TLR7 Agonist Imiquimod is a Potent Vaccine Adjuvant

Yushe Dang, Wolfgang M. Wagner, Ekram Gad, Carmen M. Berger, Mary L. Disis
Tumor Vaccine Group, Center for Translational Medicine in Women’s Health, Seattle, University of Washington

ABSTRACT

We evaluated the adjuvant effects of the TLR7 agonist imiquimod as compared with GM-CSF, which has been widely used as a vaccine adjuvant. Although both topical imiquimod and intradermal GM-CSF as adjuvant effectively induced the accumulation and activation of dermiceut (DC) in draining lymph nodes (DLN), imiquimod preferentially induced the trafficking of dermal DC to the DLN. Both GM-CSF and imiquimod augmented ovaline-specific CD4 T cell response in ova-tg mice when used in conjunction with CD4 peptide-based vaccines, as demonstrated by in vivo proliferation of CFSE labeled DO11.10 cells. Although both GM-CSF and imiquimod stimulated OVA specific CD8 T cell responses in OVA-tg mice when immunized with a CD8 peptide, the response induced by imiquimod was of greater magnitude. Finally, imiquimod was markedly more effective in stimulating OVA specific T cell immunity with a protein-based vaccine compared to GM-CSF. Thus, imiquimod is a potent vaccine adjuvant in promoting T cell specific responses and has the potential for clinical use as a vaccine adjuvant.

CONCLUSIONS

• Imiquimod can induce maturation and migration of skin APC to draining lymph nodes
• As compared to GM-CSF, imiquimod enhances the trafficking of dermal DC which have been shown to be important in initiating immune responses
• Both imiquimod and GM-CSF are effective adjuvant for peptide based vaccines
• Only imiquimod could stimulate a Th1 antigen specific T cell responses when used with a protein based vaccine
• Imiquimod is a potent immunologic adjuvant for generating Th1 responses and is potentially useful for both subcomponent and protein based vaccines

INTRODUCTION

• Potent adjuvants are key to successful vaccination against weakly immunogenic antigens such as those involved in cancer
• DC are critical in the initiation of potent immune responses
• Both dermal DC as well as Langerhans cells have been shown to be important in initiating immune responses
• We evaluated whether topical imiquimod can recruit and activate DC populations in the skin and subsequently enhance immune responses generated during active immunization as compared to another common “DC activating” adjuvant, GM-CSF

METHODS

The effect of imiquimod and GM-CSF as adjuvant on activation of DC in mouse DLN was studied using C57BL/6 mice. Mice were vaccinated with 10ug ovalbumin. Intradermal GM-CSF (5ug/mice) or topical imiquimod was applied to vaccination site on three consecutive days. The DLN cells were harvested and stained with CD11c-PE-Cy5, CD86-FITC, CD205-PE and CD8-PE-Cy7, and analyzed with FC500 flow cytometer using CXP cell quest software (Beckman Coulter).

The adjuvant effect of imiquimod and GM-CSF on peptide-based vaccines was studied using ova-tg mice DO11.10 and OT-1. Splenocytes (10x10⁸) from DO11.10 mice or OT-1 mice were labeled with CFSE and adoptively transferred to balb/c or C57BL/6 mice respectively after peptide vaccinations. Three days later, the splenocytes from receipt mice were harvested and stained with CD4-PE and CD8-PE-Cy5, and analyzed with FC500 Flow Cytometry.

The adjuvant effect on ova protein-based vaccine was also studied using C57BL/6 mice. The mice were vaccinated with 100ug ova protein twice 10 days apart. Splenocytes were harvested. A 3 days standard IFNγ ELISPOT assay and cytokine flow cytometry were used to evaluate the immunity against OVA protein (10μg/ml).

CONCLUSIONS

• Imiquimod can induce maturation and migration of skin APC to draining lymph nodes
• As compared to GM-CSF, imiquimod enhances the trafficking of dermal DC which have been shown to be superior to Langerhans cell in inducing immune responses [Fukunaga A et al, J Immunol, 2008]
• Both imiquimod and GM-CSF are effective adjuvant for peptide based vaccines
• Only imiquimod could stimulate a Th1 antigen specific T cell responses when used with a protein based vaccine
• Imiquimod is a potent immunologic adjuvant for generating Th1 responses and is potentially useful for both subcomponent and protein based vaccines