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LL-37: A powerful booster of ex vivo-prepared DC-based vaccines in prostate cancer patients and the TRAMP mouse model, without additional benefit from anti-PD1 therapy

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Abstract

Background: Prostate cancer (PCa) is one of the most common cancers in men. As a “cold tumor,” it exhibits low immunogenicity. Therefore, dendritic cells vaccines (DC) have been developed to enhance adaptive immunity. However, the efficacy of *ex vivo*-produced DC remains suboptimal. The antimicrobial peptide LL-37 has shown various immunomodulatory effects. Our previous studies demonstrated that LL-37 enhances the performance of DC produced from the peripheral blood of healthy volunteers.
Aims: In this follow-up study, we aimed to further investigate the therapeutical potential of LL-37/DC alone or in combination with anti-PD1 therapy using PCa patients’ samples and a syngeneic mouse model. Furthermore, we explored the performance of LL-37/DC under GMP conditions.
Methods: Human DC were prepared from leukaphereses of 10 biochemical recurrence (BR) PCa patients. The reactivity and cytotoxicity of these DC to the PCa cell line PC3 were assessed using flow cytometry and fluorescent microscopy. Mice bone marrow-derived DC from B6 TRAMP mice were inoculated subcutaneously into TRAMP tumor-bearing mice (n=9). The tumor growth and survival rates were monitored. Finally, we produced DC under GMP conditions and evaluated their performance *in vitro*.
Results: LL-37/DC-primed lymphocytes from BR PCa patients exhibited a two-fold increase in the expression of both IFN-γ and TNF-α and caused a three times higher contraction of co-cultured PC3 cells compared to DC prepared without LL-37. The increase in the LL-37/DC efficacy was not caused by enhanced DC maturation, as the expression levels of HLA-DR, CD83, CD86, and CD80 remained similar. Adding an anti-PD1 antibody did not improve either DC or LL-37/DC efficacy. Finally, we demonstrated that LL-37/DC prepared under GMP conditions was also significantly more reactive and caused two and a half times higher contraction of the co-cultured PC3 cell line compared to DC prepared without LL-37.
In the TRAMP mice model, LL-37/DC exhibited significantly higher expression of CD80, extended the mice survival by 30 days, and slowed down the tumor growth as compared with the DC prepared without LL-37. The anti-PD1 therapy had no additional effect.
Conclusions: We demonstrated that LL-37 is a promising compound that enhances the antitumor potential of DC both *in vitro* and *in vivo*. Furthermore, this improved potential is preserved even when DC are produced under GMP conditions. On the other hand, using anti-PD1 therapy showed no additional therapeutic impact. Taken together, LL-37/DC offers potentially advantageous treatment for patients with cold tumors, who typically respond poorly to immune checkpoint inhibitor therapy.