

# インターロイキン1受容体と細胞内シグナル伝達機構の解析

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# 1993 Fiscal Year Final Research Report Summary

## Analysis of the structure of interleukin 1 receptor and the mechanism of IL-1 signal transduction

Research Project

### Project/Area Number

03454195

### Research Category

Grant-in-Aid for General Scientific Research (B)

### Allocation Type

Single-year Grants

### Research Field

Immunology

### Research Institution

Kanazawa University

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1991 – 1993

### Keywords

Interleukin 1 / Receptor / Signal transduction / IL-8 gene activation / TNF / Interferon gamma / Transcriptional factors / 再灌流障害

### Research Abstract













The structural and functional relationship of the intracellular portion of mouse interleukin 1 receptor (IL-1R) type I was examined with regard to activation of the human IL-8 gene in the Jurkat T cell line. We found that C-terminal boundary for the function of the receptor is localized between 28-42 amino acids from C-terminal end, and that the large region of IL-1R cytoplasmic portion is required for the function to transmit IL-1 signal. In addition, the cytoplasmic region of IL-1R possess the segment homologous to gp130, beta chain of IL-6R, including box 1 and 2-like elements, and mutations within the gp130 homologous segments, abolished the capacity to induce IL-8 gene expression, suggesting similar structural requirements in the cytoplasmic portion of several cytokine receptors.

To investigate the molecular mechanism of IL-1 receptor mediated signal transduction, we examined the IL-1 responsive elements on the 5'-flanking region of the human IL-8 gene. We found that the three cis elements on the IL-8 promoter, NFkB, C/EBP and AP-1 binding sites are required for IL-1 induced IL-8 gene activation. Interestingly, in fibrosarcoma 8387 cells, NFkB and C/EBP binding sites are necessary for the responsiveness to IL-1, whereas in gastric cancer derived MKN45 cells, AP-1 and NFkB binding sites, are indispensable, indicating that the relative importance of these three sites is different among cell types. In addition synergistic action between TNF and IFN $\gamma$  was observed for the IL-8 production and the activation of IL-8 promoter. Gel retardation analysis revealed that TNF and IFN $\gamma$  synergistically induced the activation of NFkB binding activity, suggesting that IFN $\gamma$  enhance the activation of IL-8 gene by TNF through augmenting NFkB activation.

## Research Products (12 results)

All Other

All Publications (12 results)

- [Publications] Mahe,Y.: "Hepatitis B virus X protein transactivates human interleukin 8 gene through acting on nuclear factor kB and CCAAT/enhancer binding protein-like cis-elements." J.Biol.Chem.266. 13759-13763 (1991) 
- [Publications] Yasumoto,K.: "Tumor necrosis factor  $\alpha$  and interferon  $\gamma$  synergistically induce interleukin 8 production in a human gastric cancer cell line through acting concurrently on AP-1 and NF-kB like binding sites of the interleukin 8 gene." J.Biol.Chem.267. 22506-22511 (1992) 
- [Publications] Kuno,K.: "Structure and function of the intracellular portion of the mouse interleukin 1 receptor(type 1)." J.Biol.Chem.268. 13510-13518 (1993) 
- [Publications] Harada,A.: "Expression of recombinant rabbit IL-8 in Escherichia coil and establishment of the essential involvement of IL-8 in recruiting neutrophils into lipopolysaccharide-induced inflammatory site of rabbit skin." Int.Immunol.5. 681-690 (1993) 
- [Publications] Sekido,N.: "Prevention of lung reperfusion injury in rabbits by a monoclonal antibody against interleukin-8." Nature. 365. 654-657 (1993) 
- [Publications] Nomura,H.: "Molecular cloning of cDNAs encoding a LD78 receptor and putative leukocyte chemotactic peptide receptors." Int.Immunol.5. 1239-1249 (1993) 
- [Publications] Mahe, Y., Mukaida, N., Kuno, K., Akiyama, M., Ikeda, N., Matsushima, K.and Murakami, S.: "Hepatitis B virus X protein transactivates human interleukin 8 gene through acting on nuclear factor kB and CCAAT/enhancer binding protein-like ciselements." J.Biol.Chem.266. 13759-13763 (1991) 
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- [Publications] Sekido, N., Mukaida, N., Harada, A., Nakanishi, I., Watanabe, Y., and Matsushima, K.: "Prevention of lung reperfusion injury in rabbits by a monoclonal antibody against interleukin-8." Nature. 365. 654-657 (1993) 
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