

The mucosae-associated epithelial chemokine (MEC/CCL28) modulates mucosal immunity in BALB/c Mice immunized with HIV-1 virus-like particles

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Background: Mucosal transmission is the prevalent route used by infectious agents to invade host organism and secretory immunity is the main line of defence, as it generates secretory IgA that can block pathogens at the mucosal surface. MEC/CCL28 (CCL28) binds to CCR3 and CCR10 and recruits IgA-secreting plasma cells (IgA-ASCs) in the mucosal lamina propria. Virus-like Particles (VLPs) are a novel vaccine approach based on non-pathogenic particles that mimic the structure of virus particles with effective induction of both arms of the immune response. The suitability of CCL28 as an adjuvant for the elicitation of optimal innate and acquired mucosal and systemic immunity was assessed in mice using three different VLP mucosal viral infection models: HIV-1, Influenza A virus (H7N1) and HPV-16.

Materials and methods: Balb/c mice were immunized intramuscularly with a prime-boost regime based on VLP containing either gp160 from HIV-1 clade B, Influenza A H7N1 hemagglutinin or HPV-16 L1 protein in the presence/absence of CCL28 and of the parental control CCL19. Flow cytometry evaluation of CCR3 and CCR10 expression was performed on purified splenocytes. Antigen-specific Th1 and Th2 cytokine production was performed on splenocytes and either colon, lungs or uterine cervix, depending on the dominant site of infection within mucosal tissues, whereas antigen-specific IgG and IgA antibodies were evaluated in sera and mucosal secretions by ELISA. Immune sera and mucosal secretions were tested for ex vivo neutralization activity against either HIV-1 subtype B and C strains, Influenza A virus or HPV-16. IgA-ASCs recruitment at the mucosal level was verified with immune-histochemistry analyses.

Results: The following immune parameters were significantly augmented in VLP-CCL28 mice compared to either VLP-CCL19, VLP alone, CCL28-alone, CCL19-alone or saline mice: 1) the percentage and the surface density (MFI) of CCR3 and CCR10 on CD19+ splenocytes; 2) antigen-specific IFN- γ , IL-4 and IL-5 production in splenocytes and mucosal specimens; 3) total IgA titers in sera and in mucosal secretions; 4) antigen-specific IgG and IgA titers in sera and in mucosal secretions. Sera and mucosal secretions from VLP-CCL28 mice showed a significantly augmented neutralizing activity against homologous and heterologous viruses compared to controls. Furthermore, IgA-ASCs were significantly increased in either rectum, lungs or uterine cervix of VLP-CCL28 mice.

Conclusions: CCL28 used as an adjuvant has a robust immunomodulatory effect on potentially beneficial mucosal and systemic immune responses. These findings suggest that CCL28 could play a useful role in increasing the efficacy of preventive vaccines for mucosally transmitted viral infections.

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