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Pre-clinical development of BCG.HIVA(CAT) strain, an antibiotic-free selection strain for HIV-TB pediatric vaccine

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Background

Our starting platform was based on a heterologous BCG prime and MVA boost regimen delivering a common immunogen called HIVA. In this study, we have i) developed a BCG.HIVA^{CAT} strain containing an antibiotic free selection system (Cobra); ii) evaluated the specific HIV-1 immune responses induced after newborn BALB/c mice immunization with BCG.HIVA^{CAT} prime and MVA.HIVA.85A boost; iii) evaluated the specific-TB immune responses induced after newborn BALB/c mice immunization with BCG.HIVA^{CAT} prime and MVA.HIVA.85A boost and iv) evaluated the influence of age on specific HIV-1 immune responses using the same vaccination schedule.

Methods

7-days-old newborn and 7-weeks-old adult mice were either left unvaccinated or vaccinated subcutaneously with 10^5 cfu of BCG.HIVA^{CAT} or BCGwt, and 16 weeks later were boosted intramuscularly with 10^6 pfu MVA.HIVA.85A. The mice were sacrificed 2 weeks later. The HIV-1 and TB-specific cellular immune responses were analyzed in spleen cells by intracellular cytokine staining and IFN-γ ELISPOT.

Results

The frequencies of TB-specific CD8 $^+$ T-cells producing IFN-γ (P11 stimulation), and spleen cells producing IFN-γ (P11, P15 and PPD stimulation), were higher in BCG.HIVA^{CAT} or BCGwt primed and MVA.HIVA.85A boosted mice compared with mice vaccinated with MVA.HIVA.85A alone (i.e. 231, 108 and 24 sfu/10^6 PPD stimulated splenocytes respectively). The specific HIV-1 immune responses (P18I10 stimulation) were lower in BCG.HIVA^{CAT} or BCGwt primed and MVA.HIVA.85A boosted mice compared with mice vaccinated with MVA.HIVA.85A alone (i.e. 270, 276 and 412 sfu/10^6 P18I10 stimulated splenocytes respectively). When adult and newborn mice were immunized using the same vaccination schedule, the HIV-1-specific immune responses in adult mice were higher than in newborn mice (0.45% vs 0.2% CD8$^+$ T-cells producing IFN γ).

Conclusion

In conclusion we demonstrated the immunogenicity of BCG.HIVA^{CAT} and MVA.HIVA.85A in newborn mice but additional experiments should be performed in newborn mice testing different routes and doses that might provide different levels of immunogenicity.

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