



TESI DOCTORAL

LA VIA JAK/STAT COM A MEDIADORA DE RESPOSTES A L'ESTRÈS OXIDATIU, LA INFLAMACIÓ I LA IMMUNITAT INNATA EN ASTRÒCITS

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BIBLIOGRAFIA

A

Abbas,A.K., Murphy,K.M., & Sher,A. (1996) Functional diversity of helper T lymphocytes. *Nature* **383** , 787-793.

Agrawal,S., Agarwal,M.L., Chatterjee-Kishore,M., Stark,G.R., & Chisolm,G.M. (2002) Stat1-dependent, p53-independent expression of p21(waf1) modulates oxysterol-induced apoptosis. *Mol. Cell Biol.* **22**, 1981-1992.

Akira,S., Taga,T., & Kishimoto,T. (1993) Interleukin-6 in biology and medicine. *Adv. Immunol.* **54**, 1-78.

Akira,S., Nishio,Y., Inoue,M., Wang,X.J., Wei,S., Matsusaka,T., Yoshida,K., Sudo,T., Naruto,M., & Kishimoto,T. (1994) Molecular cloning of APRF, a novel IFN-stimulated gene factor 3 p91-related transcription factor involved in the gp130-mediated signaling pathway. *Cell* **77**, 63-71.

Akira,S. (1999) Functional roles of STAT family proteins: lessons from knockout mice. *Stem Cells* **17**, 138-146.

Akira,S. (2006) TLR signaling. *Curr. Top. Microbiol. Immunol.* **311**, 1-16.

Alexopoulou,L., Holt,A.C., Medzhitov,R., & Flavell,R.A. (2001) Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature* **413**, 732-738.

Allan,S.M. & Rothwell,N.J. (2001) Cytokines and acute neurodegeneration. *Nat. Rev. Neurosci.* **2**, 734-744.

Aloisi,F., Ria,F., & Adorini,L. (2000) Regulation of T-cell responses by CNS antigen-presenting cells: different roles for microglia and astrocytes. *Immunol. Today* **21**, 141-147.

Arora,T., Liu,B., He,H., Kim,J., Murphy,T.L., Murphy,K.M., Modlin,R.L., & Shuai,K. (2003) PIASx is a transcriptional co-repressor of signal transducer and activator of transcription 4. *J. Biol. Chem.* **278**, 21327-21330.

Aruoma,O.I., Halliwell,B., Laughton,M.J., Quinlan,G.J., & Gutteridge,J.M. (1989) The mechanism of initiation of lipid peroxidation. Evidence against a requirement for an iron(II)-iron(III) complex. *Biochem. J.* **258**, 617-620.

Aruoma,O.I., Evans,P.J., Kaur,H., Sutcliffe,L., & Halliwell,B. (1990) An evaluation of the antioxidant and potential pro-oxidant properties of food additives and of trolox C, vitamin E and probucol. *Free Radic. Res. Commun.* **10**, 143-157.

Avdiushko,R., Hongo,D., Lake-Bullock,H., Kaplan,A., & Cohen,D. (2001) IL-10 receptor dysfunction in macrophages during chronic inflammation. *J. Leukoc. Biol.* **70**, 624-632.

B

Bajetto,A., Bonavia,R., Barbero,S., Florio,T., & Schettini,G. (2001) Chemokines and their receptors in the central nervous system. *Front Neuroendocrinol.* **22**, 147-184.

Barone,F.C., Arvin,B., White,R.F., Miller,A., Webb,C.L., Willette,R.N., Lysko,P.G., & Feuerstein,G.Z. (1997) Tumor necrosis factor-alpha. A mediator of focal ischemic brain injury. *Stroke* **28**, 1233-1244.

Bass,N.H., Hess,H.H., Pope,A., & Thalheimer,C. (1971) Quantitative cytoarchitectonic distribution of neurons, glia, and DNA in rat cerebral cortex. *J. Comp Neurol.* **143**, 481-490.

Bastide,M., Gele,P., Petrault,O., Pu,Q., Caliez,A., Robin,E., Deplanque,D., Duriez,P., & Bordet,R. (2003) Delayed cerebrovascular protective effect of lipopolysaccharide in parallel to brain ischemic tolerance. *J. Cereb. Blood Flow Metab* **23**, 399-405.

Beckman,J.S. (1994) Peroxynitrite versus hydroxyl radical: the role of nitric oxide in superoxide-dependent cerebral injury. *Ann. N. Y. Acad. Sci.* **738**, 69-75.

Bhattacharya,S. & Schindler,C. (2003) Regulation of Stat3 nuclear export. *J. Clin. Invest* **111**, 553-559.

Bignami,A., Eng,L.F., Dahl,D., & Uyeda,C.T. (1972) Localization of the glial fibrillary acidic protein in astrocytes by immunofluorescence. *Brain Res.* **43**, 429-435.

Bindokas,V.P., Jordan,J., Lee,C.C., & Miller,R.J. (1996) Superoxide production in rat hippocampal neurons: selective imaging with hydroethidine. *J. Neurosci.* **16**, 1324-1336.

Biragyn,A., Ruffini,P.A., Leifer,C.A., Klyushnenkova,E., Shakhov,A., Chertov,O., Shirakawa,A.K., Farber,J.M., Segal,D.M., Oppenheim,J.J., & Kwak,L.W. (2002) Toll-like receptor 4-dependent activation of dendritic cells by beta-defensin 2. *Science* **298**, 1025-1029.

Bird,R.P., Hung,S.S., Hadley,M., & Draper,H.H. (1983) Determination of malonaldehyde in biological materials by high-pressure liquid chromatography. *Anal. Biochem.* **128**, 240-244.

Bodaness,R.S. (1982) The potential role of NADPH and cytoplasmic NADP-linked dehydrogenases in protection against singlet oxygen mediated cellular toxicity. *Biochem. Biophys. Res. Commun.* **108**, 1709-1715.

Boros,P. & Bromberg,J.S. (2006) New cellular and molecular immune pathways in ischemia/reperfusion injury. *Am. J. Transplant.* **6**, 652-658.

Boveris,A. & Chance,B. (1973) The mitochondrial generation of hydrogen peroxide. General properties and effect of hyperbaric oxygen. *Biochem. J.* **134**, 707-716.

Bowman,C.C., Rasley,A., Tranguch,S.L., & Marriott,I. (2003) Cultured astrocytes express toll-like receptors for bacterial products. *Glia* **43**, 281-291.

Bradford,M.M. (1976) A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. *Anal. Biochem.* **72**, 248-254.

Breen,A.P. & Murphy,J.A. (1995) Reactions of oxyl radicals with DNA. *Free Radic. Biol. Med.* **18**, 1033-1077.

Brierley,M.M. & Fish,E.N. (2005) Stats: multifaceted regulators of transcription. *J. Interferon Cytokine Res.* **25**, 733-744.

Bromberg,J.F., Horvath,C.M., Wen,Z., Schreiber,R.D., & Darnell,J.E., Jr. (1996) Transcriptionally active Stat1 is required for the antiproliferative effects of both interferon alpha and interferon gamma. *Proc. Natl. Acad. Sci. U. S. A* **93**, 7673-7678.

Bromberg,J.F., Wrzeszczynska,M.H., Devgan,G., Zhao,Y., Pestell,R.G., Albanese,C., & Darnell,J.E., Jr. (1999) Stat3 as an oncogene. *Cell* **98**, 295-303.

Bsibsi,M., Ravid,R., Gveric,D., & van Noort,J.M. (2002) Broad expression of Toll-like receptors in the human central nervous system. *J. Neuropathol. Exp. Neurol.* **61**, 1013-1021.

Bsibsi,M., Persoon-Deen,C., Verwer,R.W., Meeuwssen,S., Ravid,R., & van Noort,J.M. (2006) Toll-like receptor 3 on adult human astrocytes triggers production of neuroprotective mediators. *Glia* **53**, 688-695.

Burkitt,M.J. & Gilbert,B.C. (1989) The control of iron-induced oxidative damage in isolated rat-liver mitochondria by respiration state and ascorbate. *Free Radic. Res. Commun.* **5**, 333-344.

Burns,K., Clatworthy,J., Martin,L., Martinon,F., Plumpton,C., Maschera,B., Lewis,A., Ray,K., Tschopp,J., & Volpe,F. (2000) Tollip, a new component of the IL-1RI pathway, links IRAK to the IL-1 receptor. *Nat. Cell Biol.* **2**, 346-351.

Bus,J.S. & Gibson,J.E. (1984) Paraquat: model for oxidant-initiated toxicity. *Environ. Health Perspect.* **55**, 37-46.

Busch,G.L., Wiesinger,H., Gulbins,E., Wagner,H.J., Hamprecht,B., & Lang,F. (1996) Effect of astroglial cell swelling on pH of acidic intracellular compartments. *Biochim. Biophys. Acta* **1285**, 212-218.

Buttini,M., Sauter,A., & Boddeke,H.W. (1994) Induction of interleukin-1 beta mRNA after focal cerebral ischaemia in the rat. *Brain Res. Mol. Brain Res.* **23**, 126-134.

C

Carballo,M., Conde,M., El Bekay,R., Martin-Nieto,J., Camacho,M.J., Monteseirin,J., Conde,J., Bedoya,F.J., & Sobrino,F. (1999) Oxidative stress triggers STAT3 tyrosine phosphorylation and nuclear translocation in human lymphocytes. *J. Biol. Chem.* **274**, 17580-17586.

Carpentier,P.A., Williams,B.R., & Miller,S.D. (2007) Distinct roles of protein kinase R and toll-like receptor 3 in the activation of astrocytes by viral stimuli. *Glia* **55**, 239-252.

Carpino,N., Kobayashi,R., Zang,H., Takahashi,Y., Jou,S.T., Feng,J., Nakajima,H., & Ihle,J.N. (2002) Identification, cDNA cloning, and targeted deletion of p70, a novel, ubiquitously expressed SH3 domain-containing protein. *Mol. Cell Biol.* **22**, 7491-7500.

Carter,S.L., Muller,M., Manders,P.M., & Campbell,I.L. (2007) Induction of the genes for Cxcl9 and Cxcl10 is dependent on IFN-gamma but shows differential cellular expression in experimental autoimmune encephalomyelitis and by astrocytes and microglia in vitro. *Glia* **55**, 1728-1739.

Caso,J.R., Pradillo,J.M., Hurtado,O., Lorenzo,P., Moro,M.A. & Lizasoain,I. (2007) Toll-like receptor 4 is involved in brain damage and inflammation after experimental stroke. *Circulation* **15**, 1599-1608

Castillo,J., Alvarez-Sabin,J., Davalos,A., Diez-Tejedor,E., Lizasoain,I., Martinez-Vila,E., Vivancos,J., & Zarranz,J.J. (2003) [Consensus review. Pharmacological neuroprotection in cerebral ischemia: is it still a therapeutic option?]. *Neurologia* **18**, 368-384.

Catlett-Falcone,R., Landowski,T.H., Oshiro,M.M., Turkson,J., Levitzki,A., Savino,R., Ciliberto,G., Moscinski,L., Fernandez-Luna,J.L., Nunez,G., Dalton,W.S., & Jove,R. (1999) Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. *Immunity*. **10**, 105-115.

Chakraborty,A. & Tweardy,D.J. (1998) Granulocyte colony-stimulating factor activates a 72-kDa isoform of STAT3 in human neutrophils. *J. Leukoc. Biol.* **64**, 675-680.

Chamorro,A., Amaro,S., Vargas,M., Obach,V., Cervera,A., Torres,F., & Planas,A.M. (2006) Interleukin 10, monocytes and increased risk of early infection in ischaemic stroke. *J. Neurol. Neurosurg. Psychiatry* **77**, 1279-1281.

Chamorro,A., Urra,X., & Planas,A.M. (2007) Infection after acute ischemic stroke: a manifestation of brain-induced immunodepression. *Stroke* **38**, 1097-1103.

Chan,P.H. (1994) Oxygen radicals in focal cerebral ischemia. *Brain Pathol.* **4**, 59-65.

Chan,P.H. (2001) Reactive oxygen radicals in signaling and damage in the ischemic brain. *J. Cereb. Blood Flow Metab* **21**, 2-14.

Chance,B., Sies,H., & Boveris,A. (1979) Hydroperoxide metabolism in mammalian organs. *Physiol Rev.* **59**, 527-605.

Chang,T.L., Peng,X., & Fu,X.Y. (2000) Interleukin-4 mediates cell growth inhibition through activation of Stat1. *J. Biol. Chem.* **275**, 10212-10217.

Chen,J., Nagayama,T., Jin,K., Stetler,R.A., Zhu,R.L., Graham,S.H., & Simon,R.P. (1998) Induction of caspase-3-like protease may mediate delayed neuronal death in the hippocampus after transient cerebral ischemia. *J. Neurosci.* **18**, 4914-4928.

Chen,P., Shibata,M., Zidovetzki,R., Fisher,M., Zlokovic,B.V., & Hofman,F.M. (2001) Endothelin-1 and monocyte chemoattractant protein-1 modulation in ischemia and human brain-derived endothelial cell cultures. *J. Neuroimmunol.* **116**, 62-73.

Chen,Y. & Swanson,R.A. (2003) Astrocytes and brain injury. *J. Cereb. Blood Flow Metab* **23**, 137-149.

Chin,Y.E., Kitagawa,M., Kuida,K., Flavell,R.A., & Fu,X.Y. (1997) Activation of the STAT signaling pathway can cause expression of caspase 1 and apoptosis. *Mol. Cell Biol.* **17**, 5328-5337.

Chishti,A.H., Kim,A.C., Marfatia,S.M., Lutchman,M., Hanspal,M., Jindal,H., Liu,S.C., Low,P.S., Rouleau,G.A., Mohandas,N., Chasis,J.A., Conboy,J.G., Gascard,P., Takakuwa,Y., Huang,S.C., Benz,E.J., Jr., Bretscher,A., Fehon,R.G., Gusella,J.F., Ramesh,V., Solomon,F., Marchesi,V.T., Tsukita,S., Tsukita,S., Hoover,K.B., & . (1998) The FERM domain: a unique module involved in the linkage of cytoplasmic proteins to the membrane. *Trends Biochem. Sci.* **23**, 281-282.

Cho,S., Park,E.M., Febbraio,M., Anrather,J., Park,L., Racchumi,G., Silverstein,R.L., & Iadecola,C. (2005) The class B scavenger receptor CD36 mediates free radical production and tissue injury in cerebral ischemia. *J. Neurosci.* **25**, 2504-2512.

Cholewinski,A.J. & Wilkin,G.P. (1988) Peptide receptors on astrocytes: evidence for regional heterogeneity. *Biochem. Soc. Trans.* **16**, 429-432.

Chomczynski,P. & Sacchi,N. (1987) Single-step method of RNA isolation by acid guanidinium thiocyanate-phenol-chloroform extraction. *Anal. Biochem.* **162**, 156-159.

Chung,H.K., Lee,I.K., Kang,H., Suh,J.M., Kim,H., Park,K.C., Kim,D.W., Kim,Y.K., Ro,H.K., & Shong,M. (2002) Statin inhibits interferon-gamma-induced expression of intercellular adhesion molecule-1 (ICAM-1) in vascular endothelial and smooth muscle cells. *Exp. Mol. Med.* **34**, 451-461.

Clark,W.M., Rinker,L.G., Lessov,N.S., Hazel,K., Hill,J.K., Stenzel-Poore,M., & Eckenstein,F. (2000) Lack of interleukin-6 expression is not protective against focal central nervous system ischemia. *Stroke* **31**, 1715-1720.

Copeland,N.G., Gilbert,D.J., Schindler,C., Zhong,Z., Wen,Z., Darnell,J.E., Jr., Mui,A.L., Miyajima,A., Quelle,F.W., Ihle,J.N., & . (1995) Distribution of the mammalian Stat gene family in mouse chromosomes. *Genomics* **29**, 225-228.

Corte,E.D. & Stirpe,F. (1972) The regulation of rat liver xanthine oxidase. Involvement of thiol groups in the conversion of the enzyme activity from dehydrogenase (type D) into oxidase (type O) and purification of the enzyme. *Biochem. J.* **126**, 739-745.

Costa-Pereira,A.P., Tininini,S., Strobl,B., Alonzi,T., Schlaak,J.F., Is'harc,H., Gesualdo,I., Newman,S.J., Kerr,I.M., & Poli,V. (2002) Mutational switch of an IL-6 response to an interferon-gamma-like response. *Proc. Natl. Acad. Sci. U. S. A* **99**, 8043-8047.

Crack,P.J. & Taylor,J.M. (2005) Reactive oxygen species and the modulation of stroke. *Free Radic. Biol. Med.* **38**, 1433-1444.

Cui,Y., Riedlinger,G., Miyoshi,K., Tang,W., Li,C., Deng,C.X., Robinson,G.W., & Hennighausen,L. (2004) Inactivation of Stat5 in mouse mammary epithelium during pregnancy reveals distinct functions in cell proliferation, survival, and differentiation. *Mol. Cell Biol.* **24**, 8037-8047.

Cunningham,L.A., Wetzel,M., & Rosenberg,G.A. (2005) Multiple roles for MMPs and TIMPs in cerebral ischemia. *Glia* **50**, 329-339.

D

Dai,C.H., Price,J.O., Brunner,T., & Krantz,S.B. (1998) Fas ligand is present in human erythroid colony-forming cells and interacts with Fas induced by interferon gamma to produce erythroid cell apoptosis. *Blood* **91**, 1235-1242.

Danbolt,N.C. (1994) The high affinity uptake system for excitatory amino acids in the brain. *Prog. Neurobiol.* **44**, 377-396.

Darnell,J.E., Jr. (1997) STATs and gene regulation. *Science* **277**, 1630-1635.

Dawson,T.M. & Snyder,S.H. (1994) Gases as biological messengers: nitric oxide and carbon monoxide in the brain. *J. Neurosci.* **14**, 5147-5159.

De Bouteiller,O., Merck,E., Hasan,U.A., Hubac,S., Benguigui,B., Trinchieri,G., Bates,E.E., & Caux,C. (2005) Recognition of double-stranded RNA by human toll-like receptor 3 and downstream receptor signaling requires multimerization and an acidic pH. *J. Biol. Chem.* **280**, 38133-38145.

De Fraja,C., Conti,L., Magrassi,L., Govoni,S., & Cattaneo,E. (1998) Members of the JAK/STAT proteins are expressed and regulated during development in the mammalian forebrain. *J. Neurosci. Res.* **54**, 320-330.

De Simoni,M.G., Rossi,E., Storini,C., Pizzimenti,S., Echart,C. & Bergamaschini,L.(2004) The powerful neuroprotective action of C1-inhibitor on brain ischemia-reperfusion injury does not require C1q. *Am. J. Pathol.* **164**, 1857-1863.

De Vos,J., Jourdan,M., Tarte,K., Jasmin,C., & Klein,B. (2000) JAK2 tyrosine kinase inhibitor tyrphostin AG490 downregulates the mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STAT) pathways and induces apoptosis in myeloma cells. *Br. J. Haematol.* **109**, 823-828.

Dean,R.T., Giese,S., & Davies,M.J. (1993) Reactive species and their accumulation on radical-damaged proteins. *Trends Biochem. Sci.* **18**, 437-441.

Deby,C. & Goutier,R. (1990) New perspectives on the biochemistry of superoxide anion and the efficiency of superoxide dismutases. *Biochem. Pharmacol.* **39**, 399-405.

Dell'Albani,P., Santangelo,R., Torrisi,L., Nicoletti,V.G., de Vellis,J., & Giuffrida Stella,A.M. (2001) JAK/STAT signaling pathway mediates cytokine-induced iNOS expression in primary astroglial cell cultures. *J. Neurosci. Res.* **65**, 417-424.

Dell'Albani,P., Santangelo,R., Torrisi,L., Nicoletti,V.G., & Giuffrida Stella,A.M. (2003) Role of the JAK/STAT signal transduction pathway in the regulation of gene expression in CNS. *Neurochem. Res.* **28**, 53-64.

Della,C.E. & Stirpe,F. (1968) The regulation of rat-liver xanthine oxidase: Activation by proteolytic enzymes. *FEBS Lett.* **2**, 83-84.

Desagher,S., Glowinski,J., & Premont,J. (1996) Astrocytes protect neurons from hydrogen peroxide toxicity. *J. Neurosci.* **16**, 2553-2562.

Di Mascio,P., Bechara,E.J., Medeiros,M.H., Briviba,K., & Sies,H. (1994) Singlet molecular oxygen production in the reaction of peroxynitrite with hydrogen peroxide. *FEBS Lett.* **355**, 287-289.

Diebold,S.S., Montoya,M., Unger,H., Alexopoulou,L., Roy,P., Haswell,L.E., Al Shamkhani,A., Flavell,R., Borrow,P., & Reis e Sousa (2003) Viral infection switches non-plasmacytoid dendritic cells into high interferon producers. *Nature* **424**, 324-328.

Dignam,J.D., Lebovitz,R.M., & Roeder,R.G. (1983) Accurate transcription initiation by RNA polymerase II in a soluble extract from isolated mammalian nuclei. *Nucleic Acids Res.* **11** , 1475-1489.

Dirnagl,U., Iadecola,C., & Moskowitz,M.A. (1999) Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci.* **22**, 391-397.

Dong,Y. & Benveniste,E.N. (2001) Immune function of astrocytes. *Glia* **36**, 180-190.

Donnelly,R.P., Dickensheets,H., & Finbloom,D.S. (1999) The interleukin-10 signal transduction pathway and regulation of gene expression in mononuclear phagocytes. *J. Interferon Cytokine Res.* **19**, 563-573.

Dringen,R., Gebhardt,R., & Hamprecht,B. (1993) Glycogen in astrocytes: possible function as lactate supply for neighboring cells. *Brain Res.* **623**, 208-214.

Dringen,R. (2000) Metabolism and functions of glutathione in brain. *Prog. Neurobiol.* **62**, 649-671.

Dringen,R., Gutterer,J.M., Gros,C., & Hirrlinger,J. (2001) Aminopeptidase N mediates the utilization of the GSH precursor CysGly by cultured neurons. *J. Neurosci. Res.* **66**, 1003-1008.

Dugan,L.L. & Choi,D.W. (1994) Excitotoxicity, free radicals, and cell membrane changes. *Ann. Neurol.* **35 Suppl**, S17-S21.

Duhe,R.J., Clark,E.A., & Farrar,W.L. (2002) Characterization of the in vitro kinase activity of a partially purified soluble GST/JAK2 fusion protein. *Mol. Cell Biochem.* **236**, 23-35.

Durbin,J.E., Hackenmiller,R., Simon,M.C., & Levy,D.E. (1996) Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. *Cell* **84**, 443-450.

E

Edmond,J., Robbins,R.A., Bergstrom,J.D., Cole,R.A., & de Vellis,J. (1987) Capacity for substrate utilization in oxidative metabolism by neurons, astrocytes, and oligodendrocytes from developing brain in primary culture. *J. Neurosci. Res.* **18**, 551-561.

Ekert,P.G., Silke,J., & Vaux,D.L. (1999) Caspase inhibitors. *Cell Death. Differ.* **6**, 1081-1086.

Endres,M., Laufs,U., Huang,Z., Nakamura,T., Huang,P., Moskowitz,M.A., & Liao,J.K. (1998) Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc. Natl. Acad. Sci. U. S. A* **95**, 8880-8885.

Enkvist,M.O. & McCarthy,K.D. (1992) Activation of protein kinase C blocks astroglial gap junction communication and inhibits the spread of calcium waves. *J. Neurochem.* **59**, 519-526.

F

Facchinetti,F., Dawson,V.L., & Dawson,T.M. (1998) Free radicals as mediators of neuronal injury. *Cell Mol. Neurobiol.* **18**, 667-682.

Fagerlund,R., Melen,K., Kinnunen,L., & Julkunen,I. (2002) Arginine/lysine-rich nuclear localization signals mediate interactions between dimeric STATs and importin alpha 5. *J. Biol. Chem.* **277**, 30072-30078.

Fain,J.N., Ihle,J.H., & Bahouth,S.W. (1999) Stimulation of lipolysis but not of leptin release by growth hormone is abolished in adipose tissue from Stat5a and b knockout mice. *Biochem. Biophys. Res. Commun.* **263**, 201-205.

Faraci,F.M. & Brian,J.E., Jr. (1994) Nitric oxide and the cerebral circulation. *Stroke* **25**, 692-703.

Farina,C., Krumbholz,M., Giese,T., Hartmann,G., Aloisi,F., & Meinl,E. (2005) Preferential expression and function of Toll-like receptor 3 in human astrocytes. *J. Neuroimmunol.* **159**, 12-19.

Farina,C., Aloisi,F., & Meinl,E. (2007) Astrocytes are active players in cerebral innate immunity. *Trends Immunol.* **28**, 138-145.

Farrar,J.D., Smith,J.D., Murphy,T.L., Leung,S., Stark,G.R., & Murphy,K.M. (2000) Selective loss of type I interferon-induced STAT4 activation caused by a minisatellite insertion in mouse Stat2. *Nat. Immunol.* **1**, 65-69.

Fassbender,K., Rossol,S., Kammer,T., Daffertshofer,M., Wirth,S., Dollman,M., & Hennerici,M. (1994) Proinflammatory cytokines in serum of patients with acute cerebral ischemia: kinetics of secretion and relation to the extent of brain damage and outcome of disease. *J. Neurol. Sci.* **122**, 135-139.

Fauconneau,B., Petegnief,V., Sanfeliu,C., Piriou,A., & Planas,A.M. (2002) Induction of heat shock proteins (HSPs) by sodium arsenite in cultured astrocytes and reduction of hydrogen peroxide-induced cell death. *J. Neurochem.* **83**, 1338-1348.

Febbraio,M., Hajjar,D.P., & Silverstein,R.L. (2001) CD36: a class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. *J. Clin. Invest* **108**, 785-791.

Feng,J., Witthuhn,B.A., Matsuda,T., Kohlhuber,F., Kerr,I.M., & Ihle,J.N. (1997) Activation of Jak2 catalytic activity requires phosphorylation of Y1007 in the kinase activation loop. *Mol. Cell Biol.* **17**, 2497-2501.

Filomeni,G., Rotilio,G., & Ciriolo,M.R. (2005) Disulfide relays and phosphorylative cascades: partners in redox-mediated signaling pathways. *Cell Death. Differ.* **12**, 1555-1563.

Fiorentino,D.F., Zlotnik,A., Vieira,P., Mosmann,T.R., Howard,M., Moore,K.W., & O'Garra,A. (1991) IL-10 acts on the antigen-presenting cell to inhibit cytokine production by Th1 cells. *J. Immunol.* **146**, 3444-3451.

Fiskum,G., Murphy,A.N., & Beal,M.F. (1999) Mitochondria in neurodegeneration: acute ischemia and chronic neurodegenerative diseases. *J. Cereb. Blood Flow Metab* **19**, 351-369.

Fridovich, I. (1995) Superoxide radical and superoxide dismutases. *Annu. Rev. Biochem.* **64**, 97-112.

Frijns, C.J. & Kappelle, L.J. (2002) Inflammatory cell adhesion molecules in ischemic cerebrovascular disease. *Stroke* **33**, 2115-2122.

Fujimura, M., Morita-Fujimura, Y., Murakami, K., Kawase, M., & Chan, P.H. (1998) Cytosolic redistribution of cytochrome c after transient focal cerebral ischemia in rats. *J. Cereb. Blood Flow Metab* **18**, 1239-1247.

Fujitani, Y., Hibi, M., Fukada, T., Takahashi-Tezuka, M., Yoshida, H., Yamaguchi, T., Sugiyama, K., Yamanaka, Y., Nakajima, K., & Hirano, T. (1997) An alternative pathway for STAT activation that is mediated by the direct interaction between JAK and STAT. *Oncogene* **14**, 751-761.

Fukada, T., Hibi, M., Yamanaka, Y., Takahashi-Tezuka, M., Fujitani, Y., Yamaguchi, T., Nakajima, K., & Hirano, T. (1996) Two signals are necessary for cell proliferation induced by a cytokine receptor gp130: involvement of STAT3 in anti-apoptosis. *Immunity*. **5**, 449-460.

Funami, K., Matsumoto, M., Oshiumi, H., Akazawa, T., Yamamoto, A., & Seya, T. (2004) The cytoplasmic 'linker region' in Toll-like receptor 3 controls receptor localization and signaling. *Int. Immunol.* **16**, 1143-1154.

G

Gabryel, B., Adamek, M., & Trzeciak, H.I. (2001) Does trimetazidine exert cytoprotective activity on astrocytes subjected to hypoxia in vitro? *Neurotoxicology* **22**, 455-465.

Gaiddon, C., Moorthy, N.C., & Prives, C. (1999) Ref-1 regulates the transactivation and pro-apoptotic functions of p53 in vivo. *EMBO J.* **18**, 5609-5621.

Garau, A., Bertini, R., Colotta, F., Casilli, F., Bigini, P., Cagnotto, A., Mennini, T., Ghezzi, P., & Villa, P. (2005) Neuroprotection with the CXCL8 inhibitor repertaxin in transient brain ischemia. *Cytokine* **30**, 125-131.

Garcia, J.H., Kalimo, H., Kamijyo, Y., & Trump, B.F. (1977) Cellular events during partial cerebral ischemia. I. Electron microscopy of feline cerebral cortex after middle-cerebral-artery occlusion. *Virchows Arch. B Cell Pathol.* **25**, 191-206.

Garcia,R., Bowman,T.L., Niu,G., Yu,H., Minton,S., Muro-Cacho,C.A., COX,C.E., Falcone,R., Fairclough,R., Parsons,S., Laudano,A., Gazit,A., Levitzki,A., Kraker,A., & Jove,R. (2001) Constitutive activation of Stat3 by the Src and JAK tyrosine kinases participates in growth regulation of human breast carcinoma cells. *Oncogene* **20**, 2499-2513.

Geddes,J.W., Pettigrew,L.C., Holtz,M.L., Craddock,S.D., & Maines,M.D. (1996) Permanent focal and transient global cerebral ischemia increase glial and neuronal expression of heme oxygenase-1, but not heme oxygenase-2, protein in rat brain. *Neurosci. Lett.* **210**, 205-208.

Gewinner,C., Hart,G., Zachara,N., Cole,R., Beisenherz-Huss,C., & Groner,B. (2004) The coactivator of transcription CREB-binding protein interacts preferentially with the glycosylated form of Stat5. *J. Biol. Chem.* **279**, 3563-3572.

Giulian,D. & Baker,T.J. (1986) Characterization of ameboid microglia isolated from developing mammalian brain. *J. Neurosci.* **6**, 2163-2178.

Grace,P.A. (1994) Ischaemia-reperfusion injury. *Br. J. Surg.* **81**, 637-647.

Grilli,M., Barbieri,I., Basudev,H., Brusa,R., Casati,C., Lozza,G., & Ongini,E. (2000) Interleukin-10 modulates neuronal threshold of vulnerability to ischaemic damage. *Eur. J. Neurosci.* **12**, 2265-2272.

Guo,G.G., Patel,K., Kumar,V., Shah,M., Fried,V.A., Etlinger,J.D., & Sehgal,P.B. (2002) Association of the chaperone glucose-regulated protein 58 (GRP58/ER-60/ERp57) with Stat3 in cytosol and plasma membrane complexes. *J. Interferon Cytokine Res.* **22**, 555-563.

H

Halliwell,B. & Gutteridge,J.M.C. (1989) Free Radicals in Biology and medicine, p. 543. Clarendon Press, Oxford.

Han,H.S. & Yenari,M.A. (2003) Cellular targets of brain inflammation in stroke. *Curr. Opin. Investig. Drugs* **4**, 522-529.

Hansen,M.B., Nielsen,S.E., & Berg,K. (1989) Re-examination and further development of a precise and rapid dye method for measuring cell growth/cell kill. *J. Immunol. Methods* **119**, 203-210.

Hansson,E. & Ronnback,L. (1990) Astrocytes in neurotransmission. A review. *Cell Mol. Biol.* **36**, 487-496.

Hatashita,S. & Hoff,J.T. (1990) Brain edema and cerebrovascular permeability during cerebral ischemia in rats. *Stroke* **21**, 582-588.

Hattori,R., Maulik,N., Otani,H., Zhu,L., Cordis,G., Engelman,R.M., Siddiqui,M.A., & Das,D.K. (2001) Role of STAT3 in ischemic preconditioning. *J. Mol. Cell Cardiol.* **33**, 1929-1936.

Heil,F., Hemmi,H., Hochrein,H., Ampenberger,F., Kirschning,C., Akira,S., Lipford,G., Wagner,H., & Bauer,S. (2004) Species-specific recognition of single-stranded RNA via toll-like receptor 7 and 8. *Science* **303**, 1526-1529.

Heinrich,P.C., Behrmann,I., Muller-Newen,G., Schaper,F., & Graeve,L. (1998) Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. *Biochem. J.* **334 (Pt 2)**, 297-314.

Hemmi,H., Takeuchi,O., Kawai,T., Kaisho,T., Sato,S., Sanjo,H., Matsumoto,M., Hoshino,K., Wagner,H., Takeda,K., & Akira,S. (2000) A Toll-like receptor recognizes bacterial DNA. *Nature* **408**, 740-745.

Hemmi,H., Takeuchi,O., Sato,S., Yamamoto,M., Kaisho,T., Sanjo,H., Kawai,T., Hoshino,K., Takeda,K., & Akira,S. (2004) The roles of two IkappaB kinase-related kinases in lipopolysaccharide and double stranded RNA signaling and viral infection. *J. Exp. Med.* **199** , 1641-1650.

Herrero,C., Hu,X., Li,W.P., Samuels,S., Sharif,M.N., Kotenko,S., & Ivashkiv,L.B. (2003) Reprogramming of IL-10 activity and signaling by IFN-gamma. *J. Immunol.* **171**, 5034-5041.

Herrmann,O., Tarabin,V., Suzuki,S., Attigah,N., Coserea,I., Schneider,A., Vogel,J., Prinz,S., Schwab,S., Monyer,H., Brombacher,F., & Schwaninger,M. (2003) Regulation of body temperature and neuroprotection by endogenous interleukin-6 in cerebral ischemia. *J. Cereb. Blood Flow Metab* **23**, 406-415.

Hilkens,C.M., Is'harc,H., Lillemeier,B.F., Strobl,B., Bates,P.A., Behrmann,I., & Kerr,I.M. (2001) A region encompassing the FERM domain of Jak1 is necessary for binding to the cytokine receptor gp130. *FEBS Lett.* **505**, 87-91.

Hirano,T. (1992) Interleukin-6 and its relation to inflammation and disease. *Clin. Immunol. Immunopathol.* **62**, S60-S65.

Hirano,T., Nakajima,K., & Hibi,M. (1997) Signaling mechanisms through gp130: a model of the cytokine system. *Cytokine Growth Factor Rev.* **8**, 241-252.

Hornig,T., Barton,G.M., Flavell,R.A., & Medzhitov,R. (2002) The adaptor molecule TIRAP provides signalling specificity for Toll-like receptors. *Nature* **420**, 329-333.

Hornung,V., Guenther-Biller,M., Bourquin,C., Ablasser,A., Schlee,M., Uematsu,S., Noronha,A., Manoharan,M., Akira,S., de Fougerolles,A., Endres,S., & Hartmann,G. (2005) Sequence-specific potent induction of IFN-alpha by short interfering RNA in plasmacytoid dendritic cells through TLR7. *Nat. Med.* **11**, 263-270.

Hoshino,K., Kaisho,T., Iwabe,T., Takeuchi,O., & Akira,S. (2002) Differential involvement of IFN-beta in Toll-like receptor-stimulated dendritic cell activation. *Int. Immunol.* **14**, 1225-1231.

Hossmann,K.A. (1994) Glutamate-mediated injury in focal cerebral ischemia: the excitotoxin hypothesis revised. *Brain Pathol.* **4**, 23-36.

Hossmann,K.A. (1994) Viability thresholds and the penumbra of focal ischemia. *Ann. Neurol.* **36**, 557-565.

Huang,J., Upadhyay,U.M., & Tamargo,R.J. (2006) Inflammation in stroke and focal cerebral ischemia. *Surg. Neurol.* **66**, 232-245.

Huang,Z., Huang,P.L., Ma,J., Meng,W., Ayata,C., Fishman,M.C., & Moskowitz,M.A. (1996) Enlarged infarcts in endothelial nitric oxide synthase knockout mice are attenuated by nitro-L-arginine. *J. Cereb. Blood Flow Metab* **16**, 981-987.

I

Iadecola,C., Zhang,F., Xu,S., Casey,R., & Ross,M.E. (1995) Inducible nitric oxide synthase gene expression in brain following cerebral ischemia. *J. Cereb. Blood Flow Metab* **15**, 378-384.

Iadecola,C., Forster,C., Nogawa,S., Clark,H.B., & Ross,M.E. (1999) Cyclooxygenase-2 immunoreactivity in the human brain following cerebral ischemia. *Acta Neuropathol. (Berl)* **98**, 9-14.

Ignacio,P.C., Baldwin,B.A., Vijayan,V.K., Tait,R.C., & Gorin,F.A. (1990) Brain isozyme of glycogen phosphorylase: immunohistological localization within the central nervous system. *Brain Res.* **529**, 42-49.

Ijzermans,J.N. & Marquet,R.L. (1989) Interferon-gamma: a review. *Immunobiology* **179**, 456-473.

Imada,K., Bloom,E.T., Nakajima,H., Horvath-Arcidiacono,J.A., Udy,G.B., Davey,H.W., & Leonard,W.J. (1998) Stat5b is essential for natural killer cell-mediated proliferation and cytolytic activity. *J. Exp. Med.* **188**, 2067-2074.

Ishii,K.J. & Akira,S. (2005) Innate immune recognition of nucleic acids: beyond toll-like receptors. *Int. J. Cancer* **117**, 517-523.

Ivashkiv,L.B. & Hu,X. (2004) Signaling by STATs. *Arthritis Res. Ther.* **6**, 159-168.

J

Johnson,G.B., Brunn,G.J., Kodaira,Y., & Platt,J.L. (2002) Receptor-mediated monitoring of tissue well-being via detection of soluble heparan sulfate by Toll-like receptor 4. *J. Immunol.* **168**, 5233-5239.

Judge,A.D., Sood,V., Shaw,J.R., Fang,D., McClintock,K., & MacLachlan,I. (2005) Sequence-dependent stimulation of the mammalian innate immune response by synthetic siRNA. *Nat. Biotechnol.* **23**, 457-462.

Justicia,C., Gabriel,C., & Planas,A.M. (2000) Activation of the JAK/STAT pathway following transient focal cerebral ischemia: signaling through Jak1 and Stat3 in astrocytes. *Glia* **30**, 253-270.

Juurink,B.H. (1997) Response of glial cells to ischemia: roles of reactive oxygen species and glutathione. *Neurosci. Biobehav. Rev.* **21**, 151-166.

K

Kader,A., Frazzini,V.I., Solomon,R.A., & Trifiletti,R.R. (1993) Nitric oxide production during focal cerebral ischemia in rats. *Stroke* **24**, 1709-1716.

Kahl,R. & Hildebrandt,A.G. (1986) Methodology for studying antioxidant activity and mechanisms of action of antioxidants. *Food Chem. Toxicol.* **24**, 1007-1014.

Kahles,T., Luedike,P., Endres,M., Galla,H.J., Steinmetz,H., Busse,R., Neumann-Haefelin,T., & Brandes,R.P. (2007) NADPH Oxidase Plays a Central Role in Blood-Brain Barrier Damage in Experimental Stroke. *Stroke*.

Kaisho,T. & Akira,S. (2006) Toll-like receptor function and signaling. *J. Allergy Clin. Immunol.* **117**, 979-987.

Kaplan,M.H., Sun,Y.L., Hoey,T., & Grusby,M.J. (1996) Impaired IL-12 responses and enhanced development of Th2 cells in Stat4-deficient mice. *Nature* **382**, 174-177.

Kariko,K., Ni,H., Capodici,J., Lamphier,M., & Weissman,D. (2004) mRNA is an endogenous ligand for Toll-like receptor 3. *J. Biol. Chem.* **279**, 12542-12550.

Kariko,K., Bhuyan,P., Capodici,J., Ni,H., Lubinski,J., Friedman,H., & Weissman,D. (2004) Exogenous siRNA mediates sequence-independent gene suppression by signaling through toll-like receptor 3. *Cells Tissues. Organs* **177**, 132-138.

Karpus,W.J. (1999) Chemokine regulation of inflammatory-mediated nervous system diseases. *J. Neurovirol.* **5**, 1-2.

Kim,W.H., Hong,F., Radaeva,S., Jaruga,B., Fan,S., & Gao,B. (2003) STAT1 plays an essential role in LPS/D-galactosamine-induced liver apoptosis and injury. *Am. J. Physiol Gastrointest. Liver Physiol* **285**, G761-G768.

Kimelberg,H.K. (2005) Astrocytic swelling in cerebral ischemia as a possible cause of injury and target for therapy. *Glia* **50**, 389-397.

Kinuta,Y., Kimura,M., Itokawa,Y., Ishikawa,M., & Kikuchi,H. (1989) Changes in xanthine oxidase in ischemic rat brain. *J. Neurosurg.* **71**, 417-420.

Kisseleva,T., Bhattacharya,S., Braunstein,J., & Schindler,C.W. (2002) Signaling through the JAK/STAT pathway, recent advances and future challenges. *Gene* **285**, 1-24.

Klatzo,I., Chui,E., Fujiwara,K., & Spatz,M. (1980) Resolution of vasogenic brain edema. *Adv. Neurol.* **28**, 359-373.

Konat,G.W., Kielian,T., & Marriott,I. (2006) The role of Toll-like receptors in CNS response to microbial challenge. *J. Neurochem.* **99**, 1-12.

Kontos,H.A. (1985) George E. Brown memorial lecture. Oxygen radicals in cerebral vascular injury. *Circ. Res.* **57**, 508-516.

Kopp,E.B. & Medzhitov,R. (1999) The Toll-receptor family and control of innate immunity. *Curr. Opin. Immunol.* **11**, 13-18.

Korzus,E., Torchia,J., Rose,D.W., Xu,L., Kurokawa,R., McInerney,E.M., Mullen,T.M., Glass,C.K., & Rosenfeld,M.G. (1998) Transcription factor-specific requirements for coactivators and their acetyltransferase functions. *Science* **279**, 703-707.

Kotenko,S.V., Gallagher,G., Baurin,V.V., Lewis-Antes,A., Shen,M., Shah,N.K., Langer,J.A., Sheikh,F., Dickensheets,H., & Donnelly,R.P. (2003) IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat. Immunol.* **4**, 69-77.

Kovarik,P., Stoiber,D., Eyers,P.A., Menghini,R., Neininger,A., Gaestel,M., Cohen,P., & Decker,T. (1999) Stress-induced phosphorylation of STAT1 at Ser727 requires p38 mitogen-activated protein kinase whereas IFN-gamma uses a different signaling pathway. *Proc. Natl. Acad. Sci. U. S. A* **96**, 13956-13961.

Kramer,O.H., Baus,D., Knauer,S.K., Stein,S., Jager,E., Stauber,R.H., Grez,M., Pfitzner,E., & Heinzl,T. (2006) Acetylation of Stat1 modulates NF-kappaB activity. *Genes Dev.* **20**, 473-485.

Krasowska-Zoladek,A., Banaszewska,M., Kraszpulski,M., & Konat,G.W. (2007) Kinetics of inflammatory response of astrocytes induced by TLR 3 and TLR4 ligation. *J. Neurosci. Res.* **85**, 205-212.

Kristof,A.S., Marks-Konczalik,J., Billings,E., & Moss,J. (2003) Stimulation of signal transducer and activator of transcription-1 (STAT1)-dependent gene transcription by lipopolysaccharide and interferon-gamma is regulated by mammalian target of rapamycin. *J. Biol. Chem.* **278**, 33637-33644.

Krupinski,J., Kumar,P., Kumar,S., & Kaluza,J. (1996) Increased expression of TGF-beta 1 in brain tissue after ischemic stroke in humans. *Stroke* **27**, 852-857.

Kukreja,R.C., Jesse,R.L., & Hess,M.L. (1992) Singlet oxygen: a potential culprit in myocardial injury? *Mol. Cell Biochem.* **111**, 17-24.

Kurzer,J.H., Saharinen,P., Silvennoinen,O., & Carter-Su,C. (2006) Binding of SH2-B family members within a potential negative regulatory region maintains JAK2 in an active state. *Mol. Cell Biol.* **26**, 6381-6394.

L

Lambertsen,K.L., Gregersen,R., Meldgaard,M., Clausen,B.H., Heibol,E.K., Ladeby,R., Knudsen,J., Frandsen,A., Owens,T., & Finsen,B. (2004) A role for interferon-gamma in focal cerebral ischemia in mice. *J. Neuropathol. Exp. Neurol.* **63**, 942-955.

Larsen,L. & Ropke,C. (2002) Suppressors of cytokine signalling: SOCS. *APMIS* **110**, 833-844.

LeBel,C.P., Ischiropoulos,H., & Bondy,S.C. (1992) Evaluation of the probe 2',7'-dichlorofluorescein as an indicator of reactive oxygen species formation and oxidative stress. *Chem. Res. Toxicol.* **5**, 227-231.

Lee,C.K., Gimeno,R., & Levy,D.E. (1999) Differential regulation of constitutive major histocompatibility complex class I expression in T and B lymphocytes. *J. Exp. Med.* **190**, 1451-1464.

Lee,J., Shin,J.S., Park,J.Y., Kwon,D., Choi,S.J., Kim,S.J., & Choi,I.H. (2003) p38 mitogen-activated protein kinase modulates expression of tumor necrosis factor-related apoptosis-inducing ligand induced by interferon-gamma in fetal brain astrocytes. *J. Neurosci. Res.* **74**, 884-890.

Lee,J.M., Grabb,M.C., Zipfel,G.J., & Choi,D.W. (2000) Brain tissue responses to ischemia. *J. Clin. Invest* **106**, 723-731.

Lee,J.Y., Zhao,L., Youn,H.S., Weatherill,A.R., Tapping,R., Feng,L., Lee,W.H., Fitzgerald,K.A., & Hwang,D.H. (2004) Saturated fatty acid activates but polyunsaturated fatty acid inhibits Toll-like receptor 2 dimerized with Toll-like receptor 6 or 1. *J. Biol. Chem.* **279**, 16971-16979.

Lee,Y.J. & Benveniste,E.N. (1996) Stat1 alpha expression is involved in IFN-gamma induction of the class II transactivator and class II MHC genes. *J. Immunol.* **157**, 1559-1568.

Lehnardt,S., Lehmann,S., Kaul,D., Tschimmel,K., Hoffmann,O., Cho,S., Krueger,C., Nitsch,R., Meisel,A., & Weber,J.R. (2007) Toll-like receptor 2 mediates CNS injury in focal cerebral ischemia. *J. Neuroimmunol.* **190**, 28-33.

Lehrmann,E., Kiefer,R., Finsen,B., Diemer,N.H., Zimmer,J., & Hartung,H.P. (1995) Cytokines in cerebral ischemia: expression of transforming growth factor beta-1 (TGF-beta 1) mRNA in the postischemic adult rat hippocampus. *Exp. Neurol.* **131**, 114-123.

Levy,D.E. & Darnell,J.E., Jr. (2002) Stats: transcriptional control and biological impact. *Nat. Rev. Mol. Cell Biol.* **3**, 651-662.

Li,H.L., Kostulas,N., Huang,Y.M., Xiao,B.G., van der,M.P., Kostulas,V., Giedraitas,V., & Link,H. (2001) IL-17 and IFN-gamma mRNA expression is increased in the brain and systemically after permanent middle cerebral artery occlusion in the rat. *J. Neuroimmunol.* **116**, 5-14.

Liu,B., Mink,S., Wong,K.A., Stein,N., Getman,C., Dempsey,P.W., Wu,H., & Shuai,K. (2004) PIAS1 selectively inhibits interferon-inducible genes and is important in innate immunity. *Nat. Immunol.* **5**, 891-898.

Liu,T., Clark,R.K., McDonnell,P.C., Young,P.R., White,R.F., Barone,F.C., & Feuerstein,G.Z. (1994) Tumor necrosis factor-alpha expression in ischemic neurons. *Stroke* **25**, 1481-1488.

Livak,K.J. & Schmittgen,T.D. (2001) Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. *Methods* **25**, 402-408.

Ludwin,S.K., Kosek,J.C., & Eng,L.F. (1976) The topographical distribution of S-100 and GFA proteins in the adult rat brain: an immunohistochemical study using horseradish peroxidase-labelled antibodies. *J. Comp Neurol.* **165**, 197-207.

Lund,J.M., Alexopoulou,L., Sato,A., Karow,M., Adams,N.C., Gale,N.W., Iwasaki,A., & Flavell,R.A. (2004) Recognition of single-stranded RNA viruses by Toll-like receptor 7. *Proc. Natl. Acad. Sci. U. S. A* **101**, 5598-5603.

Luo,C. & Laaja,P. (2004) Inhibitors of JAKs/STATs and the kinases: a possible new cluster of drugs. *Drug Discov. Today* **9**, 268-275.

M

Madamanchi,N.R., Li,S., Patterson,C., & Runge,M.S. (2001) Reactive oxygen species regulate heat-shock protein 70 via the JAK/STAT pathway. *Arterioscler. Thromb. Vasc. Biol.* **21**, 321-326.

Madamanchi,N.R., Li,S., Patterson,C., & Runge,M.S. (2001) Thrombin regulates vascular smooth muscle cell growth and heat shock proteins via the JAK-STAT pathway. *J. Biol. Chem.* **276**, 18915-18924.

Malakhov,M.P., Kim,K.I., Malakhova,O.A., Jacobs,B.S., Borden,E.C., & Zhang,D.E. (2003) High-throughput immunoblotting. Ubiquitin-like protein ISG15 modifies key regulators of signal transduction. *J. Biol. Chem.* **278**, 16608-16613.

Malakhova,O.A., Yan,M., Malakhov,M.P., Yuan,Y., Ritchie,K.J., Kim,K.I., Peterson,L.F., Shuai,K., & Zhang,D.E. (2003) Protein ISGylation modulates the JAK-STAT signaling pathway. *Genes Dev.* **17**, 455-460.

Manabe,Y., Anrather,J., Kawano,T., Niwa,K., Zhou,P., Ross,M.E., & Iadecola,C. (2004) Prostanoids, not reactive oxygen species, mediate COX-2-dependent neurotoxicity. *Ann. Neurol.* **55**, 668-675.

Margaill,I., Plotkine,M., & Lerouet,D. (2005) Antioxidant strategies in the treatment of stroke. *Free Radic. Biol. Med.* **39**, 429-443.

Martindale,J.L. & Holbrook,N.J. (2002) Cellular response to oxidative stress: signaling for suicide and survival. *J. Cell Physiol* **192**, 1-15.

Maslinska,D., Laure-Kamionowska,M., & Maslinski,S. (2004) Toll-like receptors in rat brains injured by hypoxic-ischaemia or exposed to staphylococcal alpha-toxin. *Folia Neuropathol.* **42**, 125-132.

Massa,P.T. & Wu,C. (1996) The role of protein tyrosine phosphatase SHP-1 in the regulation of IFN-gamma signaling in neural cells. *J. Immunol.* **157**, 5139-5144.

Matsuda,T., Feng,J., Witthuhn,B.A., Sekine,Y., & Ihle,J.N. (2004) Determination of the transphosphorylation sites of Jak2 kinase. *Biochem. Biophys. Res. Commun.* **325**, 586-594.

Maziere,C., Alimardani,G., Dantin,F., Dubois,F., Conte,M.A., & Maziere,J.C. (1999) Oxidized LDL activates STAT1 and STAT3 transcription factors: possible involvement of reactive oxygen species. *FEBS Lett.* **448**, 49-52.

McBride,K.M., McDonald,C., & Reich,N.C. (2000) Nuclear export signal located within theDNA-binding domain of the STAT1transcription factor. *EMBO J.* **19**, 6196-6206.

McBride,K.M., Banninger,G., McDonald,C., & Reich,N.C. (2002) Regulated nuclear import of the STAT1 transcription factor by direct binding of importin-alpha. *EMBO J.* **21**, 1754-1763.

McCay,P.B., Brueggemann,G., Lai,E.K., & Powell,S.R. (1989) Evidence that alpha-tocopherol functions cyclically to quench free radicals in hepatic microsomes. Requirement for glutathione and a heat-labile factor. *Ann. N. Y. Acad. Sci.* **570**, 32-45.

McCord,J.M. (1998) Iron, free radicals, and oxidative injury. *Semin. Hematol.* **35**, 5-12.

Meeuwssen,S., Persoon-Deen,C., Bsibsi,M., Ravid,R., & van Noort,J.M. (2003) Cytokine, chemokine and growth factor gene profiling of cultured human astrocytes after exposure to proinflammatory stimuli. *Glia* **43**, 243-253.

Mehta,S.L., Manhas,N., & Raghurib,R. (2007) Molecular targets in cerebral ischemia for developing novel therapeutics. *Brain Res. Rev.* **54**, 34-66.

Meisel,C., Schwab,J.M., Prass,K., Meisel,A., & Dirnagl,U. (2005) Central nervous system injury-induced immune deficiency syndrome. *Nat. Rev. Neurosci.* **6**, 775-786.

Meraz,M.A., White,J.M., Sheehan,K.C., Bach,E.A., Rodig,S.J., Dighe,A.S., Kaplan,D.H., Riley,J.K., Greenlund,A.C., Campbell,D., Carver-Moore,K., DuBois,R.N., Clark,R., Aguet,M., & Schreiber,R.D. (1996) Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway. *Cell* **84**, 431-442.

Meydan,N., Grunberger,T., Dadi,H., Shahar,M., Arpaia,E., Lapidot,Z., Leeder,J.S., Freedman,M., Cohen,A., Gazit,A., Levitzki,A., & Roifman,C.M. (1996) Inhibition of acute lymphoblastic leukaemia by a Jak-2 inhibitor. *Nature* **379**, 645-648.

Meyer,T., Marg,A., Lemke,P., Wiesner,B., & Vinkemeier,U. (2003) DNA binding controls inactivation and nuclear accumulation of the transcription factor Stat1. *Genes Dev.* **17**, 1992-2005.

Mitomo,K., Nakayama,K., Fujimoto,K., Sun,X., Seki,S., & Yamamoto,K. (1994) Two different cellular redox systems regulate the DNA-binding activity of the p50 subunit of NF-kappa B in vitro. *Gene* **145**, 197-203.

Miyake,K. (2003) Innate recognition of lipopolysaccharide by CD14 and toll-like receptor 4-MD-2: unique roles for MD-2. *Int. Immunopharmacol.* **3**, 119-128.

Mosmann,T. (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Methods* **65**, 55-63.

Mowen,K.A., Tang,J., Zhu,W., Schurter,B.T., Shuai,K., Herschman,H.R., & David,M. (2001) Arginine methylation of STAT1 modulates IFNalpha/beta-induced transcription. *Cell* **104**, 731-741.

Myers,M.P., Andersen,J.N., Cheng,A., Tremblay,M.L., Horvath,C.M., Parisien,J.P., Salmeen,A., Barford,D., & Tonks,N.K. (2001) TYK2 and JAK2 are substrates of protein-tyrosine phosphatase 1B. *J. Biol. Chem.* **276**, 47771-47774.

N

Nadiminty,N., Lou,W., Lee,S.O., Lin,X., Trump,D.L., & Gao,A.C. (2006) Stat3 activation of NF- κ B p100 processing involves CBP/p300-mediated acetylation. *Proc. Natl. Acad. Sci. U. S. A* **103**, 7264-7269.

Nakagawa,R., Naka,T., Tsutsui,H., Fujimoto,M., Kimura,A., Abe,T., Seki,E., Sato,S., Takeuchi,O., Takeda,K., Akira,S., Yamanishi,K., Kawase,I., Nakanishi,K., & Kishimoto,T. (2002) SOCS-1 participates in negative regulation of LPS responses. *Immunity.* **17**, 677-687.

Nakaya,T., Sato,M., Hata,N., Asagiri,M., Suemori,H., Noguchi,S., Tanaka,N., & Taniguchi,T. (2001) Gene induction pathways mediated by distinct IRFs during viral infection. *Biochem. Biophys. Res. Commun.* **283**, 1150-1156.

Nathan,C. (2002) Points of control in inflammation. *Nature* **420**, 846-852.

Ndubuisi,M.I., Guo,G.G., Fried,V.A., Etlinger,J.D., & Sehgal,P.B. (1999) Cellular physiology of STAT3: Where's the cytoplasmic monomer? *J. Biol. Chem.* **274**, 25499-25509.

Nguyen,M.D., Julien,J.P., & Rivest,S. (2002) Innate immunity: the missing link in neuroprotection and neurodegeneration? *Nat. Rev. Neurosci.* **3**, 216-227.

Niu,G., Heller,R., Catlett-Falcone,R., Coppola,D., Jaroszeski,M., Dalton,W., Jove,R., & Yu,H. (1999) Gene therapy with dominant-negative Stat3 suppresses growth of the murine melanoma B16 tumor in vivo. *Cancer Res.* **59**, 5059-5063.

Noronha-Dutra,A.A., Epperlein,M.M., & Woolf,N. (1993) Reaction of nitric oxide with hydrogen peroxide to produce potentially cytotoxic singlet oxygen as a model for nitric oxide-mediated killing. *FEBS Lett.* **321**, 59-62.

O

Ohashi,K., Burkart,V., Flohe,S., & Kolb,H. (2000) Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. *J. Immunol.* **164**, 558-561.

Okamura,Y., Watari,M., Jerud,E.S., Young,D.W., Ishizaka,S.T., Rose,J., Chow,J.C., & Strauss,J.F., III (2001) The extra domain A of fibronectin activates Toll-like receptor 4. *J. Biol. Chem.* **276**, 10229-10233.

Omari,K.M. & Dorovini-Zis,K. (2003) CD40 expressed by human brain endothelial cells regulates CD4+ T cell adhesion to endothelium. *J. Neuroimmunol.* **134**, 166-178.

Ooboshi,H., Ibayashi,S., Shichita,T., Kumai,Y., Takada,J., Ago,T., Arakawa,S., Sugimori,H., Kamouchi,M., Kitazono,T., & Iida,M. (2005) Postischemic gene transfer of interleukin-10 protects against both focal and global brain ischemia. *Circulation* **111**, 913-919.

Osiak,A., Utermohlen,O., Niendorf,S., Horak,I., & Knobloch,K.P. (2005) ISG15, an interferon-stimulated ubiquitin-like protein, is not essential for STAT1 signaling and responses against vesicular stomatitis and lymphocytic choriomeningitis virus. *Mol. Cell Biol.* **25**, 6338-6345.

Ossina,N.K., Cannas,A., Powers,V.C., Fitzpatrick,P.A., Knight,J.D., Gilbert,J.R., Shekhtman,E.M., Tomei,L.D., Umansky,S.R., & Kiefer,M.C. (1997) Interferon-gamma

modulates a p53-independent apoptotic pathway and apoptosis-related gene expression. *J. Biol. Chem.* **272**, 16351-16357.

Owens,T., Babcock,A.A., Millward,J.M., & Toft-Hansen,H. (2005) Cytokine and chemokine inter-regulation in the inflamed or injured CNS. *Brain Res. Brain Res. Rev.* **48**, 178-184.

Ozinsky,A., Underhill,D.M., Fontenot,J.D., Hajjar,A.M., Smith,K.D., Wilson,C.B., Schroeder,L., & Aderem,A. (2000) The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between toll-like receptors. *Proc. Natl. Acad. Sci. U. S. A* **97**, 13766-13771.

P

Padh,H. (1991) Vitamin C: newer insights into its biochemical functions. *Nutr. Rev.* **49**, 65-70.

Pajkrt,D., Camoglio,L., Tiel-van Buul,M.C., de Bruin,K., Cutler,D.L., Affrime,M.B., Rikken,G., van der,P.T., ten Cate,J.W., & van Deventer,S.J. (1997) Attenuation of proinflammatory response by recombinant human IL-10 in human endotoxemia: effect of timing of recombinant human IL-10 administration. *J. Immunol.* **158**, 3971-3977.

Panickar,K.S. & Norenberg,M.D. (2005) Astrocytes in cerebral ischemic injury: morphological and general considerations. *Glia* **50**, 287-298.

Pantoni,L., Sarti,C., & Inzitari,D. (1998) Cytokines and cell adhesion molecules in cerebral ischemia: experimental bases and therapeutic perspectives. *Arterioscler. Thromb. Vasc. Biol.* **18**, 503-513.

Park,C., Li,S., Cha,E., & Schindler,C. (2000) Immune response in Stat2 knockout mice. *Immunity.* **13**, 795-804.

Paterson,H.M., Murphy,T.J., Purcell,E.J., Shelley,O., Kriynovich,S.J., Lien,E., Mannick,J.A., & Lederer,J.A. (2003) Injury primes the innate immune system for enhanced Toll-like receptor reactivity. *J. Immunol.* **171**, 1473-1483.

Paulson,M., Pisharody,S., Pan,L., Guadagno,S., Mui,A.L., & Levy,D.E. (1999) Stat protein transactivation domains recruit p300/CBP through widely divergent sequences. *J. Biol. Chem.* **274**, 25343-25349.

Pawate,S., Shen,Q., Fan,F., & Bhat,N.R. (2004) Redox regulation of glial inflammatory response to lipopolysaccharide and interferongamma. *J. Neurosci. Res.* **77**, 540-551.

Pelidou,S.H., Kostulas,N., Matusevicius,D., Kivisakk,P., Kostulas,V., & Link,H. (1999) High levels of IL-10 secreting cells are present in blood in cerebrovascular diseases. *Eur. J. Neurol.* **6**, 437-442.

Planas,A.M., Soriano,M.A., Rodriguez-Farre,E., & Ferrer,I. (1995) Induction of cyclooxygenase-2 mRNA and protein following transient focal ischemia in the rat brain. *Neurosci. Lett.* **200**, 187-190.

Planas,A.M., Soriano,M.A., Berruezo,M., Justicia,C., Estrada,A., Pitarch,S., & Ferrer,I. (1996) Induction of Stat3, a signal transducer and transcription factor, in reactive microglia following transient focal cerebral ischaemia. *Eur. J. Neurosci.* **8**, 2612-2618.

Planas,A.M., Justicia,C., & Ferrer,I. (1997) Stat1 in developing and adult rat brain. Induction after transient focal ischemia. *Neuroreport* **8**, 1359-1362.

Planas,A.M., Berruezo,M., Justicia,C., Barron,S., & Ferrer,I. (1997) Stat3 is present in the developing and adult rat cerebellum and participates in the formation of transcription complexes binding DNA at the sis-inducible element. *J. Neurochem.* **68**, 1345-1351.

Possel,H., Noack,H., Augustin,W., Keilhoff,G., & Wolf,G. (1997) 2,7-Dihydrodichlorofluorescein diacetate as a fluorescent marker for peroxynitrite formation. *FEBS Lett.* **416**, 175-178.

Pranada,A.L., Metz,S., Herrmann,A., Heinrich,P.C., & Muller-Newen,G. (2004) Real time analysis of STAT3 nucleocytoplasmic shuttling. *J. Biol. Chem.* **279**, 15114-15123.

Prass,K., Meisel,C., Hoflich,C., Braun,J., Halle,E., Wolf,T., Ruscher,K., Victorov,I.V., Priller,J., Dirnagl,U., Volk,H.D., & Meisel,A. (2003) Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. *J. Exp. Med.* **198**, 725-736.

Puisieux,F., Deplanque,D., Pu,Q., Souil,E., Bastide,M., & Bordet,R. (2000) Differential role of nitric oxide pathway and heat shock protein in preconditioning and lipopolysaccharide-induced brain ischemic tolerance. *Eur. J. Pharmacol.* **389**, 71-78.

R

Rahpeymai,Y., Hietala,M.A., Wilhelmsson,U., Fotheringham,A., Davies,I., Nilsson,A.K., Zwirner,J., Wetsel,R.A., Gerard,C., Pekny,M., & Pekna,M. (2006) Complement: a novel factor in basal and ischemia-induced neurogenesis. *EMBO J.* **25**, 1364-1374.

Raichle,M.E. (1983) The pathophysiology of brain ischemia. *Ann. Neurol.* **13**, 2-10.

Raps,S.P., Lai,J.C., Hertz,L., & Cooper,A.J. (1989) Glutathione is present in high concentrations in cultured astrocytes but not in cultured neurons. *Brain Res.* **493**, 398-401.

Rehncrona,S., Hauge,H.N., & Siesjo,B.K. (1989) Enhancement of iron-catalyzed free radical formation by acidosis in brain homogenates: differences in effect by lactic acid and CO₂. *J. Cereb. Blood Flow Metab* **9**, 65-70.

Reich,N.C. & Liu,L. (2006) Tracking STAT nuclear traffic. *Nat. Rev. Immunol.* **6**, 602-612.

Riley,J.K., Takeda,K., Akira,S., & Schreiber,R.D. (1999) Interleukin-10 receptor signaling through the JAK-STAT pathway. Requirement for two distinct receptor-derived signals for anti-inflammatory action. *J. Biol. Chem.* **274**, 16513-16521.

Roach,J.C., Glusman,G., Rowen,L., Kaur,A., Purcell,M.K., Smith,K.D., Hood,L.E., & Aderem,A. (2005) The evolution of vertebrate Toll-like receptors. *Proc. Natl. Acad. Sci. U. S. A* **102**, 9577-9582.

Robbins,M., Judge,A., Liang,L., McClintock,K., Yaworski,E., & MacLachlan,I. (2007) 2'-O-methyl-modified RNAs act as TLR7 antagonists. *Mol. Ther.* **15**, 1663-1669.

Robinson,K.A., Stewart,C.A., Pye,Q.N., Nguyen,X., Kenney,L., Salzman,S., Floyd,R.A., & Hensley,K. (1999) Redox-sensitive protein phosphatase activity regulates the phosphorylation state of p38 protein kinase in primary astrocyte culture. *J. Neurosci. Res.* **55**, 724-732.

Rodenas,J., Mitjavila,M.T., & Carbonell,T. (1995) Simultaneous generation of nitric oxide and superoxide by inflammatory cells in rats. *Free Radic. Biol. Med.* **18**, 869-875.

Rogers,R.S., Horvath,C.M., & Matunis,M.J. (2003) SUMO modification of STAT1 and its role in PIAS-mediated inhibition of gene activation. *J. Biol. Chem.* **278**, 30091-30097.

Romagnani,S., Parronchi,P., D'Elis,M.M., Romagnani,P., Annunziato,F., Piccinni,M.P., Manetti,R., Sampognaro,S., Mavilia,C., De Carli,M., Maggi,E., & Del Prete,G.F. (1997) An update on human Th1 and Th2 cells. *Int. Arch. Allergy Immunol.* **113**, 153-156.

Rosenberg,G.A. (1999) Ischemic brain edema. *Prog. Cardiovasc. Dis.* **42**, 209-216.

Rothwell,N.J. & Relton,J.K. (1993) Involvement of interleukin-1 and lipocortin-1 in ischaemic brain damage. *Cerebrovasc. Brain Metab Rev.* **5**, 178-198.

S

Saharinen,P., Takaluoma,K., & Silvennoinen,O. (2000) Regulation of the Jak2 tyrosine kinase by its pseudokinase domain. *Mol. Cell Biol.* **20**, 3387-3395.

Sairanen,T.R., Lindsberg,P.J., Brenner,M., Carpen,O., & Siren,A. (2001) Differential cellular expression of tumor necrosis factor-alpha and Type I tumor necrosis factor receptor after transient global forebrain ischemia. *J. Neurol. Sci.* **186**, 87-99.

Sakaguchi,S., Negishi,H., Asagiri,M., Nakajima,C., Mizutani,T., Takaoka,A., Honda,K., & Taniguchi,T. (2003) Essential role of IRF-3 in lipopolysaccharide-induced interferon-beta gene expression and endotoxin shock. *Biochem. Biophys. Res. Commun.* **306**, 860-866.

Salmeen,A. & Barford,D. (2005) Functions and mechanisms of redox regulation of cysteine-based phosphatases. *Antioxid. Redox. Signal.* **7**, 560-577.

Sanchez-Chavez,J.J. (1999) [The penumbra area]. *Rev. Neurol.* **28**, 810-816.

Satriotomo,I., Bowen,K.K., & Vemuganti,R. (2006) JAK2 and STAT3 activation contributes to neuronal damage following transient focal cerebral ischemia. *J. Neurochem.* **98**, 1353-1368.

Saura,J., Tusell,J.M., & Serratosa,J. (2003) High-yield isolation of murine microglia by mild trypsinization. *Glia* **44**, 183-189.

Schaefer,T.S., Sanders,L.K., Park,O.K., & Nathans,D. (1997) Functional differences between Stat3alpha and Stat3beta. *Mol. Cell Biol.* **17**, 5307-5316.

Schindler,C., Shuai,K., Prezioso,V.R., & Darnell,J.E., Jr. (1992) Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. *Science* **257**, 809-813.

Schindler,C., Levy,D.E., & Decker,T. (2007) JAK-STAT signaling: from interferons to cytokines. *J. Biol. Chem.* **282**, 20059-20063.

Schraufstatter,I.U., Browne,K., Harris,A., Hyslop,P.A., Jackson,J.H., Quehenberger,O., & Cochrane,C.G. (1990) Mechanisms of hypochlorite injury of target cells. *J. Clin. Invest* **85**, 554-562.

Schwartz,J.P. & Taniwaki,T. (1994) Heterogeneity of expression of neuropeptide genes by astrocytes: functional implications. *Perspect. Dev. Neurobiol.* **2**, 251-257.

Scumpia,P.O., Kelly,K.M., Reeves,W.H., & Stevens,B.R. (2005) Double-stranded RNA signals antiviral and inflammatory programs and dysfunctional glutamate transport in TLR3-expressing astrocytes. *Glia* **52**, 153-162.

Sehgal,P.B. (2003) Plasma membrane rafts and chaperones in cytokine/STAT signaling. *Acta Biochim. Pol.* **50**, 583-594.

Seya,T., Oshiumi,H., Sasai,M., Akazawa,T., & Matsumoto,M. (2005) TICAM-1 and TICAM-2: toll-like receptor adapters that participate in induction of type 1 interferons. *Int. J. Biochem. Cell Biol.* **37**, 524-529.

Sharikabad,M.N., Ostbye,K.M., Lyberg,T., & Brors,O. (2001) Effect of extracellular Mg(2+) on ROS and Ca(2+) accumulation during reoxygenation of rat cardiomyocytes. *Am. J. Physiol Heart Circ. Physiol* **280**, H344-H353.

Sharma,S., tenOever,B.R., Grandvaux,N., Zhou,G.P., Lin,R., & Hiscott,J. (2003) Triggering the interferon antiviral response through an IKK-related pathway. *Science* **300**, 1148-1151.

Sheehan,J.J. & Tsirka,S.E. (2005) Fibrin-modifying serine proteases thrombin, tPA, and plasmin in ischemic stroke: a review. *Glia* **50**, 340-350.

Shimoda,K., van Deursen,J., Sangster,M.Y., Sarawar,S.R., Carson,R.T., Tripp,R.A., Chu,C., Quelle,F.W., Nosaka,T., Vignali,D.A., Doherty,P.C., Grosveld,G., Paul,W.E., & Ihle,J.N. (1996) Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. *Nature* **380**, 630-633.

Shohami,E., Ginis,I., & Hallenbeck,J.M. (1999) Dual role of tumor necrosis factor alpha in brain injury. *Cytokine and Growth Factor Rev.* **10**, 119-130.

Shuai,K., Schindler,C., Prezioso,V.R., & Darnell,J.E., Jr. (1992) Activation of transcription by IFN-gamma: tyrosine phosphorylation of a 91-kD DNA binding protein. *Science* **258**, 1808-1812.

Siesjo,B.K. (1990) Calcium in the brain under physiological and pathological conditions. *Eur. Neurol.* **30 Suppl 2**, 3-9.

Siesjo,B.K. & Siesjo,P. (1996) Mechanisms of secondary brain injury. *Eur. J. Anaesthesiol.* **13**, 247-268.

Simon,A.R., Rai,U., Fanburg,B.L., & Cochran,B.H. (1998) Activation of the JAK-STAT pathway by reactive oxygen species. *Am. J. Physiol* **275**, C1640-C1652.

Sledz,C.A., Holko,M., de Veer,M.J., Silverman,R.H., & Williams,B.R. (2003) Activation of the interferon system by short-interfering RNAs. *Nat. Cell Biol.* **5**, 834-839.

Smith,C.J., Emsley,H.C., Gavin,C.M., Georgiou,R.F., Vail,A., Barberan,E.M., del Zoppo,G.J., Hallenbeck,J.M., Rothwell,N.J., Hopkins,S.J., & Tyrrell,P.J. (2004) Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. *BMC. Neurol.* **4**, 2.

Sola,C., Casal,C., Tusell,J.M., & Serratosa,J. (2002) Astrocytes enhance lipopolysaccharide-induced nitric oxide production by microglial cells. *Eur. J. Neurosci.* **16**, 1275-1283.

Soos,J.M., Morrow,J., Ashley,T.A., Szente,B.E., Bikoff,E.K., & Zamvil,S.S. (1998) Astrocytes express elements of the class II endocytic pathway and process central nervous system auto antigen for presentation to encephalitogenic T cells. *J. Immunol.* **161**, 5959-5966.

Sotgiu,S., Zanda,B., Marchetti,B., Fois,M.L., Arru,G., Pes,G.M., Salaris,F.S., Arru,A., Pirisi,A., & Rosati,G. (2006) Inflammatory biomarkers in blood of patients with acute brain ischemia. *Eur. J. Neurol.* **13**, 505-513.

Sparrow,J.R. (1994) Inducible nitric oxide synthase in the central nervous system. *J. Mol. Neurosci.* **5**, 219-229.

Spera,P.A., Ellison,J.A., Feuerstein,G.Z., & Barone,F.C. (1998) IL-10 reduces rat brain injury following focal stroke. *Neurosci. Lett.* **251**, 189-192.

Srivastava,S.P., Kumar,K.U., & Kaufman,R.J. (1998) Phosphorylation of eukaryotic translation initiation factor 2 mediates apoptosis in response to activation of the double-stranded RNA-dependent protein kinase. *J. Biol. Chem.* **273**, 2416-2423.

Sroka,Z. & Cisowski,W. (2003) Hydrogen peroxide scavenging, antioxidant and anti-radical activity of some phenolic acids. *Food Chem. Toxicol.* **41**, 753-758.

Stadtman,E.R. (1992) Protein oxidation and aging. *Science* **257**, 1220-1224.

Stamatovic,S.M., Shakuji,P., Keep,R.F., Moore,B.B., Kunkel,S.L., Van Rooijen,N., & Andjelkovic,A.V. (2005) Monocyte chemoattractant protein-1 regulation of blood-brain barrier permeability. *J. Cereb. Blood Flow Metab* **25**, 593-606.

Stephanou,A., Scarabelli,T.M., Townsend,P.A., Bell,R., Yellon,D., Knight,R.A., & Latchman,D.S. (2002) The carboxyl-terminal activation domain of the STAT-1 transcription factor enhances ischemia/reperfusion-induced apoptosis in cardiac myocytes. *FASEB J.* **16**, 1841-1843.

Stoll,G., Jander,S., & Schroeter,M. (1998) Inflammation and glial responses in ischemic brain lesions. *Prog. Neurobiol.* **56**, 149-171.

Strle,K., Zhou,J.H., Shen,W.H., Broussard,S.R., Johnson,R.W., Freund,G.G., Dantzer,R., & Kelley,K.W. (2001) Interleukin-10 in the brain. *Crit Rev. Immunol.* **21**, 427-449.

Sugawara,T. & Chan,P.H. (2003) Reactive oxygen radicals and pathogenesis of neuronal death after cerebral ischemia. *Antioxid. Redox. Signal.* **5**, 597-607.

Sugawara,T., Fujimura,M., Noshita,N., Kim,G.W., Saito,A., Hayashi,T., Narasimhan,P., Maier,C.M., & Chan,P.H. (2004) Neuronal death/survival signaling pathways in cerebral ischemia. *NeuroRx.* **1**, 17-25.

Suzuki,S., Tanaka,K., Nogawa,S., Dembo,T., Kosakai,A., & Fukuuchi,Y. (2001) Phosphorylation of signal transducer and activator of transcription-3 (Stat3) after focal cerebral ischemia in rats. *Exp. Neurol.* **170**, 63-71.

Swanson,R.A. & Choi,D.W. (1993) Glial glycogen stores affect neuronal survival during glucose deprivation in vitro. *J. Cereb. Blood Flow Metab* **13**, 162-169.

Symon,L. (1993) Recovery of brain function following ischemia. *Acta Neurochir. Suppl (Wien.)* **57**, 102-109.

T

Takagi,Y., Harada,J., Chiarugi,A., & Moskowitz,M.A. (2002) STAT1 is activated in neurons after ischemia and contributes to ischemic brain injury. *J. Cereb. Blood Flow Metab* **22**, 1311-1318.

Takayanagi,H., Ogasawara,K., Hida,S., Chiba,T., Murata,S., Sato,K., Takaoka,A., Yokochi,T., Oda,H., Tanaka,K., Nakamura,K., & Taniguchi,T. (2000) T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN-gamma. *Nature* **408**, 600-605.

Takeda,K., Kamanaka,M., Tanaka,T., Kishimoto,T., & Akira,S. (1996) Impaired IL-13-mediated functions of macrophages in STAT6-deficient mice. *J. Immunol.* **157**, 3220-3222.

Takeda,K., Noguchi,K., Shi,W., Tanaka,T., Matsumoto,M., Yoshida,N., Kishimoto,T., & Akira,S. (1997) Targeted disruption of the mouse Stat3 gene leads to early embryonic lethality. *Proc. Natl. Acad. Sci. U. S. A* **94**, 3801-3804.

Takeuchi,O. & Akira,S. (2001) Toll-like receptors; their physiological role and signal transduction system. *Int. Immunopharmacol.* **1**, 625-635.

Tanaka,T., Soriano,M.A., & Grusby,M.J. (2005) SLIM is a nuclear ubiquitin E3 ligase that negatively regulates STAT signaling. *Immunity*. **22**, 729-736.

Tang,S.C., Arumugam,T.V., Xu,X., Cheng,A., Mughal,M.R., Jo,D.G., Lathia,J.D., Siler,D.A., Chigurupati,S., Ouyang,X., Magnus,T., Camandola,S., & Mattson,M.P. (2007) Pivotal role for neuronal Toll-like receptors in ischemic brain injury and functional deficits. *Proc. Natl. Acad. Sci. U. S. A* **104**, 13798-13803.

Tarkowski,E., Rosengren,L., Blomstrand,C., Wikkelso,C., Jensen,C., Ekholm,S., & Tarkowski,A. (1997) Intrathecal release of pro- and anti-inflammatory cytokines during stroke. *Clin. Exp. Immunol.* **110**, 492-499.

Tarozzo,G., Campanella,M., Ghiani,M., Bulfone,A., & Beltramo,M. (2002) Expression of fractalkine and its receptor, CX3CR1, in response to ischaemia-reperfusion brain injury in the rat. *Eur. J. Neurosci.* **15**, 1663-1668.

Tawfik,A., Jin,L., Banes-Berceli,A.K., Caldwell,R.B., Oghi,S., Shirley,A., Barber,D., Catravas,J.D., Stern,D.M., Fulton,D., Caldwell,R.W., & Marrero,M.B. (2005) Hyperglycemia and reactive oxygen species mediate apoptosis in aortic endothelial cells through Janus kinase 2. *Vascul. Pharmacol.* **43**, 320-326.

Taylor,K.R., Trowbridge,J.M., Rudisill,J.A., Termeer,C.C., Simon,J.C., & Gallo,R.L. (2004) Hyaluronan fragments stimulate endothelial recognition of injury through TLR4. *J. Biol. Chem.* **279**, 17079-17084.

Teglund,S., McKay,C., Schuetz,E., van Deursen,J.M., Stravopodis,D., Wang,D., Brown,M., Bodner,S., Grosveld,G., & Ihle,J.N. (1998) Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. *Cell* **93**, 841-850.

Terada,L.S., Willingham,I.R., Rosandich,M.E., Leff,J.A., Kindt,G.W., & Repine,J.E. (1991) Generation of superoxide anion by brain endothelial cell xanthine oxidase. *J. Cell Physiol* **148**, 191-196.

Terui,K., Enosawa,S., Haga,S., Zhang,H.Q., Kuroda,H., Kouchi,K., Matsunaga,T., Yoshida,H., Engelhardt,J.F., Irani,K., Ohnuma,N., & Ozaki,M. (2004) Stat3 confers resistance against hypoxia/reoxygenation-induced oxidative injury in hepatocytes through upregulation of Mn-SOD. *J. Hepatol.* **41**, 957-965.

Thierfelder,W.E., van Deursen,J.M., Yamamoto,K., Tripp,R.A., Sarawar,S.R., Carson,R.T., Sangster,M.Y., Vignali,D.A., Doherty,P.C., Grosveld,G.C., & Ihle,J.N. (1996) Requirement for Stat4 in interleukin-12-mediated responses of natural killer and T cells. *Nature* **382**, 171-174.

Tilg,H., Trehu,E., Atkins,M.B., Dinarello,C.A., & Mier,J.W. (1994) Interleukin-6 (IL-6) as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. *Blood* **83**, 113-118.

Tsan,M.F. & Gao,B. (2004) Endogenous ligands of Toll-like receptors. *J. Leukoc. Biol.* **76**, 514-519.

Turkson,J. (2004) STAT proteins as novel targets for cancer drug discovery. *Expert. Opin. Ther. Targets.* **8**, 409-422.

U

Ungureanu,D., Saharinen,P., Junttila,I., Hilton,D.J., & Silvennoinen,O. (2002) Regulation of Jak2 through the ubiquitin-proteasome pathway involves phosphorylation of Jak2 on Y1007 and interaction with SOCS-1. *Mol. Cell Biol.* **22**, 3316-3326.

V

Vanderbist,F., Maes,P., & Neve,J. (1996) In vitro comparative assessment of the antioxidant activity of nacystelyn against three reactive oxygen species. *Arzneimittelforschung.* **46**, 783-788.

Vila,N., Reverter,J.C., Yague,J., & Chamorro,A. (2000) Interaction between interleukin-6 and the natural anticoagulant system in acute stroke. *J. Interferon Cytokine Res.* **20**, 325-329.

Vila,N., Chamorro,A., Castillo,J., & Davalos,A. (2001) Glutamate, interleukin-6, and early clinical worsening in patients with acute stroke. *Stroke* **32**, 1234-1237.

Vila,N., Castillo,J., Davalos,A., Esteve,A., Planas,A.M., & Chamorro,A. (2003) Levels of anti-inflammatory cytokines and neurological worsening in acute ischemic stroke. *Stroke* **34**, 671-675.

Vincent,A.J., Choi-Lundberg,D.L., Harris,J.A., West,A.K., & Chuah,M.I. (2007) Bacteria and PAMPs activate nuclear factor kappaB and Gro production in a subset of olfactory ensheathing cells and astrocytes but not in Schwann cells. *Glia* **55**, 905-916.

Virag,L., Szabo,E., Gergely,P., & Szabo,C. (2003) Peroxynitrite-induced cytotoxicity: mechanism and opportunities for intervention. *Toxicol. Lett.* **140-141**, 113-124.

W

Wagner,H. (2004) The immunobiology of the TLR9 subfamily. *Trends Immunol.* **25**, 381-386.

Wang,D., Stravopodis,D., Teglund,S., Kitazawa,J., & Ihle,J.N. (1996) Naturally occurring dominant negative variants of Stat5. *Mol. Cell Biol.* **16**, 6141-6148.

Wang,L.H., Kirken,R.A., Erwin,R.A., Yu,C.R., & Farrar,W.L. (1999) JAK3, STAT, and MAPK signaling pathways as novel molecular targets for the tyrphostin AG-490 regulation of IL-2-mediated T cell response. *J. Immunol.* **162**, 3897-3904.

Wang,Q., Tang,X.N., & Yenari,M.A. (2007) The inflammatory response in stroke. *J. Neuroimmunol.* **184** , 53-68.

Wang,Y., Wu,T.R., Cai,S., Welte,T., & Chin,Y.E. (2000) Stat1 as a component of tumor necrosis factor alpha receptor 1-TRADD signaling complex to inhibit NF-kappaB activation. *Mol. Cell Biol.* **20**, 4505-4512.

Weiss,D.J., Evanson,O.A., & Souza,C.D. (2005) Expression of interleukin-10 and suppressor of cytokine signaling-3 associated with susceptibility of cattle to infection with *Mycobacterium avium* subsp paratuberculosis. *Am. J. Vet. Res.* **66**, 1114-1120.

Weiss,S.J. (1989) Tissue destruction by neutrophils. *N. Engl. J. Med.* **320**, 365-376.

Wen,Z., Zhong,Z., & Darnell,J.E., Jr. (1995) Maximal activation of transcription by Stat1 and Stat3 requires both tyrosine and serine phosphorylation. *Cell* **82**, 241-250.

Wilkin,G.P., Marriott,D.R., & Cholewinski,A.J. (1990) Astrocyte heterogeneity. *Trends Neurosci.* **13** , 43-46.

Williams,L.M., Ricchetti,G., Sarma,U., Smallie,T., & Foxwell,B.M. (2004) Interleukin-10 suppression of myeloid cell activation--a continuing puzzle. *Immunology* **113**, 281-292.

Wilson,J.X. (1997) Antioxidant defense of the brain: a role for astrocytes. *Can. J. Physiol Pharmacol.* **75**, 1149-1163.

Wroblewski,F. & LaDue,J.S. (1955) Lactic dehydrogenase activity in blood. *Proc. Soc. Exp. Biol. Med.* **90**, 210-213.

Wu,T.R., Hong,Y.K., Wang,X.D., Ling,M.Y., Dragoi,A.M., Chung,A.S., Campbell,A.G., Han,Z.Y., Feng,G.S., & Chin,Y.E. (2002) SHP-2 is a dual-specificity phosphatase involved in Stat1 dephosphorylation at both tyrosine and serine residues in nuclei. *J. Biol. Chem.* **277**, 47572-47580.

X

Xanthoudakis,S. & Curran,T. (1992) Identification and characterization of Ref-1, a nuclear protein that facilitates AP-1 DNA-binding activity. *EMBO J.* **11**, 653-665.

Y

Yamamoto,M., Sato,S., Hemmi,H., Hoshino,K., Kaisho,T., Sanjo,H., Takeuchi,O., Sugiyama,M., Okabe,M., Takeda,K., & Akira,S. (2003) Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science* **301**, 640-643.

Yamasaki,Y., Matsuura,N., Shozuhara,H., Onodera,H., Itoyama,Y., & Kogure,K. (1995) Interleukin-1 as a pathogenetic mediator of ischemic brain damage in rats. *Stroke* **26**, 676-680.

Yamashita,T., Sawamoto,K., Suzuki,S., Suzuki,N., Adachi,K., Kawase,T., Mihara,M., Ohsugi,Y., Abe,K., & Okano,H. (2005) Blockade of interleukin-6 signaling aggravates ischemic cerebral damage in mice: possible involvement of Stat3 activation in the protection of neurons. *J. Neurochem.* **94**, 459-468.

Yao,Z., Cui,Y., Watford,W.T., Bream,J.H., Yamaoka,K., Hissong,B.D., Li,D., Durum,S.K., Jiang,Q., Bhandoola,A., Hennighausen,L., & O'Shea,J.J. (2006) Stat5a/b are essential for normal lymphoid development and differentiation. *Proc. Natl. Acad. Sci. U. S. A* **103**, 1000-1005.

Yilmaz,G., Arumugam,T.V., Stokes,K.Y., & Granger,D.N. (2006) Role of T lymphocytes and interferon-gamma in ischemic stroke. *Circulation* **113**, 2105-2112.

You,M., Yu,D.H., & Feng,G.S. (1999) Shp-2 tyrosine phosphatase functions as a negative regulator of the interferon-stimulated Jak/STAT pathway. *Mol. Cell Biol.* **19**, 2416-2424.

Yuan,Z.L., Guan,Y.J., Chatterjee,D., & Chin,Y.E. (2005) Stat3 dimerization regulated by reversible acetylation of a single lysine residue. *Science* **307**, 269-273.

Z

Zhang,D., Zhang,G., Hayden,M.S., Greenblatt,M.B., Bussey,C., Flavell,R.A., & Ghosh,S. (2004) A toll-like receptor that prevents infection by uropathogenic bacteria. *Science* **303**, 1522-1526.

Zhang,F., Wang,S., Cao,G., Gao,Y., & Chen,J. (2007) Signal transducers and activators of transcription 5 contributes to erythropoietin-mediated neuroprotection against hippocampal neuronal death after transient global cerebral ischemia. *Neurobiol. Dis.* **25**, 45-53.

Zhou,J.H., Broussard,S.R., Strle,K., Freund,G.G., Johnson,R.W., Dantzer,R., & Kelley,K.W. (2001) IL-10 inhibits apoptosis of promyeloid cells by activating insulin receptor substrate-2 and phosphatidylinositol 3'-kinase. *J. Immunol.* **167**, 4436-4442.

Zou,H., Henzel,W.J., Liu,X., Lutschg,A., & Wang,X. (1997) Apaf-1, a human protein homologous to C. elegans CED-4, participates in cytochrome c-dependent activation of caspase-3. *Cell* **90**, 405-413.