OPTIMIZATION OF THE MVA VACCINE POTENTIAL AFTER DELETION OF A VIRAL GENE CODING FOR THE IL-18 BINDING PROTEIN

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ABSTRACT

We described for the first time that MVA encodes for a protein with a clear biological activity that inhibits the action of IL-18, and that the deletion from its genome of the IL-18bp gene abolished this inhibitory activity. At early times post-immunization, MVAΔ18bp generated responses against T CD8+ and T CD4+ epitopes of a higher magnitude, rendering two to four-fold increments in the number of specific IFN-γ and IL-2 secreting cells against VACV peptides in both mouse strains analyzed. Importantly, we found that MVAΔ18bp administration also improved the number of CD8+ T-cells with cytotoxicity properties. Also, the optimization effect was corroborated after the inoculation of different viral doses and after i.p, i.m or i.n immunizations. At later times post-MVA administration, immune response still showed higher T CD8+ and T CD4+ VACV-specific responses, indicating the importance of IL-18 to induce and maintain long time improvements in the anti-viral T-cell immune responses. Even more, mice vaccinated with MVAΔ18bp showed an increased protection against an i.n MRV challenge at the memory T-cell phase, showing a more direct correlation between T-cell immunity induced and protection afforded. Remarkably, the delivery of HIV antigens during the booster dose from MVAΔ18bp generated an enhancement of the T-cell response against the HIV proteins, improving the amplitude, as significant responses against a wider spectrum of antigens were detected.

BACKGROUND

Modified Vaccinia Ankara (MVA) is an attenuated strain of Vaccinia virus eliciting protective immunity against several viral infections. Deletion of the viral gene 18bp from MVA improves its vaccine potential, enhancing its cellular immunogenicity. The optimization of the response it was also achieved after vaccination against HIV proteins from different clades, showing HIV responses with a higher magnitude and amplitude after a DNA prime/MVA boost schemes. These results are of significant impact in the design of future new poxvirus-based HIV vaccines.

RESULTS

1. MVA Inhibits mouse IL-18 biological activity

MVA encodes for a protein with a clear biological activity that inhibits the action of IL-18, and the deletion from its genome of the gene coding for the IL-18bp abolished this inhibitory activity.

2. MVAΔ18bp improves the magnitude and quality of the specific T-cell responses at early times post-vaccination

Δ18bp still secreting cells against VACV peptides in both mouse strains analyzed. Δ18bp secreting cells against VACV peptides in both mouse strains analyzed. Δ18bp generated responses against T CD8+ and T CD4+ VACV-specific responses, indicating the importance of IL-18 to induce and maintain long.time improvements in the anti-viral T-cell immune responses. Even more, mice vaccinated with MVAΔ18bp showed an increased protection against an i.n MRV challenge at the memory T-cell phase, showing a more direct correlation between T-cell immunity induced and protection afforded. Remarkably, the delivery of HIV antigens during the booster dose from MVAΔ18bp generated an enhancement of the T-cell response against the HIV proteins, improving the amplitude, as significant responses against a wider spectrum of antigens were detected.

AIM

To evaluate the Th1 virucoid response elicited by a MVA bearing an IL-18bp gene deletion (MVAΔ18bp), characterizing the potential improving of the vaccine vector regarding its capacity to generate T-cell responses against VACV and HIV antigens.

3. MVAΔ18bp still elicits higher cellular responses at lower doses of immunization and by different immunization routes

A) Immunization route:

Δ18bp was found to be more immunogenic than MVAwt in i.p immunizations, allowing a higher number of CD8+ T-cells secreting IL-18, a higher level of cross-reactivity against VACV peptides was also found.

B) Specific response in local DLNs to the site of immunization:

Δ18bp improved, and a higher level of cross-reactivity against B epitopes was also found.

CONCLUSIONS

Deletion of the viral gene 008L that codes for the IL-18bp from MVA improves its vaccine potential, enhancing its cellular immunogenicity. The magnitude and quality of the adaptive specific T CD8+ and CD4+ responses were improved, actually this was still observed at later times post-immunization, which was correlated with a higher protection capacity. Even more important, the optimization of the response it was also achieved against HIV proteins from different clades, showing HIV responses with a higher magnitude and amplitude after a DNA prime/MVA boost schemes. These results are of significant impact in the design of future new poxvirus-based HIV vaccines.

4. MVAΔ18bp improves T-cell memory responses conferring a higher grade of protection against a VACV challenge

Fig. 4. MVAΔ18bp improves T-cell memory responses conferring a higher grade of protection against a VACV challenge. (A) Groups of 4 BALB/c mice were i.p immunized with 10⁷ pfu of MVAwt or MVAΔ18bp, Δ18bp generates responses against T CD8+ and T CD4+ VACV-specific responses, indicating the importance of IL-18 to induce and maintain long time improvements in the anti-viral T-cell immune responses. Even more, mice vaccinated with MVAΔ18bp showed an increased protection against an i.n MRV challenge at the memory T-cell phase, showing a more direct correlation between T-cell immunity induced and protection afforded. Remarkably, the delivery of HIV antigens during the booster dose from MVAΔ18bp generated an enhancement of the T-cell response against the HIV proteins, improving the amplitude, as significant responses against a wider spectrum of antigens were detected.

5. MVAΔ18bp improves the specific T-cell responses against HIV-1 antigens

A) Immunization schemes:

Δ18bp showed a higher level of cross-reactivity against B epitopes was also found.

B) Specific response in local DLNs to the site of immunization:

Δ18bp improved, and a higher level of cross-reactivity against B epitopes was also found.

C) Total specific cells per million WBC:

Fig. 5. MVAΔ18bp improves the specific T-cell responses against HIV-1 antigens. (A) Immunization schemes: i.p immunization with 10⁷ pfu of MVAwt or MVAΔ18bp, Δ18bp generated responses against T CD8+ and T CD4+ VACV-specific responses, indicating the importance of IL-18 to induce and maintain long time improvements in the anti-viral T-cell immune responses. Even more, mice vaccinated with MVAΔ18bp showed an increased protection against an i.n MRV challenge at the memory T-cell phase, showing a more direct correlation between T-cell immunity induced and protection afforded. Remarkably, the delivery of HIV antigens during the booster dose from MVAΔ18bp generated an enhancement of the T-cell response against the HIV proteins, improving the amplitude, as significant responses against a wider spectrum of antigens were detected.