MODULATORS OF MYC, METHODS OF USING THE SAME, AND METHODS OF INDENTIFIYING AGENTS THAT MODULATE MYC

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/092,708, filed 28-August-2008, which application is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] There are multiple types of vaccines: vaccines containing dead microorganisms (e.g. the influenza and cholera vaccines); vaccines containing attenuated microorganisms (e.g. the MMR vaccine); vaccines containing toxoids (e.g. the DPT vaccine); vaccines containing subunits of the pathogen (e.g. the HPV vaccine); and nucleic acid (e.g. RNA and DNA) vaccines (e.g. avian flu vaccine, West Nile Virus vaccine, and multiple cancer vaccines). Vaccine adjuvants are agents that stimulate the immune system and increase the response of the immune system to a vaccine.

SUMMARY

[0003] There is a need for vaccine adjuvants that enhance an immunological response to an antigen. The inventors have discovered that increasing the expression of MYC or the activity of a MYC peptide enhances immunological responses to antigens. In order to increase MYC concentrations in the nucleus of cells with minimal side-effects, the inventors have designed a fusion peptide that can penetrate the nucleus of cells. This peptide can be administered topically to decrease systemic effects. This peptide also increases the viability of leukocytes, including T-cells, and B-cells. Further, the inventors have designed several assays for identifying other agents that meet this unmet need.

[0004] There is also a need for methods of treating autoimmune disorders. The inventors have discovered that decreasing the expression of MYC or the activity of a MYC peptide treats auto-immune disorders. In order to fulfill this unmet need, the inventors have designed several assays for identifying agents that inhibit (partially or fully) the activity of an immune system. In certain instances, the agents that inhibit the immune system decrease the viability of leukocytes or increase the proportion of anergic B-cells.

[0005] Disclosed hereon, in certain embodiments, is a peptide that up-regulates the expression of a MYC gene, the activity of a Myc polypeptide, or a combination thereof, comprising: (a) a transporter peptide sequence; (b) a MYC sequence; and optionally (c) one or more molecules that link the transporter peptide sequence and the MYC sequence. In some embodiments, the peptide has Formula (I):

transporter peptide sequence -MYC sequence.

In some embodiments, the peptide has Formula (II):

transporter peptide sequence-X-MYC sequence,

rubella; diphtheria; pertussis; tetanus; influenza; varicella zoster virus; rotavirus; meningococcal; pneumonia; smallpox; cholera; bubonic plague; yellow fever; tuberculosis; human papillomavirus; or combinations thereof. In some embodiments, the composition further comprises an antigenic moiety derived from a pathogen selected from: hepatitis A ; hepatitis B ; polio ; measles ; mumps ; rubella ; diphtheria ; pertussis ; tetanus ; influenza ; varicella zoster virus ; rotavirus ; meningococcal ; pneumonia ; smallpox ; cholera ; bubonic plague; yellow fever ; tuberculosis ; human papillomavirus; or combinations thereof. In some embodiments, the composition further comprises an antigenic moiety derived from a neoplastic cell. In some embodiments, the composition is formulated for topical administration.

[0006a] In one aspect, there is provided use of a pharmaceutical composition for the manufacture of a medicament for increasing one or more of activation, survival, or proliferation of one or more immune cells, wherein the pharmaceutical composition comprises:

(a) an antigenic moiety;

(b) a fusion peptide comprising:

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence; and optionally

(iii) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(c) a pharmacologically-acceptable excipient.

[0006b] In one aspect, there is provided a method, comprising:

(a) providing a composition to one or more immune cells in vitro, wherein the composition comprises:

(a) an antigenic moiety; and

(b) a fusion peptide comprising:

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence; and optionally

(iii) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(b) culturing the one or more immune cells under conditions sufficient for the composition to increase one or more of activation, survival, or proliferation of the one or more immune cells, as compared with corresponding immune cells not exposed to the composition.

[0006c] In one aspect, there is provided use of a composition for the manufacture of a medicament for increasing one or more of activation, survival, or proliferation of one or more immune cells, wherein the composition comprises:

(a) a fusion peptide having the following sequence:

MRKKRRQRRRMDFFRVVENQQPPATMPLNVSFTNRNYDLDYDSVQPYFYCDEEENF
YQQQQQSELQPPAPSEDIWKKFELLPTPPLSPSRRSGLCSPSYVAVTPFSLRGDNDGG
GGSFSTADQLEMVTELLGGDMVNQSFICDPDDETFIKNIIIQDCMWSGFSAAAKLVSE
KLASYQAARKDSGSPNPARGHSVCSTSSLYLQDLSAAASECIDPSVVFPYPLNDSSSP
KSCASQDSSAFSPSSDSLLSSTESSPQGSPEPLVLHEETPPTTSSDSEEEQEDEEEIDVVS
VEKRQAPGKRSESGSPSAGGHSKPPHSPLVLKRCHVSTHQHNYAAPPSTRKDYPAAK
RVKLDSVRVLRQISNNRKCTSPRSSDTEENVKRRTHNVLERQRRNELKRSFFALRDQI
PELENNEKAPKVVILKKATAYILSVQAEEQKLISEEDLLRKRREQLKHKLEQLRKGEL
NSKLEGKPIPNPLLGLDSTRTGHHHHHH; and

(b) a pharmacologically-acceptable excipient.

[0006d] In one aspect, there is provided use of a composition for the manufacture of a medicament for increasing one or more of activation, survival, or proliferation of one or more immune cells, wherein the composition comprises:

(a) a fusion peptide comprising:

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence;

(iii) at least two protein tags; and, optionally,

(iv) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(b) a pharmacologically-acceptable excipient.

[0006e] In one aspect, there is provided a method, comprising:

(a) providing a fusion peptide to one or more immune cells in vitro, wherein the fusion peptide comprises

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence;

(iii) at least two protein tags; and, optionally,

(iv) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(b) culturing the one or more immune cells under conditions sufficient for the fusion peptide to increase one or more of activation, survival, or proliferation of the one or more immune cells, as compared with corresponding immune cells not exposed to the fusion peptide.

[0007] Disclosed herein, in certain embodiments, is a method of inducing an immune response, comprising administering to an individual in need thereof: (a) a vaccine against at least one antigen, and (b) a fusion peptide comprising: (a) a transporter peptide sequence; (b) a MYC sequence; and optionally (c) one or more molecules that link the transporter peptide sequence and the MYC sequence. In some embodiments, the peptide has Formula (I):

transporter peptide sequence -MYC sequence.

In some embodiments, the peptide has Formula (II):

transporter peptide sequence-X-MYC sequence,

wherein -X- is a molecule that links the transporter peptide sequence and the MYC sequence. In some embodiments, the peptide has Formula (II):

transporter peptide sequence-X-MYC sequence,

wherein in X is at least one amino acid. In some embodiments, the peptide has the following amino acid sequence:

MRKKRRQRRRMDFFRVVENQQPPATMPLNVSFTNRNYDLDYDSVQPYFYCDEEENFYQQQQQSEL
QPPAPSEDIWKKFELLPTPPLSPSRRSGLCSPSYVAVTPFSLRGDNDGGGGSFSTADQLEMVTELLGG
DMVNQSFICDPDDETFIKNIIIQDCMWSGFSAAAKLVSEKLASYQAARKDSGSPNPARGHSVCSTSSL
YLQDLSAAASECIDPSVVFPYPLNDSSSPKSCASQDSSAFSPSSDSLLSSTESSPQGSPEPLVLHEETPPT
TSSDSEEEQEDEEEIDVVSVEKRQAPGKRSESGSPSAGGHSKPPHSPLVLKRCHVSTHQHNYAAPPST
RKDYPAAKRVKLDSVRVLRQISNNRKCTSPRSSDTEENVKRRTHNVLERQRRNELKRSFFALRDQIP
ELENNEKAPKVVILKKATAYILSVQAEEQKLISEEDLLRKRREQLKHKLEQLRKGELNSKLEGKPIPN
PLLGLDSTRTGHHHHHH. In some embodiments, the vaccine is selected from the group consisting of: hepatitis A vaccine; hepatitis B vaccine; polio vaccine; measles vaccine; mumps vaccine; rubella vaccine; diphtheria vaccine; pertussis vaccine; tetanus vaccine; influenza vaccine; varicella zoster virus vaccine; rotavirus vaccine; meningococcal vaccine; pneumonia vaccine; smallpox vaccine; cholera vaccine; bubonic plague vaccine; yellow fever vaccine; tuberculosis vaccine; human paplomavirus vaccine; a cancer vaccine; or combinations thereof. In some embodiments, the vaccine is administered before, after, or simultaneously with the agent that increases the nucleic concentration of a Myc polypeptide.

CLAIMS:

1. Use of a pharmaceutical composition for the manufacture of a medicament for increasing one or more of activation, survival, or proliferation of one or more immune cells, wherein the pharmaceutical composition comprises:

(a) an antigenic moiety;

(b) a fusion peptide comprising:

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence; and optionally

(iii) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(c) a pharmacologically-acceptable excipient.

2. The use of claim 1, wherein the fusion peptide has Formula (I):

transporter peptide sequence -MYC polypeptide sequence.

3. The use of claim 1, wherein the fusion peptide has Formula (II):

transporter peptide sequence-X-MYC polypeptide sequence,

wherein -X- is the one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence.

4. The use of claim 1, wherein the fusion peptide has Formula (II):

transporter peptide sequence-X-MYC polypeptide sequence,

wherein -X- is at least one amino acid that links the transporter peptide sequence and the MYC polypeptide sequence.

5. The use of claim 1, wherein the fusion peptide has the following sequence:

MRKKRRQRRRMDFFRVVENQQPPATMPLNVSFTNRNYDLDYDSVQPYFYCDEEENF
YQQQQQSELQPPAPSEDIWKKFELLPTPPLSPSRRSGLCSPSYVAVTPFSLRGDNDGG
GGSFSTADQLEMVTELLGGDMVNQSFICDPDDETFIKNIIIQDCMWSGFSAAAKLVSE
KLASYQAARKDSGSPNPARGHSVCSTSSLYLQDLSAAASECIDPSVVFPYPLNDSSSP
KSCASQDSSAFSPSSDSLLSSTESSPQGSPEPLVLHEETPPTTSSDSEEEQEDEEEIDVVS
VEKRQAPGKRSESGSPSAGGHSKPPHSPLVLKRCHVSTHQHNYAAPPSTRKDYPAAK
RVKLDSVRVLRQISNNRKCTSPRSSDTEENVKRRTHNVLERQRRNELKRSFFALRDQI

PELENNEKAPKVVILKKATAYILSVQAEEQKLISEEDLLRKRREQLKHKLEQLRKGEL
NSKLEGKPIPNPLLGLDSTRTGHHHHHH.

6. The use according to any of claims 1-5, wherein the antigenic moiety is a peptide, a nucleic acid sequence, or a polysaccharide; or derived from a neoplastic cell, a pathogen, or a toxoid; or a combination thereof.

7. The use according to any of claims 1-5, wherein the antigenic moiety is derived from a pathogen selected from: hepatitis A; hepatitis B; polio; measles; mumps; rubella; diphtheria; pertussis; tetanus; influenza; varicella zoster virus; rotavirus; meningococcal; pneumonia; smallpox; cholera; bubonic plague; yellow fever; tuberculosis; human papillomavirus; and combinations thereof.

8. Use of a composition for the manufacture of a medicament for increasing one or more of activation, survival, or proliferation of one or more immune cells, wherein the composition comprises:

(a) a fusion peptide having the following sequence:
MRKKRRQRRRMDFFRVVENQQPPATMPLNVSFTNRNYDLDYDSVQPYFYCDEEENF
YQQQQQSELQPPAPSEDIWKKFELLPTPPLSPSRRSGLCSPSYVAVTPFSLRGDNDGG
GGSFSTADQLEMVTELLGGDMVNQSFICDPDDETFIKNIIIQDCMWSGFSAAAKLVSE
KLASYQAARKDSGSPNPARGHSVCSTSSLYLQDLSAAASECIDPSVVFPYPLNDSSSP
KSCASQDSSAFSPSSDSLLSSTESSPQGSPEPLVLHEETPPTTSSDSEEEQEDEEEIDVVS
VEKRQAPGKRSESGSPSAGGHSKPPHSPLVLKRCHVSTHQHNYAAPPSTRKDYPAAK
RVKLDSVRVLRQISNNRKCTSPRSSDTEENVKRRTHNVLERQRRNELKRSFFALRDQI
PELENNEKAPKVVILKKATAYILSVQAEEQKLISEEDLLRKRREQLKHKLEQLRKGEL
NSKLEGKPIPNPLLGLDSTRTGHHHHHH; and

(b) a pharmacologically-acceptable excipient.

9. Use of a composition for the manufacture of a medicament for increasing one or more of activation, survival, or proliferation of one or more immune cells, wherein the composition comprises:

(a) a fusion peptide comprising:

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence;

(iii) at least two protein tags; and, optionally,

(iv) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(b) a pharmacologically-acceptable excipient.

10. The use of claim 9, wherein the two protein tags comprise one or more of a polyhistidine tag or an epitope tag.

11. The use of claim 9, wherein the two protein tags are a 6-histidine tag and a V5 epitope tag.

12. The use of claim 11, wherein the V5 epitope tag is GKPIPNPLLGLDST or IPNPLLGLD.

13. The use according to any of claims 1-12, formulated for topical administration, for oral administration, parenteral administration, intranasal administration, buccal administration, rectal administration, transdermal, intra-muscular, or intravenous administration.

14. The use according to any of claims 1-12, formulated as an aqueous liquid dispersion, a liquid, a gel, a syrup, an elixir, a slurry, a suspension, a self-emulsifying dispersion, a solid solution, a liposomal dispersion, an aerosol, a solid dosage form, a powder, an immediate release formulation, a controlled release formulation, a fast melt formulation, an effervescent formulation, a lyophilized formulation, a tablet, a powder, a pill, a dragee, a capsule, a delayed release formulation, an extended release formulation, a pulsatile release formulation, a multiparticulate formulation, or a mixed immediate and controlled release formulation.

15. The use of according to any one of claims 1-14, wherein the one or more immune cells comprise one or more anergic immune cells.

16. The use according to any one of claims 1-15, wherein the one or more immune cells are T-cells or B-cells.

17. A method, comprising:

(a) providing a fusion peptide to one or more immune cells in vitro, wherein the fusion peptide comprises

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence;

(iii) at least two protein tags; and, optionally,

(iv) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(b) culturing the one or more immune cells under conditions sufficient for the fusion peptide to increase one or more of activation, survival, or proliferation of the one or more immune cells, as compared with corresponding immune cells not exposed to the fusion peptide.

18. The method of claim 17, wherein the one or more immune cells are one or more factor-dependent, antigen-activated immune cells, and wherein the fusion protein is provided in the absence a cytokine.

19. A method, comprising:

(a) providing a composition to one or more immune cells in vitro, wherein the composition comprises:

(a) an antigenic moiety; and

(b) a fusion peptide comprising:

(i) a transporter peptide sequence;

(ii) a MYC polypeptide sequence; and optionally

(iii) one or more molecules that link the transporter peptide sequence and the MYC polypeptide sequence; and

(b) culturing the one or more immune cells under conditions sufficient for the composition to increase one or more of activation, survival, or proliferation of the one or more immune cells, as compared with corresponding immune cells not exposed to the composition.

20. The method of claim 19, wherein the one or more immune cells are one or more factor-dependent, antigen-activated immune cells and the composition is provided in the absence a cytokine.

21. The method according to any of claims 17-20, wherein the one or more immune cells comprise T-cells.

22. The method according to any one of claims 17-20, wherein the one or more immune cells comprise B-cells.