

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 (TRAF6) 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 TNF α , IL-6, IL-1b, RANTES, IL-17, IL-23, CCL-1, MCP-5, or CXCL2.

[00013a] In one aspect, there is provided a use of an agent comprising a p62/SQSTM1 nucleic acid that encodes a polypeptide at least 90% identical to SEQ ID NO: 2 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, wherein said agent suppresses

the expression of a proinflammatory cytokine in a subject and 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, multiple sclerosis, psoriasis, congestive heart failure, atherosclerosis, neurodegenerative disease, depression, schizophrenia, gout, asbestosis, and silicosis.

[00013b] In one aspect, there is provided a use of an agent comprising a p62/SQSTM1 nucleic acid that encodes a polypeptide at least 90% identical to SEQ ID NO: 2 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, wherein said agent suppresses the expression of a proinflammatory cytokine in a subject and said non-cancer-related chronic inflammatory disease is selected from the group consisting of: osteoporosis and osteoarthritis.

[00013c] 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. Use of an agent comprising a p62/SQSTM1 nucleic acid that encodes a polypeptide at least 90% identical to SEQ ID NO: 2 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, wherein said agent suppresses the expression of a proinflammatory cytokine in a subject and 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, multiple sclerosis, psoriasis, congestive heart failure, atherosclerosis, neurodegenerative disease, depression, schizophrenia, gout, asbestosis, and silicosis.
2. The use of claim 1, wherein said agent is to be administered with one or more anti-inflammatory therapies.
3. The use of claim 2, wherein said one or more anti-inflammatory therapies is selected from the group consisting of: anti-inflammatory chemotherapeutic agent and biological agent.
4. The use of claim 3, wherein said anti-inflammatory chemotherapeutic agent is selected from the group consisting of: a nonsteroidal anti-inflammatory drug, a glucocorticoid, methotrexate, cyclosporine, and rapamycin.
5. The use of claim 3, 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.
6. The use of claim 1, 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.
7. The use of claim 1, wherein said neurodegenerative disease is selected from the group consisting of: amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, and Alzheimer's disease.
8. Use of an agent comprising a p62/SQSTM1 nucleic acid that encodes a polypeptide at least 90% identical to SEQ ID NO: 2 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, wherein said agent suppresses the expression of a proinflammatory cytokine in a subject and said non-cancer-related chronic inflammatory disease is selected from the group consisting of: osteoporosis and osteoarthritis.
9. The use of claim 8, wherein said agent is to be administered with one or more anti-inflammatory therapies.

10. The use of claim 9, wherein said one or more anti-inflammatory therapies is selected from the group consisting of: anti-inflammatory chemotherapeutic agent and biological agent.
11. The use of claim 10, wherein said anti-inflammatory chemotherapeutic agent is selected from the group consisting of: a nonsteroidal anti-inflammatory drug, a glucocorticoid, methotrexate, cyclosporine, and rapamycin.
12. The use of claim 10, 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.
13. 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.
14. The use of claim 8, wherein said agent modulates the expression of an osteogenic transcription factor in a subject.
15. The use of claim 14, wherein said osteogenic transcription factor is selected from the group consisting of: osterix and runx2.
16. The use of claim 8, wherein said agent modulates the expression of a bone resorptive factor.
17. The use of claim 16, wherein said bone resorptive factor is selected from the group consisting of: TNF-alpha and RANKL.