A candidate HIV/AIDS vaccine (MVA-B) that enhances the magnitude and polyfunctionality of memory HIV-1-specific T-cell responses

Juan Garcia-Arriaza1, José Luis Nájera1, Carmen E. Gómez1, Nolawt Tewabe1, Carlos Oscar S. Sorzano1, Thierry Calandra1, Thierry Roger2, Mariano Esteban1

1 Department of Molecular and Cellular Biology, Centro Nacional de Biotecnología, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain; 2 Biocatalysis unit, Centro Nacional de Biotecnología, Consejo Superior de Investigaciones Científicas (CSIC), Madrid, Spain.

INTRODUCTION

The vaccinia virus (MVA) C6 protein has sequence similarities with the poxvirus family Pox_A46, involved in regulation of the immune response. C6 protein has been demonstrated to modulate the immune response to vaccine antigens. Here, we have characterized the C6 protein and its effects in virus replication, innate immune sensing and polyfunctionality in vitro. We analyzed the effects of the C6 protein in virus replication, innate immune sensing and polyfunctionality in vitro. We analyzed the effects of the C6 protein in virus replication, innate immune sensing and polyfunctionality in vitro.

RESULTS

Generation of MVA-B

MVA-B was generated by deleting vaccinia virus gene C6 using a deletion mutant. (A) The vaccinia virus (VACV) C6 protein has sequence similarities with the poxvirus family Pox_A46, involved in regulation of the immune response. C6 protein has been demonstrated to modulate the immune response to vaccine antigens. Here, we have characterized the C6 protein and its effects in virus replication, innate immune sensing and polyfunctionality in vitro. We analyzed the effects of the C6 protein in virus replication, innate immune sensing and polyfunctionality in vitro. We analyzed the effects of the C6 protein in virus replication, innate immune sensing and polyfunctionality in vitro. We analyzed the effects of the C6 protein in virus replication, innate immune sensing and polyfunctionality in vitro. We analyzed the effects of the C6 protein in virus replication, innate immune sensing and polyfunctionality in vitro.

Characterization of C6 expression and localization

Characterization of C6 expression and localization. (A) Flow cytometry analysis of Env, Gag and GPN HIV-1 specific CD4+ and CD8+ T-cells. CD44 and CD62L expression was used to identify central memory (CM: CD44hiCD62Llo), effector memory (EM: CD44hiCD62Lhi) and TEMRA (CD44hiCD62Llo) T-cells. The percentage of each subset was determined and the results are shown. (B) Flow cytometry analysis of IFN-γ and IL-2 production by CM and TEMRA T-cells. The percentage of IFN-γ+ and IL-2+ cells was determined and the results are shown. (C) Flow cytometry analysis of IFN-γ and IL-2 production by CM and TEMRA T-cells. The percentage of IFN-γ+ and IL-2+ cells was determined and the results are shown.

CONCLUSIONS

- MVA-B c6L deletion mutant was generated, contains deletion in C6L viral gene, and express HIV-1 antigens sgp120 and sgpGPN at the same level as their parental virus MVA-B. Deletion of C6L gene in the MVA-B c6L deletion mutant does not affect virus replication and infection, this gene is not essential for virus propagation in cultured cells.
- C6 is expressed early in cells infected with VACV vectors, and localizes to the cytoplasm of infected cells.
- MVA-B c6L up-regulated the expression of IFN-β and IFN-α-inducible genes (IFIT1 and IFIT2) in human THP-1 cells and moDCs.
- MVA-B c6L enhanced the magnitude and polyfunctionality of the HIV-1-specific T-cell memory immune responses.
- MVA-B c6L induced preferentially Env-specific responses.
- MVA-B c6L triggered higher levels of antibodies against HIV-1 Env.

These findings revealed that both vectors induced robust, polyfunctional and durable T-cell responses to HIV-1 antigens, but MVA-B c6L deletion mutant showed enhanced memory and quality of HIV-1 responses. Our observations are relevant in the improvement of MVA vectors as HIV-1 vaccines.