyNic-OVA formulated with mIONPsp-Xcc LOS as adjuvant was investigated in mice against the highly aggressive model for murine tumor immunotherapy, B16-F10 melanoma expressing OVA. The results showed that the nanovaccines led to a higher-level tumor antigen-specific cytotoxic T lymphocyte (CTL) effector and memory responses without inducing toxicity, and that when combined with abrogation of the immunosuppressive programmed death-ligand 1 (PD-L1), provided 100% long-term protection against repeated tumor challenge[4]. The mIONPsp and antigen conjugation strategy in combination with immune checkpoint inhibition of PD-L1 represent a promising approach to improve cancer immunotherapy of vaccines exploiting TLR4 agonists.

[1]: Mastelic, B. et al., Mode of action of adjuvants: Implications for vaccine safety and design. Biologicals 38, 594–601 (2010).
[2]: Zhuting, H. et al., Towards personalized, tumour-specific, therapeutic vaccines for cancer. Nature Reviews Immunology 18, 168–182 (2018).
[3]: Blanco-Canosa, J. B. et al., Rapid covalent ligation of fluorescent peptides to water solubilized Quantum Dots. J. Am. Chem. Soc. 132, 10027–10033 (2010).
[4] Traini, G. et al., Cancer immunotherapy of TLR4 agonist-antigen constructs enhanced with pathogen-mimicking magnetite nanoparticles and checkpoint blockade of PD-L1. Small 15, 1803993 (2015).