

# IL8抗体のヒト型化とサイトカイン遺伝子調節因子 NFkBを標的とした抗炎症剤開発

著者	松島 綱治
著者別表示	Matsushima Kouji
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# 1997 Fiscal Year Final Research Report Summary

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

Research Project

### Project/Area Number

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07557031

### Research Category

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Grant-in-Aid for Scientific Research (A)

### Allocation Type

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Single-year Grants

### Section

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展開研究

### Research Field

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Immunology

### Research Institution

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

### Principal Investigator

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**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)

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

### Project Period (FY)

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1995 - 1997

### Keywords

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## 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 means of complementarity determining region grafting and succeeded to purify the large amount of this antibody. For the application of this antibody on various clinical conditions, we established various acute inflammatory animal models. Especially, we have established preclinical condition animal models such as acute respiratory distress syndrome-like lung injury and brain reperfusion injury. In these models, we showed that anti-IL-8 antibody treatment almost completely prevented these injuries. These results strongly suggest the possibility of clinical application of humanized anti-human IL-8 antibody against acute inflammatory diseases.

We have identified a kinase in cell extracts from the LPS-stimulated human monocytic cell line, THP-1, that specifically binds and phosphorylates IκBα. LPS-stimulation transiently enhanced the IκBα-bound kinase activity in THP-1 cells. Mutation analysis of IκBα and competition experiments with the synthetic peptides identified the major phosphorylation site by the bound kinase as Ser and Thr residues in the C-terminal acidic domain of IκBα. Moreover, this IκBα-bound kinase is a novel kinase but not IκKα, β which are related to the signal pathway of TNF-α 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 sequence 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 IκBα-associated protein kinase in a human cell line and determination of its phosphorylation sites on IκBα." *J. Biol. Chem.* 270. 27914-27919 (1995) ▼
- [Publications] Ishikawa, Y. et al.: "Establishment of lipopolysaccharide-dependent nuclear factor-κB 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 and infarct in reperfusion injury by an antibody to interleukin-8." *Lab. Invest.* 77. 119-125 (1997) ▼
- [Publications] Khabar, K.S.A. 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.: "Pivotal 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 Factor Rev." Interleukin-8 and monocyte chemoattractant 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 an IκBα-associated protein kinase in a human cell line and determination of its phosphorylation sites on IκBα" *J. Biol. Chem.* 270. 27914-27919 (1995) ▼
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- [Publications] Mukaida, N., Ishikawa, Y., Ikeda, N., Fujioka, N., Watanabe, S., Kuno, K., and Matsushima, K.: "Novel insight into 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.: "Prevention 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.: "Interleukin-8 and monocyte chemoattractant protein 1 (MCP-1), chemokines essentially involved in inflammatory and immune reactions" ▼

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

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