Humanization of mouse anti-human IL-8 antibody and development of anti-inflammatory agent against cytokine regulatory factor, NFkB

1997 Fiscal Year Final Research Report Summary

Humanization of mouse anti-human IL-8 antibody and development of anti-inflammatory agent against cytokine regulatory factor, NFkB

Research Project

Project/Area Number

07557031

Research Category

Grant-in-Aid for Scientific Research (A)

Allocation Type

Single-year Grants

Section

展開研究

Research Field

Immunology

Research Institution

University of Tokyo (1996-1997)
Kanazawa University (1995)

Principal Investigator

MATSUSHIMA Kouji University of Tokyo, Graduate School of Medicine, Development Preventive Medicine, Professor, 大学院・医学系研究科, 教授 (50222427)

Co-Investigator(Kenkyū-buntansha)

YAMAZAKI Tatsumi Chugai Pharmaceutical Company, Chief Director, 所長(研究職)

Project Period (FY)

1995 – 1997

Keywords

interleukin-8 / anti-inflammatory agent / acute inflammation / anti-interleukin-8 antibody / humanization / NF-kB / IkB-bound kinase / phosphorylation

Research Abstract

IL-8 is essentially involved in neutrophil-dependent tissue damage in acute inflammatory reactions. We established the humanized mouse anti-human IL-8 by mean of complementarity determining region grafting and succeeded to purify the large amount of this antibody. For the application of this antibody on various clinical condition, we established various acute inflammatory ananimal models. Especially, we have established preclinical condition animal models such as acute respiratory distress syndrom-like lung injury and brain reperfusion injury. In these models, we showed that anti-IL-8 antibody treatment almostly prevented these injury. These results strongly suggest the possibility of clinical application of humarized anti-human IL-8 antibody against acute inflammatory dieases.
We have identified a kinase in cell extracts from the LPS-stimulated human monocytic cell line, THP-1, that specifically bind and phosphorylates IkBa. LPS-stimulation transiently enhanced the IkBa-bound kinase activity in THP-1 cells. Mutation analysis of IkBa and competition experiments with the synthetic peptides identified major phosphorylation site by the bound kinase as Ser and Thr residues in the C-terminal acidic domain of IkBa. Moreover, this IkBa-boundkinase is novel kinase but not Ikka, b which are related to signal pathway of TNF-a and IL-1. So that we try to purify the kinase SDS-PAGE analysis showed that the kinase. is 40 Kd. We are now analyzing the amino acid squence of the sample and trying to clone the gene.

Research Products (17 results)

All | Other

All | Publications (17 results)

[Publications] Kuno, K.et al.: "Identification of an IkBa-associated protein kinase in a human cell lineand determination of its phosphorylation sites on IkBa." J.Biol.Chem.270. 27914-27919 (1995)

[Publications] Ishikawa, Y.et al.: "Establishment of lipopolysaccharide-dependent nulear factor-kB activation in a cell-free system." J.Biol.Chem.270. 4158-4164 (1995)

[Publications] Mukaida, N.et al.: "Novel insight into molecular mechanism of endotoxin shock" J.Leukocyte Biol.59. 145-151 (1996)

[Publications] Yokoi, K.et al.: "Prevention of endotoxemia-induced acute respiratory distress syndrome-like lung injury in rabbits by a monoclonal antibody to IL-8." Lab.Invest.76. 375-384 (1997)

[Publications] Matsumoto, T.et al.: "Prevention of cerebral edema andinfarct in reperfuion injury by an antibody to interleukin-8." Lad.Invest.77. 119-125 (1997)

[Publications] Khabar, KSA.et al.: "The α chemokine,interleukin 8,inhibits the antiviral action of interferon α." J.Exp.Med.186. 1077-1085 (1997)

[Publications] Matsumoto, T.et al.: "Rivotal role of interleukin-8(IL-8)in acute inflammation (Invited Review)" J.Leukocyte Biol.62, 7(581-587) (1997)

[Publications] Mukaida, N.et al.: "Cytokine Growth Fact.Rev." Interleukin-8 and monocyte chemotactic and activating factor (MCAF/MCP-1),chemokines essentially involved in inflammatory and immune reactions.(in press), (1997)

[Publications] Kuno, K., Ishikawa, Y., Ernst, M.K., Ogata, M., Rice, N.R., Mukaida, N., and Matsushima, K.: "Identification of a IkBa-associated protein kinase in a human cell line and determination of its phosphorylation sites on IkBa" J.Biol.Chem.270. 27914-2791 (1995)

[Publications] Ishikawa, Y., Mukaida, N., Kuno, K., Rice, N., Okamoto, S., and Matsushima, K.: "Establishment of lipopolysaccharide-dependent nuclear factor-kB activation in a cell-free system." J.Biol.Chem.270. 4158-4164 (1995)

[Publications] Mukaida, N., Ishikawa, Y., Ikeda, N., Fujioka, N., Watanabe, S., Kuno, K., and Matsushima, K.: "Novel insight in to molecular mechanism of endotoxin shock." J.Leukocyte.Biol. 59. 145-151 (1996)

[Publications] Yokoi, K., Mukaida, N., Harada, A., Watanabe, Y., Matsushima, K.: "Prevention of endotoxemia-induced acute respiratory distress syndrome-like lung injury in rabbits by a monoclonal antibody to IL-8" Lab.Invest.76. 375-384 (1997)

[Publications] Matsumoto, T., Yokoi, K., Mukaida, N., Harada, A., Yamashita, J., Watanabe, Y., and Matsushima, K.: "Prevetion of cerebral edema and infarct in cerebral reperfusion injury by an antibody to interleukin-8" Lab.Invest.62. 119-125 (1997)

[Publications] Khabar, K.S., Al-Zoghaibi, F., Al-Ahdal, M.N., Murayama, T., Dhalla, M., Mukaida, N., Taha, M., Al-Sedairy, S.T., Siddiqui, Y., Kessie, G., and Matsushima, K.: "The alpha chemokine, interleukin 8, inhibits the antiviral action of interferon alpha." J.Exp.Med.186. 1077-1085 (1997)

[Publications] Matsumoto, T., Yokoi, K., Mukaida, N., Harada, A., Yamashita, J., Watanabe, Y., and Matsushima, K.: "Pivotal role of interleukin-8 in the acute respiratory distress syndrome and cerebral reperfusion injury." J.Leukocyte.Biol.62. 581-587 (1997)

[Publications] Mukaida, N., Harada, A., and Matsushima, K.: "Interkeukin-8 and monocyte chemotactic and activating factor (MCAF/MCP-1), chemokines essentially involvedin inflammatory and immune reaactions"

[Publications] Cytokine Growth Factor.Rev.(1997)