RECOMBINANT MODIFIED VACCINIA VIRUS ANKARA (MVA)

The present invention relates generally to a recombinant modified vaccinia virus Ankara (MVA) encoding at least one antigen or antigenic epitope, wherein expression of said antigen or antigenic epitope is regulated by a transcriptional control element comprising an early/late promoter driving expression of said antigen or antigenic epitope, a composition comprising the MVA, uses of the MVA and a kit comprising the MVA.

Background of the Invention

Live attenuated, replicating vaccines, rather than inactivated preparations, have provided the most effective protection against viral infection and disease. These vaccines elicit essentially life-long protective immunity. In contrast, immunity induced by inactivated or subunit vaccines is generally of more limited duration. A key factor in pursuit of the latter approaches is safety. An overview of replicating and non-replicating viral vectors for vaccine development is given in the publication of Marjorie Robert-Guroff, Replicating and Non-replicating Viral Vectors for Vaccine Development, Curr. Opin. Biotechnol. 18:546-556, 2007.

Recombinant viruses are widely used to express foreign antigens in infected cells. Specifically, recombinant poxviruses are currently tested as promising vaccines to induce an immune response against a foreign antigen expressed from the poxvirus vector. Most popular are avipoxviruses on the one side and vaccinia viruses (VACV) on the other side. US 5,736,368 and US 6,051,410 disclose recombinant vaccinia virus strain Wyeth which expresses HIV antigens and proteins. US 5,747,324 discloses a recombinant VACV strain NYCBH expressing lentivirus genes. EP 0 243 029 discloses a recombinant VACV strain Western Reserve expressing human retrovirus genes. For the expression of heterologous genes in poxviruses several promoters are known to the person skilled in the art, such as the 30K and 40K promoters (see, e.g., US 5,747,324), a strong synthetic early/late promoter (see, e.g., Sutter et al., A recombinant vector derived from the host range-restricted and highly attenuated MVA strain of vaccinia virus stimulates protective immunity in mice to influenza virus, Vaccine 12, 1032-40, 1994), the p7.5 promoter (see, e.g., Endo et al., Homotypic and heterotypic protection against influenza virus infection in mice by recombinant vaccinia virus expressing the haemagglutinin or nucleoprotein of influenza virus, J. Gen. Virol. 72,699-703, 1991) and the promoter derived from the

Summary of the invention

Aspects of the invention are defined in the independent claims. Some optional features of the invention are defined in the dependent claims.

The present disclosure also relates to a replication deficient recombinant virus encoding at least one antigen and/or antigenic epitope, wherein expression of said antigen and/or antigenic epitope is regulated by a transcriptional control element comprising at least two elements driving early expression of said antigen and/or antigenic epitope.

The disclosure further relates to said replication deficient recombinant virus for use as medicament or vaccine and its use for the preparation of a medicament or vaccine.

In another aspect the present disclosure relates to a pharmaceutical composition or vaccine comprising the replication deficient recombinant virus and, optionally, a pharmaceutically acceptable carrier, diluent, adjuvant and/or additive.

The disclosure also relates to said replication deficient recombinant virus or said pharmaceutical composition or vaccine for inducing a T cell response in a host to said at least one antigen and/or antigenic epitope.

In a further aspect it relates to the use of said replication deficient recombinant virus or said pharmaceutical composition or vaccine for the preparation of a medicament for inducing a T cell response in a host to said at least one antigen and/or antigenic epitope.

The disclosure also encompasses a kit comprising at least two vials for prime/boost immunization comprising said replication deficient recombinant virus for a first inoculation ("priming inoculation") in a first vial/container and for an at least second and/or third and/or further inoculation ("boosting inoculation") in a second and/or further vial/container.

The disclosure further relates to a method of inducing a T cell response, preferably a CD8 T cell response, in a host, including a human, said method comprising a least three or at least four administrations of the replication deficient recombinant virus to the host.

Also encompassed by the present disclosure is a promoter comprising at least 2 nucleotide sequence elements according to nt 48-81 of SEQ ID NO:1 and/or at least 2 nucleotide sequence elements having at least 80% identity to nt 48-81 of SEQ ID NO:1.

Detailed description of the invention

Aspects of the invention will now be described, by way of non-limiting example.

The present invention relates to a replication deficient recombinant virus encoding at least one antigen and/or antigenic epitope, wherein expression of said antigen and/or antigenic epitope is regulated by a transcriptional control element comprising at least two elements driving early expression of said antigen and/or antigenic epitope.

It was surprisingly found that with replication deficient recombinant viruses the expression of an antigen regulated by a transcriptional control element comprising at least two elements driving early expression occurred significantly earlier in the viral replication cycle and was also significantly higher at any given time point after infection than expression driven by a conventional transcriptional control element. Additionally, the advantage in strong early antigen expression even persists until at least 6 h after infection.

Accordingly, in a preferred embodiment of the present invention, the at least two elements drive immediate early expression of the antigen and/or antigenic epitope, i.e. within the first hour after infection, preferably within the first 30 minutes after infection.

The ability of a very early expressed antigen under control of the transcriptional control element according to the invention to outcompete vector-derived early antigens during recall responses was investigated by administering the replication deficient recombinant virus and subsequent determination of T cell responses. Immunization unexpectedly resulted in highly efficient antigen-specific T cell responses, in particular in CD8 T cell responses. Even more surprising, in some of the experiments, this approach was even able to reverse immunodominance hierarchy and convert a subdominant CD8 T cell epitope into the immunodominant epitope. This result could not be achieved with conventional transcriptional control elements even after four consecutive immunizations. Moreover, the antigen-specific CD8 T cell response after three or more immunization rounds with the viruses according to the present invention was stronger than with a transcriptional control element conventionally used.

Claims

1. A recombinant modified vaccinia virus Ankara (MVA) encoding at least one antigen or antigenic epitope, wherein expression of said antigen or antigenic epitope is regulated by a transcriptional control element comprising an early/late promoter driving expression of said antigen or antigenic epitope, and wherein the early/late promoter comprises at least one copy of a late promoter element and at least five copies of an early promoter element, wherein the recombinant MVA expresses in HeLa cells a level of the encoded antigen in the presence of 40 µg/ml AraC that is at least 50% of the level of the encoded antigen in the absence of AraC.

2. The MVA according to claim 1, wherein the MVA has the capability of reproductive replication in vitro in chicken embryo fibroblasts (CEF) cells, but no capability of reproductive replication in the human keratinocyte cell line HaCaT, the human embryo kidney cell line 293, the human bone osteosarcoma cell line 143B, and in the human cervix adenocarcinoma cell line HeLa.

3. The MVA according to claim 2, wherein the MVA is MVA-BN as deposited at the ECACC under number V00083008.

4. The MVA according to claim 1, wherein the early promoter element is sequence optimized.

5. The MVA according to claim 1, wherein the early/late promoter comprises a cowpox ATI late promoter element.

6. The MVA according to claim 1, wherein the early/late promoter comprises at least five copies of a p7.5 early promoter element.

7. The MVA according to claim 5, wherein the early/late promoter comprises at least five copies of a p7.5 early promoter element.

8. The MVA according to claim 1, wherein the early/late promoter comprises the nucleotide sequence of SEQ ID NO:1.

9. A composition comprising the MVA of claim 8 and a pharmaceutically acceptable carrier, diluent, adjuvant, or additive.

10. The MVA of claim 8 for use in therapy.

11. The MVA of claim 8 for use as a medicament.

12. Use of the MVA of claim 8 in the manufacture of a medicament for inducing a T cell response in a host to at least one antigen or antigenic epitope.

13. The use of claim 12, wherein said T cell response is a CD8 T cell response.

14. The use of claim 12, comprising homologous prime/boost administrations of MVA.

15. The use of claim 14, wherein the medicament is to be administered in at least three administrations.

16. The use of claim 14, wherein the medicament is to be administered in at least four administrations.

17. A kit comprising at least two vials/containers, each comprising the MVA of claim 8, wherein the first vial/container is for a first or priming inoculation and the second vial/container is for a further or boosting inoculation.

18. The MVA according to claim 1, wherein the recombinant MVA expresses in HeLa cells a level of the encoded antigen in the presence of 40 µg/ml AraC that is at least 75% of the level of the encoded antigen in the absence of AraC.

19. The MVA according to claim 1, wherein the recombinant MVA expresses in HeLa cells a level of the encoded antigen in the presence of 40 µg/ml AraC that is higher than the level of the encoded antigen in the absence of AraC.