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A toll-like receptor 2 agonist-fused antigen enhanced antitumor immunity by increasing antigen presentation and the CD8 memory T cells population

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We have established a platform technology for high-yield production of recombinant lipoproteins. The lipid moiety of the produced lipoproteins is identical to that of bacterial lipoproteins, which are recognized as danger signals by the immune system. Thus, both innate and adaptive immune responses can be induced by lipoproteins. Ag473 (a lipoprotein from N. *meningitidis*) can be produced in high yields using E. *coli* strain C43 (DE3). We then identified a fusion sequence, D1, and fused with dengue envelop domain 3 (E3) to express a recombinant lipoprotein, rlipo-D1E3, at high level. The rlipo-D1E3 cold elicits stronger virus neutralizing antibody responses than those from rE3 alone or rE3 formulated with alum adjuvant. Moreover, an inactive human papillomavirus (HPV) E7 (E7m) biologically linked to a bacterial lipid moiety (rlipo-E7m) induced the maturation of mouse bone marrow-derived dendritic cells through toll-like receptor 2, skewed the immune responses toward the Th1 responses and induced E7-specific CTL responses. The therapeutic efficacy of E7m was dramatically increased in its lipidated form. Using ovalbumin (Ova) as a model antigen, we further studied the mechanism of lipidated antigens for immunotherapy. We found that immunization with rlipo-OVA increased antigen presentation by major histocompatibility complex (MHC) class I via TLR2 and induced higher numbers of effector memory (CD44+CD62L-) CD8+ T cells compared with recombinant ovalbumin (rOVA) alone or rOVA mixed with the TLR2 agonist Pam3CSK4. We also demonstrated that the CD27+CD43+ effector memory CD8+ T cells expressed high levels of the long-lived CD127 marker. The administration of rlipo-OVA could induce antitumor immunity, but the anti-tumor effects were lost after the depletion of CD8 or CD127 cells *in vivo*. These findings suggested that the TLR2 agonist-fused antigen induced long-lived memory CD8+ T cells for efficient cancer therapy.

Biography

Chih-Hsiang Leng has completed his PhD from the National Defense Medical Center, Taiwan and Post-doctoral studies from the Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes (NHRI). He is a Research Fellow and Deputy Director in National Institute of Infectious Diseases and Vaccinology, NHRI. He is now working for the development of novel and effective recombinant subunit-based vaccines. He collaborated with his colleagues to develop novel polymer-based adjuvant for enhancing the potency of subunit vaccines and to establish a novel lipoprotein expression system to produce high potent lipoimmunogens for the development of novel subunit vaccines.

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