担癌宿主に於けるサイトカインネットワーク分子機構の解析

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Research Abstract

担癌生体を分子制御するサイトカインネットワーク機構のモデルとしてマウス大腸癌に伴う悪液質誘導分子機構を詳細に解析して以下のような結果を得た。1)マウス大腸癌細胞株colon26で癌悪液質を起こすclone(clone20)と起こさないclone(clone5)のin vitroに於ける単独培養、線維芽細胞ならびに脾細胞との混合培養時に産生されるサイトカインとこれらの癌細胞をBalb/cマウスに移植した時の癌組織でのサイトカインの発現を比較した結果in vitroとin vivoで発現されるサイトカインの種類が全く異なることが明確になった。2)悪液質を起こすclone20では選択的にin vivoでのみIL6を発現し、悪液質を起こさないclone5ではIL1のナチュラルアンタゴニストが特異的に発現していることが判明した。抗IL6抗体投与実験、ILRa cDNAトランスフェクションの実験結果よりIL6が悪液質誘導には重要であるけれども部分的であり他の因子の関与が推定された3)それ故未知のcachectinを同定する方法の一つとして、Clone20/5特異的に発現する遺伝子をPCR-differential display methodによりscreeningした。その結果4つの新規cDNAをクローニングした。そのうちの一つは、哺乳動物では全く新規のTSP-モチーフを有するZn-結合性メタロプロテアーゼをコードすることが判明した。さらに、研究代表者は、癌組織への好中球、リンパ球浸潤を制御すると考えられるケモカイン、IL8の遺伝子発現調節機構の解析の結果AP-1,NF-IL6,NFkB結合エンハンサーがIL8遺伝子発現の正/負の調節に関与することを明かにした。またNFkBの活性化経路を明らかにするためにLPS-依存性cell-freeでのNFkB活性化システムを確立し、IkBαのリン酸化部位を同定した。一方、班員の審良は、IL6遺伝子の発現調節を解析する中でNF-IL6とAPRFを発見するとともに、gp130を介するシグナル伝達機構を明らかにした。班員の藤原は担癌宿主では腫瘍由来TGFbによるCD4+Thのサイトカイン産生抑制に加え担癌宿主が産生するIL6によってもTNF産生が抑制され相乗的に抗腫瘍免疫能の低下が惹起されることを明かにした。また、IL12の癌免疫原性の回復力について評価し、IL12は免疫不全を是正し、腫瘍拒絶を惹起させることを明らかにした。班員の栗林はCD4+のCTL誘導抑制性Tsの存在を示し、CTL、ヘルパーT細胞エピトープを決定した。班員の吉田はgp130,NF-IL6ノックアウトマウスを作製しそれらの形質を評価した。班員の横田はIL5遺伝子がPKCとPKA依存的に活性化されることを見つけその反応要素NFAT,CLEO配列を決定した。班員の小野崎は種々の細胞が産生するがん細胞増殖抑制因子を精製することによりカタラーゼだと同定した。

Report (1 results)

1995 Annual Research Report

Research Products (61 results)

All Other

All Publications (61 results)

[Publications] Okamoto,S.-i.: "The interleukin-8 AP-1 and kB-like sites are genetic end targets of FK506-sensitive pathway accompanied by calcium mobilization." J.Biol.Chem.269. 8582-8589 (1994)

[Publications] Mukaida,N.: "Novel mechanism of glucocorticoid-mediated gene repression:Nuclear factor-kB is target for glucocorticoid-mediated interleukin 8 gene repression." J.Biol.Chem.269. 13289-13295 (1994)

[Publications] Nakano,Y.: "Protection against lethal bacterial infection in mice by monocyte-chemotactic and-activating factor(MACF)." Infect.Immun.62. 377-383 (1994)

[Publications] Murakami,S.: "Transactivation of human hepatitis B virus X protein,HBx,operates through a mechanism distinct from protein kinase C and okadaic acid activation pathway." Virology. 199. 243-246 (1994)

[Publications] Asano,T.: "Liposomal muramyl tripeptide up-regulates interleukin-1 alpha,interleukin-1 beta,tumor necrosis factor-alpha,interleukin-6 and interleukin-8 gene expression in human monocytes." J.Pharmacol.Exp.Ther.268. 1032-1039 (1994)

[Publications] Kuno,K.,: "Acid sphingomyelinase is not essential for the IL 1 and tumor necrosis factor receptor signaling pathway leading to NFkB activation." Int.Immunol.6. 1269-1272 (1994)

[Publications] Kuno,K.: "The IL 1 receptor signaling pathway" J.Leukocyte Biology. 56. 542-547 (1994)

[Publications] Endo,H.: "Experimental arthritis induced by continuous infusion of IL-8 into rabbit knee joints." Clin.Exp.Immunol.96. 31-35 (1994)

[Publications] Harada,A.: "Cloning of a cDNA encoding a mouse homolog of the interleukin-8 receptor." Gene. 142. 297-300 (1994)

[Publications] Deleuran,B.: "Localisation of interleukin 8 in the synovial membrane,cartilage-pannus junction and chondrocytes in rheumatoid arthritis.Scand." Scand.J.Rheumatol.23. 2-7 (1994)

[Publications] Asano,T.: "Liposome-encapsulated muramyl tripeptide up-regulates monocyte chemotactic and activating factor gene expression in human monocytes at the transcriptional and post-transcriptional levels." Cancer Immunology and Immunotherapy. 38. 16-22 (1994)

[Publications] Oliveira,I.C.: "Transcriptional inhibition of the interleukin-8 gene by interferon is mediated by the NF-kB site." Mol.Cell Biol.14. 5300-5308 (1994)

[Publications] Akahoshi,T.: "Essential involvement of interleukin-8 in neutrophil recruitment in rabbits with acute experimental arthritis induced by lipopolysaccharide and interleukin-1." Lymphokine Cytokine Res.13. 113-116 (1994)

[Publications] Itoh,R.: "Interleukin-8 in Behcet's Disease." J.Dermatology. 21. 397-404 (1994)

[Publications] Mizuno,K.: "Spontaneous production of interleukin-8 by human lung cancer cells and its augmentation by tumor necrosis factor alpha and interleukin-1 at protein and mRNA levels." Oncology. 51. 467-471 (1994)

[Publications] Ito,A.: "Suppression of interleukin 8 production by progesterone in rabbit uterine cervix." Biochem.J.301. 183-186 (1994)

[Publications] Kasahara,K.: "Selective expression of monocyte chemotactic and activating factor/monocyte chemoattractant protein 1 in human blood monocytes by mycobacterium tuberculosis." J.Infectious Dis.170. 1238-1247 (1994)

[Publications] Murayama,T.: "Elevated cytokine levels in synovial fluid of rheumatoid arthritis correlates with the presence of cytomegalovirus genome." Autoimmunity. 17. 333-337 (1994)

[Publications] Wada,T.: "Detection of urinary interleukin-8 in glomerular diseases." Kidney Int.46. 455-460 (1994)

[Publications] Nakamoto,Y.: "Detection of the putative E2 protein of hepatitis C virus in human liver." J.Med.Virology. 42. 374-379 (1994)

[Publications] Wada,T.: "Appearance of Interleukin-8 in the Urine Predicts Acute rejection of Renal Transplantation." Nephrol.Dial.Transplant.9. 874-875 (1994)

[Publications] Wada,T.: "Prevention of proteinuria in acute immune complex-mediated glomerulonephritis by an antibody against interleukin 8." J.Exp.Med.180. 1135-1140 (1994)

[Publications] Murayama,T.: "Enhancement of human cytomegalovirus replication in human lung fibroblast cell line by interleukin 8." J.Virol.68. 7582-7584 (1994)

[Publications] Mukaida,N.: "Molecular mechanism of interleukin 8(IL-8)gene expression." J.Leukocyte Biology. 56. 554-558 (1994)

[Publications] Harada,A.: "Essential involvement of interleukin 8(IL8)in acute inflammation." J.Leukocyte Biology. 56. 559-564 (1994)

[Publications] Oishi,K.: "Role of interleukin-8(IL-8)and an inhibitory effect of erythromycin on IL-8 release in the airways of patients with chronic airway diseases." Infect.Immun.62. 4145-4152 (1995)

[Publications] Ko,Y.-C.: "Specific elevation of interleukin-8 levels in peritoneal dialysates of patients on continous ambulatory peritoneal dialysis with peritonitis." J.Clin.Pathol.48. 115-119 (1995)

[Publications] Morohashi,H.: "Expression of both types of human interleukin 8(IL-8)receptors on mature neurtophils,monocyts,and CD16+lymphocytes." J.Leukocyte Biol.57. 180-187 (1995)

[Publications] Yano,S.: "Differential effects of anti-inflammatory cytokines(IL-4,IL-10,and IL-13)on tumorcidal and chemotactic properties of human monocytes induced by monocyte chmotactic and activating factor(MCAF)." J.Leukcyte Biol.57. 303-309 (1995)

[Publications] Yasumoto,K.: "Molecular analysis of cytokine network involved in causing cachexia in colon 26 adenocarcinoma-bearing mice." Cancer Res.55. 921-927 (1995)

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

[Publications] Watanabe,S.-i.: "Prevention of endotoxin shock by an antibody against leukocyte integrin b2 through inhibiting production and action of tumor necrosis factor." Intl.Immunol.7. 1037-1046 (1995)

[Publications] Hoshino,Y.: "Monocyte chemoattractant protein 1 stimukates tumor necrosis and recruitment of macrophages into tumor in tumo-beaning mude mice:Increased granulocyte/macrophage progenitors in murine bone marrow." Exp.Hematol.3. 1035-1039 (1995)

[Publications] Sagawa,K.: "Production of IL-8 and the other cytokines by T cell clones established from the ocular fluid of patients with Behcet's disease." Ocular Immunol.Inflamm.3. 62-71 (1995)

[Publications] Fujioka,N.: "Preparation of specific antibodies against murine interleukin 1 receptor antagonist(IL-1 ra)and the establishment of IL-1 ra as endogenous regulator of bacteria-induced fulminant hepatitis in mice." J.Leukocyte Biol.58. 90-98 (1995)

[Publications] Hirose,K.: "Chemokine gene transfer into tumor cells reduced tumorigenicity in vivo mediated through neutroophilic infiltrate." Brit.J.Cancer.72. 708-714 (1995)

[Publications] Sugiyama,Y.: "Chemokines in bronchoalveolar lavage fluid in summer-type hypersenitivity penumonitis." Eur.Respir.J.8. 1084-1090 (1995)

[Publications] Ikeda,N.: "Prevention of bacterial induced hepatocelluar necrosis in rabbits by an antibody to leukocyte integrin b2 with concomitant inhibition of cytokine production." Infect.Immun.63. 4812-4817 (1995)

[Publications] Nakashima,E.: "MCAF gene transfer enhances themetastatic capacity of mouse cachectic adenocarcinoma cell line." Pharmaceutical Res.12. 1598-1604 (1995)

[Publications] Zhang,Y.: "TNFa as a physiological regulator of hematopoietic progenitor cells:Increase of early hematopoietic progenitor cells in TNF-R55-/- mice in vivo and potent inhibition of progenitor cell proliferation by TNFa in vitro." Blood. 6. 2930-2937 (1995)

[Publications] Teranishi,Y.: "Increased spontaneous production of IL-8 in peripheral blood monocytes from the psoriatic patient:relation to focal infection and response to treatments." J.Dermatol.Science. 10. 8-15 (1995)

[Publications] Larsen,C.G.: "The delayed-type hypersensitivity reaction is dependent on IL-8.Inhibition of a tuberculin skin reaction by an anti-IL-8 monoclonal antibody." J.Immunol.155. 2151-2157 (1995)

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

[Publications] Xiu,Q.: "Bronchial hyperresponsiveness and airway neutrophil accumulation induced by interleukin-8 and the effect of the thromboxane A2 antagonist S-1452 in guinea-pigs." Clin.Exp.Allergy.25. 51-59 (1995)

[Publications] Yamamoto,N.: "Regulatory mechanisms for production of interferon-g and TNF by anti-tumor T cells or macrophages in the tumor-bearing state." J.Immunol.154. 2281-2289 (1995)

[Publications] Jinquan,T.: "Recombinant human growth-regulated oncogene-a induces T lymphocyte chemotaxis." J.Immunol.155. 5359-5368 (1995)

[Publications] Inoue,H.: "Expression of cytokines and adhesion molecules in hemodialysis-associated amyloidosis" Nephrol.Dialysis Transplant.(in press.).

[Publications] Wada,T.: "Monitoring urinary levels of monocyte chemotactic and activating factor(MCAF)reflects disease activity of lupus nephritis." Kidney Int.(in press.).

[Publications] Su,S-b.: "Rapid secretion of intracellularly pre-stored interleukin-8 from rabbit platelets upon the activation." J.Leukocyte Biol.(in press.).

[Publications] Mukaida,N.: "Novel insight into molecular mechanism of endotoxin shock:biochemical analysis of LPS receptor signaling in a cell-free svstem taraetina NF-kB and reaulation of cvtokine production/action throuah inteann b2 in vivo." J.Leukocyte Biol.(in press.).

[Publications] Nielsen,B.W.: "Macrophage-Pathogene Interactions" Marcel Dekker, 11 (1994)

[Publications] Harada,A.: "Ares-Sereno Symposia-Publications" Challenges of Modern Medicine Vol.3, 6 (1994)

[Publications] Matsushima,K.: "Proceeding of IIIrd International Mochida Memorial Symposium" The Mochida Memorial Foundation for Medical and Pharmaceutical Research, 8 (1994)

[Publications] Okamoto,S.: "In the Chemokines Proceeding of IIIrd International Symposium of Chemotactic Cytokines" Plenum, 10 (1994)

[Publications] Murakami,S.: "Viral Hepatitis and Liver Disease" 4 (1994)

[Publications] Mukaida,N.: "In Leukocyte Typing V" Oxford University Press, 3 (1995)

[Publications] Morohashi,H.: "In Leukocyte Typing V" Oxford University Press, 3 (1995)

[Publications] Mukaida,N.: "Cytokines:interleukins and their receptors." Kluwer Academic Publishers(in press.),

[Publications] Harada,A.: "In Growth factor and cytokines in health and disease." JAl press(in press.),

[Publications] Harada,A.: "In ImmunoMethod on Chemokine" Academic press(in press.),

[Publications] Harada,A.: "The Roles of Chemokines in Disease." R.G.Landes Company(in press.),

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