[Patent Document 6] WO2004/004763

[Non-patent Documents]

[Non-patent Document 1] Bustin *et al.*, Mol Cell Biol, 19: 5237-5246, 1999
[Non-patent Document 2] Hori *et al.*, J. Biol. Chem., 270, 25752-25761, 1995
[Non-patent Document 3] Wang *et al.*, Science, 285: 248-251, 1999
[Non-patent Document 4] Muller *et al.*, EMBO J, 20: 4337-4340, 2001
[Non-patent Document 5] Wang *et al.*, Science, 285: 248-251, 1999
[Non-patent Document 6] Germani *et al.*, J Leukoc Biol., 81(1): 41-5, 2007
[Non-patent Document 7] Palumbo *et al.*, J. Cell Biol., 164: 441-449, 2004
[Non-patent Document 8] Merenmies *et al.*, J. Biol. Chem., 266: 16722-16729, 1991
[Non-patent Document 9] Wu Y *et al.*, Stem cells, 25: 2648-2659, 2007
[Non-patent Document 10] Tamai *et al.*, Proc Natl Acad Sci U S A., 108(16): 6609-6614, 2011
[Non-patent Document 11] Yang *et al.*, J Leukoc Biol., 81(1): 59-66, 2007
[Non-patent Document 12] Basso *et al.*, J Neurotrauma., 23(5): 635-659, 2006
[Non-patent Document 13] Rahimi-Movaghar *et al.*, Int J Neurosci., 118(10): 1359-1373, 2008
[Non-patent Document 14] Quertainmont R *et al.*, PloS One., 7(6):e39500, 2012

Summary ~~of the Invention~~

[Problems to be Solved by the ~~Invention~~disclosure]

Spinal cord injury is a disease where patients experience extreme loss of quality of life such as difficulty in walking due to paralysis of the lower half of the body. However, spontaneous recovery cannot be expected and effective treatment methods have not been established. As described above, currently, there are expectations in applying regenerative medicine such as cell therapy to treatment of spinal cord injury, but it is still in the process of development. Furthermore, even if it is put to practical use, the problem of large medical expense has not yet been solved.

However, if healing of spinal cord injury can be promoted by administering a pharmaceutical having an activity of mobilizing bone marrow mesenchymal stem cells to the damaged site, it is expected that inexpensive and safe therapeutic methods can be provided to patients with spinal cord injury for which effective methods of treatment hardly exist at present.

[Means for Solving the Problems]

So far, the present inventors have revealed that High Mobility Group Box 1 (HMGB1) is a protein that has an activity of stimulating the migration of mesenchymal stem cells in the bone marrow and mobilizing the cells into blood. HMGB1 is primarily known to be a major

component of a non-histone nuclear protein, and has two DNA-binding domains, Box A and Box B, in the molecule. Furthermore, a known function of HMGB1 in the nucleus is to relax the nucleosome structure and to form a structure optimal for transcription reaction. However, in recent years, it has become clear that the nuclear protein HMGB1 is secreted to the outside of cells to exert various activities, even though it does not have a secretion signal. Research on its function as a mediator of inflammation is most advanced. For example, in a mouse sepsis model (LPS administration model), HMGB1 secreted from macrophages due to TNFα stimulation was found to be a mediator of sepsis (Wang *et al.*: Science 1999; 285: 248-251), and TLR4 is known to be a candidate receptor. Furthermore, the most well-known HMGB1 receptor is RAGE, and binding between this receptor and HMGB1 has been reported to influence migration activity of cells and inflammatory signal transduction.

The present ~~invention~~ disclosure discloses novel therapeutic pharmaceutical compositions for injury of the spinal cord which comprises an HMGB1 fragment, and uses thereof.

Specifically, the present inventors produced a peptide consisting of the amino acids at positions 1 to 44 of the HMGB1 protein (SEQ ID NO: 5), and an HMGB1 fragment consisting of the amino acids at positions 11 to 44 (SEQ ID NO: 4) by peptide synthesis. Each of the produced HMGB1 fragments was administered to disease model mice that enable evaluation of therapeutic effects on injury of the spinal cord, and therapeutic effects of the fragments on injury of the spinal cord were confirmed.

Based on these findings, the present application provides the following ~~invention~~disclosure:

[1] a pharmaceutical composition for use in the treatment of injury of the spinal cord, which comprises a HMGB1 fragment peptide;

[2] the pharmaceutical composition of [1], wherein the HMGB1 fragment peptide is a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5;

[3] the pharmaceutical composition of [1], wherein the HMGB1 fragment peptide is a peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5;

[4] a method for treating injury of the spinal cord, comprising the step of administering an HMGB1 fragment peptide;

[5] the method of [4], wherein the HMGB1 fragment peptide is a peptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5;

[6] the method of [4], wherein the HMGB1 fragment peptide is a peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5;

In one aspect, there is provided a pharmaceutical composition for use in the treatment of injury of the spinal cord, which comprises a HMGB1 fragment peptide.

In another aspect, there is provided the use of a pharmaceutical composition comprising a HMGB1 fragment peptide in the manufacture of a medicament for the treatment of injury of the spinal cord.

CLAIMS

1. A pharmaceutical composition for use in the treatment of injury of the spinal cord, which comprises a HMGB1 fragment peptide.

2. The pharmaceutical composition of claim 1, wherein the HMGB1 fragment peptide is a peptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5.

3. The pharmaceutical composition of claim 1, wherein the HMGB1 fragment peptide is a peptide consisting of an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5.

4 Use of a pharmaceutical composition comprising a HMGB1 fragment peptide in the manufacture of a medicament for the treatment of injury of the spinal cord.

5. The use of claim 4, wherein the HMGB1 fragment peptide is a peptide comprising the amino acid sequences selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5.

6. The use of claim 4, wherein the HMGB1 fragment peptide is a peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5.