23 DEC 2003

Method for preventing tumor growth

Description

The present invention relates to a method for preventing inflammations, autoimmune diseases and tumor growth by suppressing the activation mediated via the lymphotoxin-β receptor (LTBR).

The membrane protein lymphotoxin-β (Browning et al., Cell Vol. 72, 847-856, 1993) binds in homomeric and heteromeric form to a specific lymphotoxin-β receptor (LTBR) (Crowe et al., Science Vol. 264, 29 April 1994, 707-709).

Browning et al. (J. Exp. Med. Vol. 183, March 1996, 867-878) describe that signaling through the LTBR system induces the cell death of some adenocarcinoma tumor cells. Therefore, they suggest LTBR activation as a possible anticancer therapy.

Degli-Esposti et al. (Journal of Immunology, 1997, 158: 1756-1762) report that the growth of melanoma cells could be inhibited by activating the LTBR system. Therefore, they also suggest the treatment of solid tumors with lymphotoxin-β.

By contrast, our findings show that tumor growth can be slowed down or prevented by suppressing LTBR activation.

The object of the present invention is therefore a method for preventing inflammations, autoimmune diseases and tumor growth by suppressing or at least reducing LTBR-mediated activation.

The method is particularly suited in acute and chronic inflammations, such as rheumatoid arthritis or colitis and in solid tumors.

The LTBR system can be suppressed at various levels.

For instance, LTBR gene expression can be suppressed by using antisense molecules. A further possibility of specifically suppressing LTBR gene expression consists in eliminating the mRNA of the LTBR, for instance by specific hydrolysis by means of suitable ribozymes.

A further possibility of suppressing LTBR gene expression consists in blocking the corresponding transcription signal sequences, for instance the promoter region of the LTBR gene.

Another possibility of suppressing the activation of the LTBR system consists in using lymphotoxin-β antagonists, i.e. molecules which are capable of binding to LTBR but cannot effect any activation of the receptor system. Such substances can be found by checking the substances to be tested in a cellular test system as to their ability to reduce the activation of the LTBR system in the presence of added lymphotoxin-β.

A further object of the present invention is the use of substances which suppress LTBR-mediated activation, for preparing cytostatic and inflammation-inhibiting drugs.

It has been observed that the suppression of the LTBR activation effects an inhibition of tumor angiogenesis, thereby having an inhibiting effect on the growth of solid tumors.

Therefore, the prevention of LTBR activation with the above-mentioned agents and methods is particularly suited for inhibiting tumor angiogenesis.

The following experiments will explain the invention.

Experiment 1

Tumor cells (BFS-1) were transfected with a fusion protein of LTBR and immunoglobulin (BFS-LTR). This fusion protein of LTBR and immunoglobulin acts as LTBR inhibitor. In comparison with wild-type tumor cells, these transfected tumor cells showed an inhibited tumor growth if introduced into syngenic mice (figure).

Experiment 2

When in a second experiment these tumor cells were introduced into ligand-deficient mice (i.e. double-knockout mice which produce neither lymphotoxin-alpha nor lymphotoxin-beta), no significant differences were detected in the tumor growth of the transfected tumor cell over the wild-type tumor cell (figure).

Experiment 3

Observation of tumor growth in mice by intravital microscopy

Normal tumor cells or tumor cells which had been transfected with the LTβ-receptor inhibitor (BSF-1-LTβR-IG:Fc) or with a control plasmid (p55TNF-receptor-Ig:Fc) were subcutaneously applied to mice (C57BL/6) into a skin chamber, and tumor cell

growth or angioneogenesis was studied by intravital microscopy. Edema formation on day 2 after tumor cell application was already considerably smaller in the animals that had received the LTβ-receptor inhibitor transfected tumor cells than in the controls. While the normal tumor cells and the tumor cells transfected with a control construct induced pronounced angiogenesis after 5 to 9 days and then grew as tumors accordingly, no angioneogenesis in the tumor region and surroundings of the skin was observed in tumors transfected with the LTβ-receptor inhibitor. These tumors will also not grow any further.

The figures show photographs of the control tumors (top) and the LTβ-receptor inhibitor transfected tumors (bottom) on day 2 (Fig. 2) and on day 9 (Fig. 3) after tumor cell application.

CLAIMS:

1. Use of a compound capable of suppressing lymphotoxin-ß receptor-mediated activation for preparing a medicament for preventing inflammations, autoimmune diseases and tumor growth.

2. Use according to claim 1, wherein lymphotoxin-ß receptor -mediated activation is suppressed by suppressing LTBR gene expression.

3. Use according to claim 2, wherein lymphotoxin-ß receptor-gene expression is suppressed by using LTBR antisense molecules.

4. Use according to claim 2, wherein the compound specifically hydrolizes lymphotoxin-ß receptor mRNA.

5. Use according to claim 2, wherein the compound specifically blocks lymphotoxin-ß receptor transcription signal sequences.

6. Use according to claim 2, wherein the compound specifically blocks the transcription factors acting on the lymphotoxin-ß receptor transcription signal sequences.

7. Use according to claim 2, wherein lymphotoxin-ß receptor -mediated activation is suppressed by lymphotoxin-ß receptor antagonists.

8. Use according to claim 1, wherein the lymphotoxin-ß receptor -mediated activation is suppressed by interception using endogenous lymphotoxin-ß receptor ligands.

9. Use of substances which suppress the lymphotoxin-ß receptor -mediated activation, for preparing cytostatic and inflammation-inhibiting drugs.

10. Use according to claim 9 for inhibiting tumor angiogenesis.