model of MS. By varying the genetic background and immunization protocol, EAE can reproduce the symptoms of the major forms of human MS.

[00010] There are two major classes of anti-inflammatory drugs, chemicals and biologicals. The first class includes such well-known drugs as aspirin, glucocorticoids, non-steroidal anti-inflammatory agents (celecoxib) and other agents (e.g., methotrexate, cyclosporine, rapamycin etc.). The second class includes agents that reduce activity of specific cytokines or their receptors, e.g., antibodies to TNF (see scheme below). Despite a variety of drugs, there is no treatment to cure chronic inflammation. In many instances existing drugs are not quite effective, very expensive and have numerous side effects. For instance, major drawbacks of anti-cytokine therapy is a decreased host immune defense against infection and expense.

[00011] p62 is a multifunctional protein that binds ubiquitin and regulates autophagy, activity of the nuclear factor kappa-B and some other signaling pathways. The protein functions as a scaffolding/adaptor protein in concert with TNF receptor-associated factor 6 (TRF6) to mediate activation of NF-kappa-B in response to upstream signals. Alternatively spliced transcript variants encoding either the same or different isoforms have been identified for this gene.

[00012] p62 was identified as 62-kDa protein that binds the src homology 2 (SH2) domain of tyrosine kinase Lckp56 in a phosphotyrosine-independent manner (Moscat et al. 2007. Signal integration and diversification through the p62 scaffold protein. Trends Biochem Sci 32:95-100). The primary sequence of p62 is known, and p62 was shown to bind ubiquitin.(Moscat et al. 2007. Signal integration and diversification through the p62 scaffold protein. Trends Biochem Sci 32:95-100). FIG. 1 shows the nucleic acid sequence of the cDNA and FIG. 2 the amino acid sequence.

SUMMARY OF THE INVENTION

[00013] Provided herein are methods to modulate the expression of a proinflammatory cytokine in a subject by administering to the subject an agent that includes: (a) at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof; or, (b) a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof. The proinflammatory cytokine can be TNFα, IL-6, IL-1b, RANTES, IL-17, IL-23, CCL-1, MCP-5, or CXCL2.

[00013a] Provided herein is the use of an agent comprising:

a. at least 30 consecutive amino acids of a p62/SQSTM1 polypeptide;

b. a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 consecutive amino acids of a p62/SQSTM1 polypeptide;

c. a p62/SQSTM1 polypeptide at least 90% identical to SEQ ID NO. 2;

d. a p62/SQSTM1 polypeptide with at least one or more domain deletions;

e. a p62/SQSTM1 nucleic acid that encodes a polypeptide at least 90% identical to SEQ ID NO: 2; or

f. a p62/SQSTM1 nucleic acid that encodes a polypeptide with at least one or more domain deletions;

in the manufacture of a medicament for treating, alleviating, ameliorating, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms of a non-cancer-related chronic inflammatory disease in a subject.

[00014] Also provided herein are methods to modulate the expression of an osteogenic transcription factor in a subject by administering to the subject an agent that includes: (a) at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof; or, (b) a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30

Claims

What is claimed is:

1. A method to modulate the expression of a proinflammatory cytokine in a subject comprising administering to said subject an agent comprising:
   a. at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof; or,
   b. a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof.
2. The method according to claim 1, wherein said proinflammatory cytokine is selected from the group consisting of: TNFα, IL-6, IL-1b, RANTES, IL-17, IL-23, CCL-1, MCP-5, and CXCL2.
3. A method to modulate the expression of an osteogenic transcription factor in a subject comprising administering to said subject an agent comprising:
   a. at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof; or,
   b. a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof.
4. The method according to claim 3, wherein said osteogenic transcription factor is selected from the group of osterix and runx2.
5. A method to modulate the expression of bone resorptive factors in a subject comprising administering to said subject an agent comprising:
   a. at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof; or,
   b. a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof.
6. The method according to claim 5, wherein said bone resorptive factor is selected from the group of TNFα and RANKL.
7. A method to modulate the expression of endogenous p62/SQSTM1 in a subject comprising administering to said subject an agent comprising:
   a. at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof; or,
   b. a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof.
8. A method to treat, alleviate, ameliorate, relieve, delay onset of, inhibit progression of, reduce severity of, or reduce incidence of one or more symptoms of a non-cancer-related chronic inflammatory disease in a subject comprising administering to said subject an agent comprising:

a. at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof; or,
b. a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 amino acids of a p62/SQSTM1 polypeptide or a variant thereof.

9. The method according to any of claims 1-8, wherein said variant is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% homologous to SEQ. ID. NO. 2.

10. The method according to any of claims 1-8, wherein said variant is at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence homology to SEQ. ID. NO. 2.

11. The method according to any claim 1-8, wherein said p62-encoding nucleic acid comprises the sequence of SEQ ID NO:1

12. The method according to any claim 1-8, wherein said p62 polypeptide or variant thereof has at least one domain deletion.

13. The method according to claim 12, wherein said domain deletion is selected from the group consisting of: PB1, ZZ, NLS2, TB, NLS1, NES, LIR, KIR, and UBA.

14. The method according to any of claims 1-8, wherein said agent comprises a p62 encoding nucleic acid, wherein said p62 encoding nucleic acid encodes a polypeptide, which is at least 95% identical to SEQ ID NO. 2, and wherein said p62 encoding nucleic acid further comprises a plasmid, RNA or a viral vector.

15. The method according to any of claims 1-14, wherein said p62/SQSTM1 polypeptide or p62/SQSTM1 encoding nucleic acid further comprises a fusion polypeptide or nucleic acid encoding for a fusion polypeptide, respectively.

16. The method according to any of claims 1-14, wherein said p62/SQSTM1 polypeptide or p62/SQSTM1 encoding nucleic acid comprises a vaccine and further comprising administering an adjuvant to said subject.

17. The method according to claim 17, wherein said adjuvant is selected from the group consisting of: gel-type, microbial, particulate, oil-emulsion, surfactant-based, and synthetic adjuvant.

18. The method according to claim 8, wherein said non-cancer chronic inflammatory disease is selected from the group consisting of: obesity, metabolic syndrome, type 2 diabetes, fat liver, Crohn's Disease, pancreatitis, asthma, chronic obstructive pulmonary disease, arthritis, osteoporosis, osteoarthritis, multiple sclerosis, psoriasis, congestive heart failure, atherosclerosis, neurodegenerative disease, depression, schizophrenia, gout, asbestosis, and silicosis.

19. The method according to claim 18, wherein said neurodegenerative disease is selected from the group consisting of: amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, and Alzheimer's disease.

20. The method according to any of claims 1-8, further comprising administering an anti-inflammatory therapy to said subject.

21. The method according to any of claims 1-8, wherein said subject is selected from the group consisting of: a subject diagnosed with an inflammatory disease, a subject previously treated for an inflammatory disease, a subject with a family history of inflammatory disease, and a subject predisposed to an inflammatory disease.

22. The method according to any of claims 1-8, wherein said agent is a p62 encoding nucleic acid, and further comprising a strategy for improving the efficiency of nucleic acid-based expression of p62 in subjects.

23. The method of claim 22 wherein said strategy is selected from the group consisting of: including a self-replicating viral replicon, codon optimization, in vivo electroporation, incorporation of a CpG stimulatory motif, including a sequence for targeting of the endocytic or ubiquitin-processing pathways, including a Marek's disease virus type 1 VP22 sequence, a prime-boost regimen, a mucosal delivery vector, and a nucleic acid delivery system.

24. The method of claim 23, wherein said nucleic acid delivery system is selected from the group consisting of: a polymer gene delivery system, a liposomal delivery system, and a cell-penetrating peptide gene delivery system.

25. The method according to any of claims 1-8, further comprising administering an anti-inflammatory chemotherapeutic or biological agent.

26. The method according to claim 25, wherein said chemotherapeutic agent is selected from the group consisting of: a nonsteroidal anti-inflammatory drug, a glucocorticoid, methotrexate, cyclosporine, and rapamycin.

27. The method of claim 26 wherein said anti-inflammatory biological agent is selected from the group consisting of: an anti-TNF antibody, an anti-IL1 antibody, an anti-IL6 antibody, an anti-IL6 receptor antibody, an anti-IL12/23 antibody, an anti-IL17 antibody, an anti-IL1R antibody, an anti-IL1 receptor antagonist, and a soluble IL-1 receptor.

CLAIMS

What is claimed is:

1. Use of an agent comprising:

   a. at least 30 consecutive amino acids of a p62/SQSTM1 polypeptide;

   b. a p62/SQSTM1 encoding nucleic acid, wherein said p62/SQSTM1 encoding nucleic acid encodes at least 30 consecutive amino acids of a p62/SQSTM1 polypeptide;

   c. a p62/SQSTM1 polypeptide at least 90% identical to SEQ ID NO. 2;

   d. a p62/SQSTM1 polypeptide with at least one or more domain deletions;

   e. a p62/SQSTM1 nucleic acid that encodes a polypeptide at least 90% identical to SEQ ID NO: 2; or

   f. a p62/SQSTM1 nucleic acid that encodes a polypeptide with at least one or more domain deletions;

in the manufacture of a medicament for treating, alleviating, ameliorating, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms of a non-cancer-related chronic inflammatory disease in a subject.

2. The use of claim 1, wherein said agent is to be administered with an adjuvant and/or one or more co-stimulatory components and/or one or more molecules that block suppressive or negative regulatory immune mechanisms.

3. The use of claim 2, wherein said adjuvant is selected from the group consisting of: gel-type, microbial, particulate, oil-emulsion, surfactant-based, and synthetic adjuvants; and/or, wherein said one or more co-stimulatory components is selected from the group consisting of cell surface proteins, cytokines, chemokines, and signaling molecules; and/or wherein said one or more molecules that block suppressive or negative regulatory immune mechanisms is selected from the group consisting of: anti-CTLA-4 antibody, anti-CD25 antibody, anti-CD4 antibody, and the fusion protein IL13Ra2-Fc.

4. The use of any one of claims 1-3, wherein said agent is to be administered with one or more anti-inflammatory therapies.

5. The use of claim 4 wherein said one or more anti-inflammatory therapies is selected from the group consisting of: anti-inflammatory chemotherapeutic agent and biological agent.

6. The use of claim 5 wherein said anti-inflammatory chemotherapeutic agent is selected from the group consisting of: a nonsteroidal anti-inflammatory drug, a glucocorticoid, methotrexate, cyclosporine, and rapamycin.

7. The use of claim 5 wherein said biological agent is selected from the group consisting of: an anti-TNF antibody, an anti-I L1 antibody, an anti-IL6 antibody, an anti-I L6 receptor antibody, an anti-I L12/23 antibody, an anti-I L17 antibody, an anti-I L1 R antibody, an anti-I L1 receptor antagonist, and a soluble IL-1 receptor.

8. The use of any one of claims 1-7, wherein said agent modulates the expression of a proinflammatory cytokine in a subject.

9. The use of claim 8, wherein said proinflammatory cytokine is selected from the group consisting of: TNF-alpha, IL-6, IL-1 beta, RANTES, IL-17, IL-23, CCL-1 , MCP- 5, and CXCL2.

10. The use of any one of claims 1-7, wherein said agent modulates the expression of an osteogenic transcription factor in a subject.

11. The use of claim 10, wherein said osteogenic transcription factor is selected from the group consisting of: osterix and runx2.

12. The use of any one of claims 1-7, wherein said agent modulates the expression of a bone resorptive factor.

13. The use of claim 12, wherein said bone resorptive factor is selected from the group consisting of: TNF-alpha and RANKL.

14. The use of any one of claims 1-13, wherein said non-cancer-related chronic inflammatory disease is selected from the group consisting of: obesity, metabolic syndrome,

type 2 diabetes, fat liver, Crohn's Disease, pancreatitis, asthma, chronic obstructive pulmonary disease, arthritis, osteoporosis, osteoarthritis, multiple sclerosis, psoriasis, congestive heart failure, atherosclerosis, neurodegenerative disease, depression, schizophrenia, gout, asbestosis, and silicosis.

15. The use of claim 14, wherein said neurodegenerative disease is selected from the group consisting of: amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, and Alzheimer's disease.