沙士/冠狀病毒 刺激 樹突細胞 分泌 MCP-1

(1)

Blood. 2005 Oct 1;106(7):2366-74. Epub 2005 Apr 28.

Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells.

Law HK[1], Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, Nicholls JM, Peiris JS, Lau YL.

Author information

1 Department of Paediatrics and Adolescent Medicine, Hong Kong Jockey Club Clinical Research Centre, Faculty of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong, China.

Abstract

Lymphopenia and increasing viral load in the first 10 days of severe acute respiratory syndrome (SARS) suggested immune evasion by SARS-coronavirus (CoV). In this study, we focused on dendritic cells (DCs) which play important roles in linking the innate and adaptive immunity. SARS-CoV was shown to infect both immature and mature human monocyte-derived DCs by electron microscopy and immunofluorescence. The detection of negative strands of SARS-CoV RNA in DCs suggested viral replication. However, no increase in viral RNA was observed. Using cytopathic assays, no increase in virus titer was detected in infected DCs and cell-culture supernatant, confirming that virus replication was incomplete. No induction of apoptosis or maturation was detected in SARS-CoV-infected DCs. The SARS-CoV-infected DCs showed low expression of antiviral cytokines (interferon alpha [IFN-alpha], IFN-beta, IFN-gamma, and interleukin 12p40 [IL-12p40]), moderate up-regulation of proinflammatory cytokines (tumor necrosis factor alpha [TNF-alpha] and IL-6) but significant up-regulation of inflammatory chemokines (macrophage inflammatory protein 1alpha [MIP-1alpha], regulated on activation normal T cell expressed and secreted [RANTES]), interferon-inducible protein of 10 kDa [IP-10], and monocyte chemoattractant protein 1 [MCP-1]). The lack of antiviral cytokine response against a background of intense chemokine up-regulation could represent a mechanism of immune evasion by SARS-CoV.

PMID: 15860669 PMCID: PMC1895271 DOI: 10.1182/blood-2004-10-4166

[Indexed for MEDLINE] Free PMC Article

MCP-1 令血管的T淋巴走入肺 ②

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Format: Abstract

J Clin Invest. 1995 Mar;95(3):1370-6.

Monocyte chemotactic protein-1 (MCP-1), -2, and -3 are chemotactic for human T lymphocytes.

Taub DD[1], Proost P, Murphy WJ, Anver M, Longo DL, van Damme J, Oppenheim JJ.

Author information

1 Clinical Services Program, Program Resources, Inc., DynCorp, National Cancer Institute-Frederick Cancer Research and Development Center, Maryland 21702.

Abstract

Monocyte chemotactic protein (MCP)-1, -2, and -3 all have been shown to induce monocyte/macrophage migration in vitro and MCP-1, also known as MCAF, chemoattracts basophils and mast cells. We report here that natural MCP-1 as well as synthetic preparations of MCP-2 and MCP-3 stimulate significant in vitro chemotaxis of human peripheral blood T lymphocytes. This MCP-induced migration was dose-dependent and directional, but not chemokinetic. Phenotypic analysis of the T cell population responsive to MCP-1, MCP-2, and MCP-3 demonstrates that both CD4+ and CD8+ T cells migrated in response to these chemokines. Similar results were observed using human CD4+ and CD8+ T cell clones. Neutralizing antisera to MCAF or MCP-2 abrogated T cell migration in response to MCP-1 and MCP-2, respectively, but not to RANTES. Subcutaneous administration of purified MCP-1 into the hind flanks of SCID mice engrafted with human peripheral blood lymphocytes (PBL) induced significant human CD3+ T cell infiltration into the site of injection at 4 h. These results demonstrate that MCP-1, MCP-2, and MCP-3 are inflammatory mediators that specifically stimulate the directional migration of T cells as well as monocytes and may play an important role in immune cell recruitment into sites of antigenic challenge.

PMID: 7883984 PMCID: PMC441477 DOI: 10.1172/JCI117788

[Indexed for MEDLINE] **Free PMC Article**

T-淋巴细胞分泌丙型干扰素 (IFN_g)

③

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Format: Abstract

Blood. 2004 Jul 1;104(1):200-6. Epub 2004 Mar 11.

Identification of an HLA-A*0201-restricted CD8+ T-cell epitope SSp-1 of SARS-CoV spike protein.

Wang B[1], Chen H, Jiang X, Zhang M, Wan T, Li N, Zhou X, Wu Y, Yang F, Yu Y, Wang X, Yang R, Cao X.

Author information

1 Institute of Immunology, Second Military Medical University, Shanghai, People's Republic of China.

Abstract

A novel coronavirus, severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV), has been identified as the causal agent of SARS. Spike (S) protein is a major structural glycoprotein of the SARS virus and a potential target for SARS-specific cell-mediated immune responses. A panel of S protein-derived peptides was tested for their binding affinity to HLA-A*0201 molecules. Peptides with high affinity for HLA-A*0201 were then assessed for their capacity to elicit specific immune responses mediated by cytotoxic T lymphocytes (CTLs) both in vivo, in HLA-A2.1/K(b) transgenic mice, and in vitro, from peripheral blood lymphocytes (PBLs) harvested from healthy HLA-A2.1(+) donors. SARS-CoV protein-derived peptide-1 (SSp-1 RLNEVAKNL), induced peptide-specific CTLs both in vivo (transgenic mice) and in vitro (human PBLs), which specifically released interferon-gamma (IFN-gamma) upon stimulation with SSp-1-pulsed autologous dendritic cells (DCs) or T2 cells. SSp-1-specific CTLs also lysed major histocompatibility complex (MHC)-matched tumor cell lines engineered to express S proteins. HLA-A*0201-SSp-1 tetramer staining revealed the presence of significant populations of SSp-1-specific CTLs in SSp-1-induced CD8(+) T cells. We propose that the newly identified epitope SSp-1 will help in the characterization of virus control mechanisms and immunopathology in SARS-CoV infection, and may be relevant to the development of immunotherapeutic approaches for SARS.

PMID: 15016646 DOI: 10.1182/blood-2003-11-4072

[Indexed for MEDLINE]

IFNγ 殺死 病毒

④

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ELSEVIER FULL-TEXT ARTICLE

Format: Abstract

Antiviral Res. 2009 Nov;84(2):168-77. doi: 10.1016/j.antiviral.2009.09.004. Epub 2009 Sep 11.

Efficient induction of cytotoxic T lymphocytes specific for severe acute respiratory syndrome (SARS)-associated coronavirus by immunization with surface-linked liposomal peptides derived from a non-structural polyprotein 1a.

Kohyama S[1], Ohno S, Suda T, Taneichi M, Yokoyama S, Mori M, Kobayashi A, Hayashi H, Uchida T, Matsui M.

Author information

1 Department of Microbiology, Faculty of Medicine, Saitama Medical University, Iruma-gun, Saitama, Japan.

Abstract

Spike and nucleocapsid are structural proteins of severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) and major targets for cytotoxic T lymphocytes (CTLs). In contrast, non-structural proteins encoded by two-thirds of viral genome are poorly characterized for cell-mediated immunity. We previously demonstrated that nucleocapsid-derived peptides chemically coupled to the surface of liposomes effectively elicited SARS-CoV-specific CTLs in mice. Here, we attempted to identify HLA-A*0201-restricted CTL epitopes derived from a non-structural polyprotein 1a (pp1a) of SARS-CoV, and investigated whether liposomal peptides derived from pp1a were effective for CTL induction. Out of 30 peptides predicted on computational algorithms, nine peptides could significantly induce interferon gamma (IFN-gamma)-producing CD8(+) T cells in mice. These peptides were coupled to the surface of liposomes, and inoculated into mice. Six liposomal peptides effectively induced IFN-gamma-producing CD8(+) T cells and seven liposomal peptides including the six peptides primed CTLs showing in vivo killing activities. Further, CTLs induced by the seven liposomal peptides lysed an HLA-A*0201 positive cell line expressing naturally processed, pp1a-derived peptides. Of note, one of the liposomal peptides induced high numbers of long-lasting memory CTLs. These data suggest that surface-linked liposomal peptides derived from pp1a might offer an efficient CTL-based vaccine against SARS.

PMID: 19748524 DOI: 10.1016/j.antiviral.2009.09.004

IFNg 又會令巨噬細胞分泌 外皮細胞生長因子 (5)

PubMed

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Format: Abstract

Growth Factors. 1993;9(3):223-30.

Secretion of epidermal growth factor-like molecular species by lung parenchymal macrophages: induction by interferon-gamma.

外皮 生長 因子

Kumar RK[1], O'Grady R, Li W, Rajkovic I.

Author information

1 School of Pathology, University of New South Wales, Kensington, Australia.

Abstract

A population of cells enriched for pulmonary interstitial macrophages was obtained by differential adherence of lung parenchymal cells released by dissociation with trypsin. These cells secreted a molecule or molecules that bound to epidermal growth factor (EGF) receptors expressed on pulmonary fibroblasts. Secretion was reproducibly stimulated by exposure of the macrophages to interferon-gamma. Binding to EGF receptors could be blocked by a polyclonal antibody to EGF. It could also be partially blocked by incubation with heparin, suggesting that at least a component of the activity might be due to a member of the heparin-binding subgroup of the EGF family of growth factors. Because pulmonary fibrosis is consistently associated with inflammatory accumulation of activated T-lymphocytes, induction by interferon-gamma of growth factor secretion by macrophages could have pathogenetic importance. We speculate that similar cellular interactions may play a role in the progression of other chronic inflammatory lesions to fibrosis.

PMID: 8274299 DOI: 10.3109/08977199309010834

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

EGF 刺激 成纖維細胞 (Fibroblast) 的 激酶 (kinase) 6

PubMed

Full text links

PMC FREE Full text

Format: Abstract

Cell Regul. 1991 Aug;2(8):663-73.

Temperature-dependent tyrosine phosphorylation of microtubule-associated protein kinase in epidermal growth factor-stimulated human fibroblasts.

Campos-González R[1], Glenney JR Jr.

Author information

1 Lucille P. Markey Cancer Center, University of Kentucky, Lexington 40536-0084.

Abstract

Treatment of normal human fibroblasts with epidermal growth factor (EGF) results in the rapid (0.5 min) and simultaneous tyrosine phosphorylation of the EGF receptor (EGFr) and several other proteins. An exception to this tyrosine phosphorylation wave was a protein (42 kDa) that became phosphorylated on tyrosine only after a short lag time (5 min). We identified this p42 kDa substrate as the microtubule-associated protein (MAP) kinase using a monoclonal antibody to a peptide corresponding to the C-terminus of the predicted protein (Science 249, 64-67, 1990). EGF treatment of human fibroblasts at 37 degrees C for 5 min resulted in the tyrosine phosphorylation of 60-70% of MAP kinase as determined by the percent that was immunoprecipitated with antiphosphotyrosine antibodies. Like other tyrosine kinase growth factor receptors, the EGFr is activated and phosphorylated at 4 degrees C but is not internalized. Whereas most other substrates were readily tyrosine phosphorylated at 4 degrees C, MAP kinase was not. When cells were first stimulated with EGF at 4 degrees C and then warmed to 37 degrees C without EGF, tyrosine phosphorylation of MAP kinase was again observed. Treatment of cells with the protein kinase C activator phorbol myristate acetate (PMA) also resulted in the tyrosine phosphorylation of MAP kinase, and again only at 37 degrees C. Tryptic phosphopeptide maps demonstrated that EGF and PMA both induced the phosphorylation of the same peptide on tyrosine and threonine. This temperature and PMA sensitivity distinguishes MAP kinase from most other tyrosine kinase substrates in activated human fibroblasts.

PMID: 1663789 PMCID: PMC361856 DOI: 10.1091/mbc.2.8.663

冠狀病毒 含有 甲基 轉移酶 的基因
(Methyl) (Transferase)

7

PubMed

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Format: Abstract

Virus Res. 2014 Dec 19;194:191-9. doi: 10.1016/j.virusres.2014.09.009. Epub 2014 Sep 30.

Coronavirus non-structural protein 16: evasion, attenuation, and possible treatments.

Menachery VD[1], Debbink K[2], Baric RS[2].

Author information

1 Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27599, USA. Electronic address: vineet@email.unc.edu.

2 Department of Epidemiology, University of North Carolina, Chapel Hill, NC 27599, USA; Department of Microbiology and Immunology, University of North Carolina, Chapel Hill, NC 27599, USA.

Abstract

The recent emergence of Middle East Respiratory Syndrome Coronavirus (MERS-CoV), nearly a decade after the Severe Acute Respiratory Syndrome (SARS) CoV, highlights the importance of understanding and developing therapeutic treatment for current and emergent CoVs. This manuscript explores the role of NSP16, a 2'O-methyl-transferase (2'O-MTase), in CoV infection and the host immune response. The review highlights conserved motifs, required interaction partners, as well as the attenuation of NSP16 mutants, and restoration of these mutants in specific immune knockouts. Importantly, the work also identifies a number of approaches to exploit this understanding for therapeutic treatment and the data clearly illustrate the importance of NSP16 2'O-MTase activity for CoV infection and pathogenesis.

KEYWORDS: 2'O-MTase; 2'O-Methyl-transferase; CoV; MDA5; NSP16; SARS-CoV

PMID: 25278144 PMCID: PMC4260984 DOI: 10.1016/j.virusres.2014.09.009

[Indexed for MEDLINE] **Free PMC Article**

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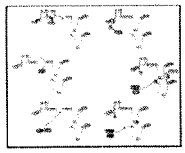
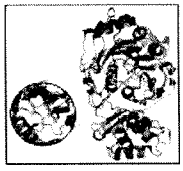
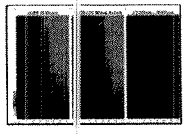
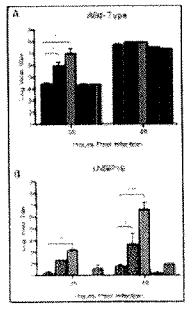
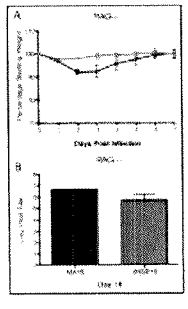
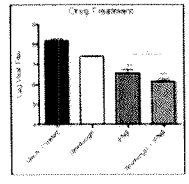

甲基化 EGF 接受體 (EGFR)

8

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Format: Abstract

J Clin Invest. 2015 Dec;125(12):4529-43. doi: 10.1172/JCI82826. Epub 2015 Nov 16.

PRMT1-mediated methylation of the EGF receptor regulates signaling and cetuximab response.

Liao HW, Hsu JM, Xia W, Wang HL, Wang YN, Chang WC, Arold ST, Chou CK, Tsou PH, Yamaguchi H, Fang YF, Lee HJ, Lee HH, Tai SK, Yang MH, Morelli MP, Sen M, Ladbury JE, Chen CH, Grandis JR, Kopetz S, Hung MC.

Abstract

Posttranslational modifications to the intracellular domain of the EGFR are known to regulate EGFR functions; however, modifications to the extracellular domain and their effects remain relatively unexplored. Here, we determined that methylation at R198 and R200 of the EGFR extracellular domain by protein arginine methyltransferase 1 (PRMT1) enhances binding to EGF and subsequent receptor dimerization and signaling activation. In a mouse orthotopic colorectal cancer xenograft model, expression of a methylation-defective EGFR reduced tumor growth. Moreover, increased EGFR methylation sustained signaling activation and cell proliferation in the presence of the therapeutic EGFR monoclonal antibody cetuximab. In colorectal cancer patients, EGFR methylation level also correlated with a higher recurrence rate after cetuximab treatment and reduced overall survival. Together, these data indicate that R198/R200 methylation of the EGFR plays an important role in regulating EGFR functionality and resistance to cetuximab treatment.

Comment in

Old dog, new tricks: extracellular domain arginine methylation regulates EGFR function. [J Clin Invest. 2015]

PMID: 26571401 PMCID: PMC4665782 DOI: 10.1172/JCI82826

[Indexed for MEDLINE] **Free PMC Article**

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Publication types, MeSH terms, Substances, Grant support

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激活了 EGFR，令肺纖維化

Antiviral Res. 2017 Jul;143:142-150. doi: 10.1016/j.antiviral.2017.03.022. Epub 2017 Apr 5.

The role of epidermal growth factor receptor (EGFR) signaling in SARS coronavirus-induced pulmonary fibrosis.

Venkataraman T[1], Frieman MB[2].

Author information

1 Department of Microbiology and Immunology, University of Maryland at Baltimore, 685 West Baltimore St. Room 380, Baltimore, MD, 21201, USA.

2 Department of Microbiology and Immunology, University of Maryland at Baltimore, 685 West Baltimore St. Room 380, Baltimore, MD, 21201, USA. Electronic address: mfrieman@som.umaryland.edu.

Abstract

Many survivors of the 2003 outbreak of severe acute respiratory syndrome (SARS) developed residual pulmonary fibrosis with increased severity seen in older patients. Autopsies of patients that died from SARS also showed fibrosis to varying extents. Pulmonary fibrosis can be occasionally seen as a consequence to several respiratory viral infections but is much more common after a SARS coronavirus (SARS-CoV) infection. Given the threat of future outbreaks of severe coronavirus disease, including Middle East respiratory syndrome (MERS), it is important to understand the mechanisms responsible for pulmonary fibrosis, so as to support the development of therapeutic countermeasures and mitigate sequelae of infection. In this article, we summarize pulmonary fibrotic changes observed after a SARS-CoV infection, discuss the extent to which other respiratory viruses induce fibrosis, describe available animal models to study the development of SARS-CoV induced fibrosis and review evidence that pulmonary fibrosis is caused by a hyperactive host response to lung injury mediated by epidermal growth factor receptor (EGFR) signaling. We summarize work from our group and others indicating that inhibiting EGFR signaling may prevent an excessive fibrotic response to SARS-CoV and other respiratory viral infections and propose directions for future research.

綠茶素（EGCG）↓EGFR

(10)

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Format: Abstract

Int J Mol Sci. 2008 Jun;9(6):1034-49. doi: 10.3390/ijms9061034. Epub 2008 Jun 20.

Targeting receptor tyrosine kinases for chemoprevention by green tea catechin, EGCG.

Shimizu M[1], Shirakami Y, Moriwaki H.

Author information

1 Department of Medicine, Gifu University Graduate School of Medicine, Japan. shimim-gif@umin.ac.jp <shimim-gif@umin.ac.jp>

Abstract

Tea is one of the most popular beverages consumed worldwide. Epidemiologic studies show an inverse relationship between consumption of tea, especially green tea, and development of cancers. Numerous in vivo and in vitro studies indicate strong chemopreventive effects for green tea and its constituents against cancers of various organs. (-)-Epigallocatechin-3-gallate (EGCG), the major catechin in green tea, appears to be the most biologically active constituent in tea with respect to inhibiting cell proliferation and inducing apoptosis in cancer cells. Recent studies indicate that the receptor tyrosine kinases (RTKs) are one of the critical targets of EGCG to inhibit cancer cell growth. EGCG inhibits the activation of EGFR (erbB1), HER2 (neu/erbB2) and also HER3 (neu/erbB3), which belong to subclass I of the RTK superfamily, in various types of human cancer cells. The activation of IGF-1 and VEGF receptors, the other members of RTK family, is also inhibited by EGCG. In addition, EGCG alters membrane lipid organization and thus inhibits the dimerization and activation of EGFR. Therefore, EGCG inhibits the Ras/MAPK and PI3K/Akt signaling pathways, which are RTK-related cell signaling pathways, as well as the activation of AP-1 and NF-kappaB, thereby modulating the expression of target genes which are associated with induction of apoptosis and cell cycle arrest in cancer cells. These findings are significant because abnormalities in the expression and function of RTKs and their downstream effectors play a critical role in the development of several types of human malignancies. In this paper we review evidence indicating that EGCG exerts anticancer effects, at least in part, through inhibition of activation of the specific RTKs and conclude that targeting