

7 Literatur

- Adachi, M., Fukuda, M. and Nishida, E. (1999). Two co-existing mechanisms for nuclear import of MAP kinase: passive diffusion of a monomer and active transport of a dimer. *EMBO J.* **18**, 5347-5358.
- Akira, S. (2000). Roles of STAT3 defined by tissue-specific gene targeting. *Oncogene* **19**, 2607-2611.
- Allen, T. D., Cronshaw, J. M., Bagley, S., Kiseleva, E. and Goldberg, M. W. (2000). The nuclear pore complex: mediator of translocation between nucleus and cytoplasm. *J. Cell Sci.* **113**, 1651-1659.
- Alonso, G., Ambrosino, C., Jones, M. and Nebreda, A. R. (2000). Differential activation of p38 mitogen-activated protein kinase isoforms depending on signal strength. *J. Biol. Chem.* **275**, 40641-40648.
- Andrews, R. P., Erickson, M. B., Cunningham, C. M., Daines, M. O. and Hershey, G. K. (2002). Analysis of the life cycle of stat6. Continuous cycling of STAT6 is required for IL-4 signaling. *J. Biol. Chem.* **277**, 36563-36569.
- Azam, M., Lee, C., Strehlow, I. and Schindler, C. (1997). Functionally distinct isoforms of STAT5 are generated by protein processing. *Immunity*. **6**, 691-701.
- Banninger, G. and Reich, N. C. (2004). STAT2 nuclear trafficking. *J. Biol. Chem.* **279**, 39199-39206.
- Bayliss, R., Corbett, A. H. and Stewart, M. (2000). The molecular mechanism of transport of macromolecules through nuclear pore complexes. *Traffic*. **1**, 448-456.
- Becker, S., Groner, B. and Müller, C. W. (1998). Three-dimensional structure of the Stat3beta homodimer bound to DNA. *Nature* **394**, 145-151.
- Bednenko, J., Cingolani, G. and Gerace, L. (2003a). Importin beta contains a COOH-terminal nucleoporin binding region important for nuclear transport. *J. Cell Biol.* **162**, 391-401.
- Bednenko, J., Cingolani, G. and Gerace, L. (2003b). Nucleocytoplasmic transport: navigating the channel. *Traffic*. **4**, 127-135.
- Begitt, A., Meyer, T., van Rossum, M. and Vinkemeier, U. (2000). Nucleocytoplasmic translocation of Stat1 is regulated by a leucine-rich export signal in the coiled-coil domain. *Proc. Natl. Acad. Sci. U. S. A* **97**, 10418-10423.
- Ben Efraim, I. and Gerace, L. (2001). Gradient of increasing affinity of importin beta for nucleoporins along the pathway of nuclear import. *J. Cell Biol.* **152**, 411-417.

- Beyermann, M., Fechner, K., Ferkert, J., Krause, E. and Bienert, M. (1996). A single-point slight alteration set as a tool for structure-activity relationship studies of ovine corticotropin releasing factor. *J Med Chem.* **39**, 3324-30.
- Bhattacharya, S. and Schindler, C. (2003). Regulation of Stat3 nuclear export. *J. Clin. Invest.* **111**, 553-559.
- Bild, A. H., Turkson, J. and Jove, R. (2002). Cytoplasmic transport of Stat3 by receptor-mediated endocytosis. *EMBO J.* **21**, 3255-3263.
- Boehm, U., Klamp, T., Groot, M. and Howard, J. C. (1997). Cellular responses to interferon-gamma. *Annu. Rev. Immunol.* **15**, 749-795.
- Bowman, T., Garcia, R., Turkson, J. and Jove, R. (2000). STATs in oncogenesis. *Oncogene* **19**, 2474-2488.
- Brivanlou, A. H. and Darnell, J. E., Jr. (2002). Signal transduction and the control of gene expression. *Science* **295**, 813-818.
- Bromberg, J. and Darnell, J. E., Jr. (2000). The role of STATs in transcriptional control and their impact on cellular function. *Oncogene* **19**, 2468-2473.
- Bromberg, J. F., Horvath, C. M., Wen, Z., Schreiber, R. D. and 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.
- Caldenhoven, E., van Dijk, T. B., Solari, R., Armstrong, J., Raaijmakers, J. A., Lammers, J. W., Koenderman, L. and de Groot, R. P. (1996). STAT3beta, a splice variant of transcription factor STAT3, is a dominant negative regulator of transcription. *J. Biol. Chem.* **271**, 13221-13227.
- Cartwright, P. and Helin, K. (2000). Nucleocytoplasmic shuttling of transcription factors. *Cell Mol. Life Sci.* **57**, 1193-1206.
- Chakraborty, A. and Tweardy, D. J. (1998). Granulocyte colony-stimulating factor activates a 72-kDa isoform of STAT3 in human neutrophils. *J. Leukoc. Biol.* **64**, 675-680.
- Chatterjee-Kishore, M., Wright, K. L., Ting, J. P. and Stark, G. R. (2000). How Stat1 mediates constitutive gene expression: a complex of unphosphorylated Stat1 and IRF1 supports transcription of the LMP2 gene. *EMBO J.* **19**, 4111-4122.
- Chen, X., Vinkemeier, U., Zhao, Y., Jeruzalmi, D., Darnell, J. E., Jr. and Kuriyan, J. (1998). Crystal structure of a tyrosine phosphorylated STAT-1 dimer bound to DNA. *Cell* **93**, 827-839.
- Conti, E. and Izaurrealde, E. (2001). Nucleocytoplasmic transport enters the atomic age. *Curr. Opin. Cell Biol.* **13**, 310-319.

- Cronshaw, J. M., Krutchinsky, A. N., Zhang, W., Chait, B. T. and Matunis, M. J. (2002). Proteomic analysis of the mammalian nuclear pore complex. *J. Cell Biol.* **158**, 915-927.
- Darnell, J. E., Jr., Kerr, I. M. and Stark, G. R. (1994). Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science* **264**, 1415-1421.
- Deb, D. K., Sassano, A., Lekmine, F., Majchrzak, B., Verma, A., Kambhampati, S., Uddin, S., Rahman, A., Fish, E. N. and Platanias, L. C. (2003). Activation of protein kinase C delta by IFN-gamma. *J. Immunol.* **171**, 267-273.
- Decker, T. and Kovarik, P. (1999). Transcription factor activity of STAT proteins: structural requirements and regulation by phosphorylation and interacting proteins. *Cell Mol. Life Sci.* **55**, 1535-1546.
- Decker, T. and Kovarik, P. (2000). Serine phosphorylation of STATs. *Oncogene* **19**, 2628-2637.
- Denning, D. P., Patel, S. S., Uversky, V., Fink, A. L. and Rexach, M. (2003). Disorder in the nuclear pore complex: the FG repeat regions of nucleoporins are natively unfolded. *Proc. Natl. Acad. Sci. U. S. A* **100**, 2450-2455.
- Der, S. D., Zhou, A., Williams, B. R. and Silverman, R. H. (1998). Identification of genes differentially regulated by interferon alpha, beta, or gamma using oligonucleotide arrays. *Proc. Natl. Acad. Sci. U. S. A* **95**, 15623-15628.
- Durbin, J. E., Hackenmiller, R., Simon, M. C. and Levy, D. E. (1996). Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. *Cell* **84**, 443-450.
- Ehret, G. B., Reichenbach, P., Schindler, U., Horvath, C. M., Fritz, S., Nabholz, M. and Bucher, P. (2001). DNA binding specificity of different STAT proteins. Comparison of in vitro specificity with natural target sites. *J. Biol. Chem.* **276**, 6675-6688.
- Eleftheriou, A., Yoshida, M. and Henderson, B. R. (2001). Nuclear export of human beta-catenin can occur independent of CRM1 and the adenomatous polyposis coli tumor suppressor. *J. Biol. Chem.* **276**, 25883-25888.
- Fabbro, M. and Henderson, B. R. (2003). Regulation of tumor suppressors by nuclear-cytoplasmic shuttling. *Exp. Cell Res.* **282**, 59-69.
- Fagerlund, R., Melén, K., Kinnunen, L. and Julkunen, I. (2002). Arginine/lysine-rich nuclear localization signals mediate interactions between dimeric STATs and importin alpha 5. *J. Biol. Chem.* **277**, 30072-30078.
- Frucht, D. M., Fukao, T., Bogdan, C., Schindler, H., O'Shea, J. J. and Koyasu, S. (2001). IFN-gamma production by antigen-presenting cells: mechanisms emerge. *Trends Immunol.* **22**, 556-560.

- Gao, J. J., Filla, M. B., Lorsbach, R. B., Pace, J. L., Crespo, A., Russell, S. W. and Murphy, W. J. (2000). Prolonged exposure of mouse macrophages to IFN-beta suppresses transcription of the inducible nitric oxide synthase gene: altered availability of transcription factor Stat1alpha. *Eur. J. Immunol.* **30**, 1551-1561.
- Gerhardt, C., Heesel, B., Sasse, J., Hemmann, U., Landgraf, C., Schneider-Mergener, J., Horn, F., Heinrich, P. C. and Graeve, L. (1996). Differential activation of acute phase response factor/STAT3 and STAT1 via the cytoplasmic domain of the interleukin 6 signal transducer gp130. I. Definition of a novel phosphotyrosine motif mediating STAT1 activation. *J. Biol. Chem.* **271**, 12991-12998.
- Ginger, R. S., Dalton, E. C., Ryves, W. J., Fukuzawa, M., Williams, J. G. and Harwood, A. J. (2000). Glycogen synthase kinase-3 enhances nuclear export of a Dictyostelium STAT protein. *EMBO J.* **19**, 5483-5491.
- Goenka, S., Marlar, C., Schindler, U. and Boothby, M. (2003). Differential roles of C-terminal activation motifs in the establishment of Stat6 transcriptional specificity. *J. Biol. Chem.* **278**, 50362-50370.
- Goh, K. C., Haque, S. J. and Williams, B. R. (1999). p38 MAP kinase is required for STAT1 serine phosphorylation and transcriptional activation induced by interferons. *EMBO J.* **18**, 5601-5608.
- Goodbourn, S., Didcock, L. and Randall, R. E. (2000). Interferons: cell signalling, immune modulation, antiviral response and virus countermeasures. *J. Gen. Virol.* **81**, 2341-2364.
- Görlich, D. and Kutay, U. (1999). Transport between the cell nucleus and the cytoplasm. *Annu. Rev. Cell Dev. Biol.* **15**, 607-660.
- Grant, R. P., Hurt, E., Neuhaus, D. and Stewart, M. (2002). Structure of the C-terminal FG-nucleoporin binding domain of Tap/NXF1. *Nat. Struct. Biol.* **9**, 247-251.
- Greenlund, A. C., Farrar, M. A., Viviano, B. L. and Schreiber, R. D. (1994). Ligand-induced IFN gamma receptor tyrosine phosphorylation couples the receptor to its signal transduction system (p91). *EMBO J.* **13**, 1591-1600.
- Greenlund, A. C., Morales, M. O., Viviano, B. L., Yan, H., Krolewski, J. and Schreiber, R. D. (1995). Stat recruitment by tyrosine-phosphorylated cytokine receptors: an ordered reversible affinity-driven process. *Immunity*. **2**, 677-687.
- Haspel, R. L., Salditt-Georgieff, M. and Darnell, J. E., Jr. (1996). The rapid inactivation of nuclear tyrosine phosphorylated Stat1 depends upon a protein tyrosine phosphatase. *EMBO J.* **15**, 6262-6268.
- Haspel, R. L. and Darnell, J. E., Jr. (1999). A nuclear protein tyrosine phosphatase is required for the inactivation of Stat1. *Proc. Natl. Acad. Sci. U. S. A* **96**, 10188-10193.
- Heim, M. H., Kerr, I. M., Stark, G. R. and Darnell, J. E., Jr. (1995). Contribution of STAT SH2 groups to specific interferon signaling by the Jak-STAT pathway. *Science* **267**, 1347-1349.

- Henderson, B. R. (2005). Regulation of BRCA1, BRCA2 and BARD1 intracellular trafficking. *Bioessays* **27**, 884-893.
- Hendry, L. and John, S. (2004). Regulation of STAT signalling by proteolytic processing. *Eur. J. Biochem.* **271**, 4613-4620.
- Herrington, J., Rui, L., Luo, G., Yu-Lee, L. Y. and Carter-Su, C. (1999). A functional DNA binding domain is required for growth hormone-induced nuclear accumulation of Stat5B. *J. Biol. Chem.* **274**, 5138-5145.
- Hoey, T. and Schindler, U. (1998). STAT structure and function in signaling. *Curr. Opin. Genet. Dev.* **8**, 582-587.
- Hoey, T., Zhang, S., Schmidt, N., Yu, Q., Ramchandani, S., Xu, X., Naeger, L. K., Sun, Y. L. and Kaplan, M. H. (2003). Distinct requirements for the naturally occurring splice forms Stat4alpha and Stat4beta in IL-12 responses. *EMBO J.* **22**, 4237-4248.
- Holaska, J. M., Black, B. E., Love, D. C., Hanover, J. A., Leszyk, J. and Paschal, B. M. (2001). Calreticulin Is a receptor for nuclear export. *J. Cell Biol.* **152**, 127-140.
- Horvath, C. M. and Darnell, J. E., Jr. (1996). The antiviral state induced by alpha interferon and gamma interferon requires transcriptionally active Stat1 protein. *J. Virol.* **70**, 647-650.
- Horvath, C. M. (2000). STAT proteins and transcriptional responses to extracellular signals. *Trends Biochem. Sci.* **25**, 496-502.
- Inman, G. J., Nicolás, F. J. and Hill, C. S. (2002). Nucleocytoplasmic shuttling of Smads 2, 3, and 4 permits sensing of TGF-beta receptor activity. *Mol. Cell* **10**, 283-294.
- Isaacs, A. and Lindenmann, J. (1957). Virus interference. I. The interferon. *Proc. R. Soc. Lond B Biol. Sci.* **147**, 258-267.
- Janeway, C. A., Travers, P., Walport, M. and Shlomchik, M. J. (2005). Immunobiology: the immune system in health and disease. *Garland science publishing, New York, U. S. A.*
- John, S., Vinkemeier, U., Soldaini, E., Darnell, J. E., Jr. and Leonard, W. J. (1999). The significance of tetramerization in promoter recruitment by Stat5. *Mol. Cell Biol.* **19**, 1910-1918.
- Johnson, H. M., Torres, B. A., Green, M. M., Szente, B. E., Siler, K. I., Larkin, J., III and Subramaniam, P. S. (1998). Cytokine-receptor complexes as chaperones for nuclear translocation of signal transducers. *Biochem. Biophys. Res. Commun.* **244**, 607-614.
- Kaffman, A. and O'Shea, E. K. (1999). Regulation of nuclear localization: a key to a door. *Annu. Rev. Cell Dev. Biol.* **15**, 291-339.
- Kaplan, D. H., Shankaran, V., Dighe, A. S., Stockert, E., Aguet, M., Old, L. J. and Schreiber, R. D. (1998). Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. *Proc. Natl. Acad. Sci. U. S. A* **95**, 7556-7561.

- Kaplan, M. H., Sun, Y. L., Hoey, T. and Grusby, M. J. (1996a). Impaired IL-12 responses and enhanced development of Th2 cells in Stat4-deficient mice. *Nature* **382**, 174-177.
- Kaplan, M. H., Schindler, U., Smiley, S. T. and Grusby, M. J. (1996b). Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. *Immunity*. **4**, 313-319.
- Kim, T. K. and Maniatis, T. (1996). Regulation of interferon-gamma-activated STAT1 by the ubiquitin-proteasome pathway. *Science* **273**, 1717-1719.
- Kisseleva, T., Bhattacharya, S., Braunstein, J. and Schindler, C. W. (2002). Signaling through the JAK/STAT pathway, recent advances and future challenges. *Gene* **285**, 1-24.
- Komeili, A. and O'Shea, E. K. (2001). New perspectives on nuclear transport. *Annu. Rev. Genet.* **35**, 341-364.
- Köster, M. and Hauser, H. (1999). Dynamic redistribution of STAT1 protein in IFN signaling visualized by GFP fusion proteins. *Eur. J. Biochem.* **260**, 137-144.
- Köster, M., Frahm, T. and Hauser, H. (2005). Nucleocytoplasmic shuttling revealed by FRAP and FLIP technologies. *Curr. Opin. Biotechnol.* **16**, 28-34.
- Kovarik, P., Stoiber, D., Novy, M. and Decker, T. (1998). Stat1 combines signals derived from IFN-gamma and LPS receptors during macrophage activation. *EMBO J.* **17**, 3660-3668.
- Kovarik, P., Stoiber, D., Eyers, P. A., Menghini, R., Neininger, A., Gaestel, M., Cohen, P. and 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.
- Kovarik, P., Mangold, M., Ramsauer, K., Heidari, H., Steinborn, R., Zotter, A., Levy, D. E., Müller, M. and Decker, T. (2001). Specificity of signaling by STAT1 depends on SH2 and C-terminal domains that regulate Ser727 phosphorylation, differentially affecting specific target gene expression. *EMBO J.* **20**, 91-100.
- Kubitscheck, U., Grunwald, D., Hoekstra, A., Rohleider, D., Kues, T., Siebrasse, J. P. and Peters, R. (2005). Nuclear transport of single molecules: dwell times at the nuclear pore complex. *J. Cell Biol.* **168**, 233-243.
- Kudo, N., Matsumori, N., Taoka, H., Fujiwara, D., Schreiner, E. P., Wolff, B., Yoshida, M. and Horinouchi, S. (1999). Leptomycin B inactivates CRM1/exportin 1 by covalent modification at a cysteine residue in the central conserved region. *Proc. Natl. Acad. Sci. U. S. A* **96**, 9112-9117.
- Kuersten, S., Arts, G. J., Walther, T. C., Englmeier, L. and Mattaj, I. W. (2002). Steady-state nuclear localization of exportin-t involves RanGTP binding and two distinct nuclear pore complex interaction domains. *Mol. Cell Biol.* **22**, 5708-5720.

- Kumar, A., Commane, M., Flickinger, T. W., Horvath, C. M. and Stark, G. R. (1997). Defective TNF-alpha-induced apoptosis in STAT1-null cells due to low constitutive levels of caspases. *Science* **278**, 1630-1632.
- Kurisaki, A., Kose, S., Yoneda, Y., Heldin, C. H. and Moustakas, A. (2001). Transforming growth factor-beta induces nuclear import of Smad3 in an importin-beta1 and Ran-dependent manner. *Mol. Biol. Cell* **12**, 1079-1091.
- Kutay, U., Bischoff, F. R., Kostka, S., Kraft, R. and Görlich, D. (1997). Export of importin alpha from the nucleus is mediated by a specific nuclear transport factor. *Cell* **90**, 1061-1071.
- Lee, C. K., Bluysen, H. A. and Levy, D. E. (1997). Regulation of interferon-alpha responsiveness by the duration of Janus kinase activity. *J. Biol. Chem.* **272**, 21872-21877.
- Lei, E. P. and Silver, P. A. (2002). Protein and RNA export from the nucleus. *Dev. Cell* **2**, 261-272.
- Lerner, L., Henriksen, M. A., Zhang, X. and Darnell, J. E., Jr. (2003). STAT3-dependent enhanceosome assembly and disassembly: synergy with GR for full transcriptional increase of the alpha 2-macroglobulin gene. *Genes Dev.* **17**, 2564-2577.
- Levy, D. E. and Darnell, J. E., Jr. (2002). Stats: transcriptional control and biological impact. *Nat. Rev. Mol. Cell Biol.* **3**, 651-662.
- Lillemeier, B. F., Köster, M. and Kerr, I. M. (2001). STAT1 from the cell membrane to the DNA. *EMBO J.* **20**, 2508-2517.
- Lippincott-Schwartz, J., Altan-Bonnet, N. and Patterson, G. H. (2003). Photobleaching and photoactivation: following protein dynamics in living cells. *Nat. Cell Biol.* **5**, S7-14.
- Liu, L., McBride, K. M. and Reich, N. C. (2005). STAT3 nuclear import is independent of tyrosine phosphorylation and mediated by importin-alpha3. *Proc. Natl. Acad. Sci. U. S. A* **102**, 8150-8155.
- Macara, I. G. (2001). Transport into and out of the nucleus. *Microbiol. Mol. Biol. Rev.* **65**, 570-94.
- Mao, X., Ren, Z., Parker, G. N., Sondermann, H., Pastorello, M. A., Wang, W., McMurray, J. S., Demeler, B., Darnell, J. E., Jr. and Chen, X. (2005). Structural bases of unphosphorylated STAT1 association and receptor binding. *Mol. Cell* **17**, 761-771.
- Marg, A., Shan, Y., Meyer, T., Meissner, T., Brandenburg, M. and Vinkemeier, U. (2004). Nucleocytoplasmic shuttling by nucleoporins Nup153 and Nup214 and CRM1-dependent nuclear export control the subcellular distribution of latent Stat1. *J. Cell Biol.* **165**, 823-833.
- Maritano, D., Sugrue, M. L., Tininini, S., Dewilde, S., Strobl, B., Fu, X., Murray-Tait, V., Chiarle, R. and Poli, V. (2004). The STAT3 isoforms alpha and beta have unique and specific functions. *Nat. Immunol.* **5**, 401-409.

- Matsubayashi, Y., Fukuda, M. and Nishida, E. (2001). Evidence for existence of a nuclear pore complex-mediated, cytosol-independent pathway of nuclear translocation of ERK MAP kinase in permeabilized cells. *J. Biol. Chem.* **276**, 41755-41760.
- McBride, K. M., McDonald, C. and Reich, N. C. (2000). Nuclear export signal located within the DNA-binding domain of the STAT1transcription factor. *EMBO J.* **19**, 6196-6206.
- McBride, K. M., Banninger, G., McDonald, C. and Reich, N. C. (2002). Regulated nuclear import of the STAT1 transcription factor by direct binding of importin-alpha. *EMBO J.* **21**, 1754-1763.
- Meissner, T., Krause, E. and Vinkemeier, U. (2004). Ratjadone and leptomycin B block CRM1-dependent nuclear export by identical mechanisms. *FEBS Lett.* **576**, 27-30.
- Meissner, T. (2005). Structure-function analysis of the STAT1 N-domain.
- Melén, K., Kinnunen, L. and Julkunen, I. (2001). Arginine/lysine-rich structural element is involved in interferon-induced nuclear import of STATs. *J. Biol. Chem.* **276**, 16447-16455.
- 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. and 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.
- Meyer, T., Gavenis, K. and Vinkemeier, U. (2002a). Cell type-specific and tyrosine phosphorylation-independent nuclear presence of STAT1 and STAT3. *Exp. Cell Res.* **272**, 45-55.
- Meyer, T., Begitt, A., Lödige, I., van Rossum, M. and Vinkemeier, U. (2002b). Constitutive and IFN-gamma-induced nuclear import of STAT1 proceed through independent pathways. *EMBO J.* **21**, 344-354.
- Meyer, T., Marg, A., Lemke, P., Wiesner, B. and Vinkemeier, U. (2003). DNA binding controls inactivation and nuclear accumulation of the transcription factor Stat1. *Genes Dev.* **17**, 1992-2005.
- Meyer, T., Hendry, L., Begitt, A., John, S. and Vinkemeier, U. (2004). A single residue modulates tyrosine dephosphorylation, oligomerization, and nuclear accumulation of stat transcription factors. *J. Biol. Chem.* **279**, 18998-19007.
- Milocco, L. H., Haslam, J. A., Rosen, J. and Seidel, H. M. (1999). Design of conditionally active STATs: insights into STAT activation and gene regulatory function. *Mol. Cell Biol.* **19**, 2913-2920.
- Moriggl, R., Gouilleux-Gruart, V., Jahne, R., Berchtold, S., Gartmann, C., Liu, X., Henighausen, L., Sotiropoulos, A., Groner, B. and Gouilleux, F. (1996). Deletion of the carboxyl-terminal transactivation domain of MGF-Stat5 results in sustained DNA binding and a dominant negative phenotype. *Mol. Cell Biol.* **16**, 5691-5700.

- Moriggl, R., Berchtold, S., Friedrich, K., Standke, G. J., Kammer, W., Heim, M., Wissler, M., Stocklin, E., Gouilleux, F. and Groner, B. (1997). Comparison of the transactivation domains of Stat5 and Stat6 in lymphoid cells and mammary epithelial cells. *Mol. Cell Biol.* **17**, 3663-3678.
- Mowen, K. and David, M. (1998). Role of the STAT1-SH2 domain and STAT2 in the activation and nuclear translocation of STAT1. *J. Biol. Chem.* **273**, 30073-30076.
- Mowen, K. and David, M. (2000). Regulation of STAT1 nuclear export by Jak1. *Mol. Cell Biol.* **20**, 7273-7281.
- Müller, M., Laxton, C., Briscoe, J., Schindler, C., Improta, T., Darnell, J. E., Jr., Stark, G. R. and Kerr, I. M. (1993). Complementation of a mutant cell line: central role of the 91 kDa polypeptide of ISGF3 in the interferon-alpha and -gamma signal transduction pathways. *EMBO J.* **12**, 4221-4228.
- Murphy, T. L., Geissal, E. D., Farrar, J. D. and Murphy, K. M. (2000). Role of the Stat4 N domain in receptor proximal tyrosine phosphorylation. *Mol. Cell Biol.* **20**, 7121-7131.
- Nachury, M. V. and Weis, K. (1999). The direction of transport through the nuclear pore can be inverted. *Proc. Natl. Acad. Sci. U. S. A* **96**, 9622-9627.
- Nair, J. S., DaFonseca, C. J., Tjernberg, A., Sun, W., Darnell, J. E., Jr., Chait, B. T. and Zhang, J. J. (2002). Requirement of Ca²⁺ and CaMKII for Stat1 Ser-727 phosphorylation in response to IFN-gamma. *Proc. Natl. Acad. Sci. U. S. A* **99**, 5971-5976.
- Nakajima, H., Suzuki, K. and Iwamoto, I. (2003). Lineage-specific negative regulation of STAT-mediated signaling by proteolytic processing. *Cytokine Growth Factor Rev.* **14**, 375-380.
- Nguyen, H., Ramana, C. V., Bayes, J. and Stark, G. R. (2001). Roles of phosphatidylinositol 3-kinase in interferon-gamma-dependent phosphorylation of STAT1 on serine 727 and activation of gene expression. *J. Biol. Chem.* **276**, 33361-33368.
- Nicolás, F. J., De Bosscher, K., Schmierer, B. and Hill, C. S. (2004). Analysis of Smad nucleocytoplasmic shuttling in living cells. *J. Cell Sci.* **117**, 4113-4125.
- O'Shea, J. J., Gadina, M. and Schreiber, R. D. (2002). Cytokine signaling in 2002: new surprises in the Jak/Stat pathway. *Cell* **109**, S121-S131.
- Oelgeschläger, T., Tao, Y., Kang, Y. K. and Roeder, R. G. (1998). Transcription activation via enhanced preinitiation complex assembly in a human cell-free system lacking TAFIIs. *Mol. Cell* **1**, 925-931.
- Ouchi, T., Lee, S. W., Ouchi, M., Aaronson, S. A. and Horvath, C. M. (2000). Collaboration of signal transducer and activator of transcription 1 (STAT1) and BRCA1 in differential regulation of IFN-gamma target genes. *Proc. Natl. Acad. Sci. U. S. A* **97**, 5208-5213.

- Palmer, A., Gavin, A. C. and Nebreda, A. R. (1998). A link between MAP kinase and p34(cdc2)/cyclin B during oocyte maturation: p90(rsk) phosphorylates and inactivates the p34(cdc2) inhibitory kinase Myt1. *EMBO J.* **17**, 5037-5047.
- Park, C., Li, S., Cha, E. and Schindler, C. (2000a). Immune response in Stat2 knockout mice. *Immunity*. **13**, 795-804.
- Park, O. K., Schaefer, L. K., Wang, W. and Schaefer, T. S. (2000b). Dimer stability as a determinant of differential DNA binding activity of Stat3 isoforms. *J. Biol. Chem.* **275**, 32244-32249.
- Paulson, M., Pisharody, S., Pan, L., Guadagno, S., Mui, A. L. and Levy, D. E. (1999). Stat protein transactivation domains recruit p300/CBP through widely divergent sequences. *J. Biol. Chem.* **274**, 25343-25349.
- Pemberton, L. F. and Paschal, B. M. (2005). Mechanisms of receptor-mediated nuclear import and nuclear export. *Traffic*. **6**, 187-198.
- Peters, R. (2005). Translocation through the nuclear pore complex: selectivity and speed by reduction-of-dimensionality. *Traffic*. **6**, 421-427.
- Pilz, A., Ramsauer, K., Heidari, H., Leitges, M., Kovarik, P. and Decker, T. (2003). Phosphorylation of the Stat1 transactivating domain is required for the response to type I interferons. *EMBO Rep.* **4**, 368-373.
- Pine, R., Canova, A. and Schindler, C. (1994). Tyrosine phosphorylated p91 binds to a single element in the ISGF2/IRF-1 promoter to mediate induction by IFN alpha and IFN gamma, and is likely to autoregulate the p91 gene. *EMBO J.* **13**, 158-167.
- Plataniatis, L. C. (2005). Mechanisms of type-I- and type-II-interferon-mediated signalling. *Nat. Rev. Immunol.* **5**, 375-386.
- Poon, I. K. and Jans, D. A. (2005). Regulation of nuclear transport: central role in development and transformation? *Traffic*. **6**, 173-186.
- Pranada, A. L., Metz, S., Herrmann, A., Heinrich, P. C. and Muller-Newen, G. (2004). Real time analysis of STAT3 nucleocytoplasmic shuttling. *J. Biol. Chem.* **279**, 15114-15123.
- Raingeaud, J., Gupta, S., Rogers, J. S., Dickens, M., Han, J., Ulevitch, R. J. and Davis, R. J. (1995). Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *J. Biol. Chem.* **270**, 7420-7426.
- Ram, P. A., Park, S. H., Choi, H. K. and Waxman, D. J. (1996). Growth hormone activation of Stat 1, Stat 3, and Stat 5 in rat liver. Differential kinetics of hormone desensitization and growth hormone stimulation of both tyrosine phosphorylation and serine/threonine phosphorylation. *J. Biol. Chem.* **271**, 5929-5940.

- Ramana, C. V., Chatterjee-Kishore, M., Nguyen, H. and Stark, G. R. (2000). Complex roles of Stat1 in regulating gene expression. *Oncogene* **19**, 2619-2627.
- Reguly, T. and Wrana, J. L. (2003). In or out? The dynamics of Smad nucleocytoplasmic shuttling. *Trends Cell Biol.* **13**, 216-220.
- Sanger, F., Nicklen, S. and Coulson, A. R. (1977). DNA sequencing with chain-terminating inhibitors. *Proc. Natl. Acad. Sci. U. S. A* **74**, 5463-5467.
- Schaefer, T. S., Sanders, L. K. and Nathans, D. (1995). Cooperative transcriptional activity of Jun and Stat3 beta, a short form of Stat3. *Proc. Natl. Acad. Sci. U. S. A* **92**, 9097-9101.
- Schaefer, T. S., Sanders, L. K., Park, O. K. and Nathans, D. (1997). Functional differences between Stat3alpha and Stat3beta. *Mol. Cell Biol.* **17**, 5307-5316.
- Schindler, C., Fu, X. Y., Imrota, T., Aebersold, R. and Darnell, J. E., Jr. (1992). Proteins of transcription factor ISGF-3: one gene encodes the 91-and 84-kDa ISGF-3 proteins that are activated by interferon alpha. *Proc. Natl. Acad. Sci. U. S. A* **89**, 7836-7839.
- Schindler, C., Shuai, K., Prezioso, V. R. and Darnell, J. E., Jr. (1992). Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. *Science* **257**, 809-813.
- Schindler, C. and Darnell, J. E., Jr. (1995). Transcriptional responses to polypeptide ligands: the JAK-STAT pathway. *Annu. Rev. Biochem.* **64**, 621-651.
- Schindler, C. and Strehlow, I. (2000). Cytokines and STAT signaling. *Adv. Pharmacol.* **47**, 113-174.
- Schindler, U., Wu, P., Rothe, M., Brasseur, M. and McKnight, S. L. (1995). Components of a Stat recognition code: evidence for two layers of molecular selectivity. *Immunity* **2**, 689-697.
- Sekimoto, T., Nakajima, K., Tachibana, T., Hirano, T. and Yoneda, Y. (1996). Interferon-gamma-dependent nuclear import of Stat1 is mediated by the GTPase activity of Ran/TC4. *J. Biol. Chem.* **271**, 31017-31020.
- Sekimoto, T., Imamoto, N., Nakajima, K., Hirano, T. and Yoneda, Y. (1997). Extracellular signal-dependent nuclear import of Stat1 is mediated by nuclear pore-targeting complex formation with NPI-1, but not Rch1. *EMBO J.* **16**, 7067-7077.
- Shen, Y. and Darnell, J. E., Jr. (2001). Antiviral response in cells containing Stat1 with heterologous transactivation domains. *J. Virol.* **75**, 2627-2633.
- Shuai, K., Schindler, C., Prezioso, V. R. and Darnell, J. E., Jr. (1992). Activation of transcription by IFN-gamma: tyrosine phosphorylation of a 91-kD DNA binding protein. *Science* **258**, 1808-1812.
- Shuai, K., Stark, G. R., Kerr, I. M. and Darnell, J. E., Jr. (1993). A single phosphotyrosine residue of Stat91 required for gene activation by interferon-gamma. *Science* **261**, 1744-1746.

- Shuai, K., Horvath, C. M., Huang, L. H., Qureshi, S. A., Cowburn, D. and Darnell, J. E., Jr. (1994). Interferon activation of the transcription factor Stat91 involves dimerization through SH2-phosphotyrosyl peptide interactions. *Cell* **76**, 821-828.
- Shuai, K., Liao, J. and Song, M. M. (1996). Enhancement of antiproliferative activity of gamma interferon by the specific inhibition of tyrosine dephosphorylation of Stat1. *Mol. Cell Biol.* **16**, 4932-4941.
- Shuai, K. and Liu, B. (2003). Regulation of JAK-STAT signalling in the immune system. *Nat. Rev. Immunol.* **3**, 900-911.
- Socolovsky, M., Nam, H., Fleming, M. D., Haase, V. H., Brugnara, C. and Lodish, H. F. (2001). Ineffective erythropoiesis in Stat5a(-/-)5b(-/-) mice due to decreased survival of early erythroblasts. *Blood* **98**, 3261-3273.
- Soler-Lopez, M., Petosa, C., Fukuzawa, M., Ravelli, R., Williams, J. G. and Müller, C. W. (2004). Structure of an activated Dictyostelium STAT in its DNA-unbound form. *Mol. Cell* **13**, 791-804.
- Stark, G. R., Kerr, I. M., Williams, B. R., Silverman, R. H. and Schreiber, R. D. (1998). How cells respond to interferons. *Annu. Rev. Biochem.* **67**, 227-264.
- Stephanou, A., Scarabelli, T. M., Brar, B. K., Nakanishi, Y., Matsumura, M., Knight, R. A. and Latchman, D. S. (2001). Induction of apoptosis and Fas receptor/Fas ligand expression by ischemia/reperfusion in cardiac myocytes requires serine 727 of the STAT-1 transcription factor but not tyrosine 701. *J. Biol. Chem.* **276**, 28340-28347.
- Strehlow, I. and Schindler, C. (1998). Amino-terminal signal transducer and activator of transcription (STAT) domains regulate nuclear translocation and STAT deactivation. *J. Biol. Chem.* **273**, 28049-28056.
- Subramaniam, P. S., Larkin, J., III, Mujtaba, M. G., Walter, M. R. and Johnson, H. M. (2000). The COOH-terminal nuclear localization sequence of interferon gamma regulates STAT1 alpha nuclear translocation at an intracellular site. *J. Cell Sci.* **113**, 2771-2781.
- Suh, E. K. and Gumbiner, B. M. (2003). Translocation of beta-catenin into the nucleus independent of interactions with FG-rich nucleoporins. *Exp. Cell Res.* **290**, 447-456.
- Sun, W., Xu, W., Snyder, M., He, W., Ho, H., Ivashkiv, L. B. and Zhang, J. J. (2005). The conserved Leu-724 residue is required for both serine phosphorylation and co-activator recruitment for Stat1-mediated transcription activation in response to interferon-gamma. *J. Biol. Chem.* **280**, 41844-41851.
- Suntharalingam, M. and Wente, S. R. (2003). Peering through the pore: nuclear pore complex structure, assembly, and function. *Dev. Cell* **4**, 775-789.
- Swameye, I., Müller, T. G., Timmer, J., Sandra, O. and Klingmüller, U. (2003). Identification of nucleocytoplasmic cycling as a remote sensor in cellular signaling by databased modeling. *Proc. Natl. Acad. Sci. U. S. A* **100**, 1028-1033.

- Teglund, S., McKay, C., Schuetz, E., van Deursen, J. M., Stravopodis, D., Wang, D., Brown, M., Bodner, S., Grosveld, G. and Ihle, J. N. (1998). Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. *Cell* **93**, 841-850.
- ten Dijke, P. and Hill, C. S. (2004). New insights into TGF-beta-Smad signalling. *Trends Biochem. Sci.* **29**, 265-273.
- ten Hoeve, J., de, J., I, Fu, Y., Zhu, W., Tremblay, M., David, M. and Shuai, K. (2002). Identification of a nuclear Stat1 protein tyrosine phosphatase. *Mol. Cell Biol.* **22**, 5662-5668.
- Towbin, H., Staehelin, T. and Gordon, J. (1979). Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets: procedure and some applications. *Proc. Natl. Acad. Sci. U. S. A* **76**, 4350-4354.
- Uddin, S., Sassano, A., Deb, D. K., Verma, A., Majchrzak, B., Rahman, A., Malik, A. B., Fish, E. N. and Platanias, L. C. (2002). Protein kinase C-delta (PKC-delta) is activated by type I interferons and mediates phosphorylation of Stat1 on serine 727. *J. Biol. Chem.* **277**, 14408-14416.
- Varinou, L., Ramsauer, K., Karaghiosoff, M., Kolbe, T., Pfeffer, K., Müller, M. and Decker, T. (2003). Phosphorylation of the Stat1 transactivation domain is required for full-fledged IFN-gamma-dependent innate immunity. *Immunity* **19**, 793-802.
- Vinkemeier, U., Cohen, S. L., Moarefi, I., Chait, B. T., Kuriyan, J. and Darnell, J. E., Jr. (1996). DNA binding of in vitro activated Stat1 alpha, Stat1 beta and truncated Stat1: interaction between NH₂-terminal domains stabilizes binding of two dimers to tandem DNA sites. *EMBO J.* **15**, 5616-5626.
- Vinkemeier, U., Moarefi, I., Darnell, J. E., Jr. and Kuriyan, J. (1998). Structure of the amino-terminal protein interaction domain of STAT-4. *Science* **279**, 1048-1052.
- Vinkemeier, U. (2004). Getting the message across, STAT! Design principles of a molecular signaling circuit. *J. Cell Biol.* **167**, 197-201.
- Visconti, R., Gadina, M., Chiariello, M., Chen, E. H., Stancato, L. F., Gutkind, J. S. and O'Shea, J. J. (2000). Importance of the MKK6/p38 pathway for interleukin-12-induced STAT4 serine phosphorylation and transcriptional activity. *Blood* **96**, 1844-1852.
- Walter, M. J., Look, D. C., Tidwell, R. M., Roswit, W. T. and Holtzman, M. J. (1997). Targeted inhibition of interferon-gamma-dependent intercellular adhesion molecule-1 (ICAM-1) expression using dominant-negative Stat1. *J. Biol. Chem.* **272**, 28582-28589.
- Wang, D., Stravopodis, D., Teglund, S., Kitazawa, J. and Ihle, J. N. (1996). Naturally occurring dominant negative variants of Stat5. *Mol. Cell Biol.* **16**, 6141-6148.
- Wang, D., Moriggl, R., Stravopodis, D., Carpino, N., Marine, J. C., Teglund, S., Feng, J. and Ihle, J. N. (2000). A small amphipathic alpha-helical region is required for transcriptional activities and proteasome-dependent turnover of the tyrosine-phosphorylated Stat5. *EMBO J.* **19**, 392-399.

- Wen, Z., Zhong, Z. and Darnell, J. E., Jr. (1995). Maximal activation of transcription by Stat1 and Stat3 requires both tyrosine and serine phosphorylation. *Cell* **82**, 241-250.
- Wen, Z. and Darnell, J. E., Jr. (1997). Mapping of Stat3 serine phosphorylation to a single residue (727) and evidence that serine phosphorylation has no influence on DNA binding of Stat1 and Stat3. *Nucleic Acids Res.* **25**, 2062-2067.
- Whitehurst, A. W., Wilsbacher, J. L., You, Y., Luby-Phelps, K., Moore, M. S. and Cobb, M. H. (2002). ERK2 enters the nucleus by a carrier-independent mechanism. *Proc. Natl. Acad. Sci. U. S. A* **99**, 7496-7501.
- Wozniak, R. W., Rout, M. P. and Aitchison, J. D. (1998). Karyopherins and kissing cousins. *Trends Cell Biol.* **8**, 184-188.
- Wurster, A. L., Tanaka, T. and Grusby, M. J. (2000). The biology of Stat4 and Stat6. *Oncogene* **19**, 2577-2584.
- Xiao, Z., Liu, X. and Lodish, H. F. (2000). Importin beta mediates nuclear translocation of Smad3. *J. Biol. Chem.* **275**, 23425-23428.
- Xu, L., Kang, Y., Col, S. and Massague, J. (2002). Smad2 nucleocytoplasmic shuttling by nucleoporins CAN/Nup214 and Nup153 feeds TGFbeta signaling complexes in the cytoplasm and nucleus. *Mol. Cell* **10**, 271-282.
- Xu, L., Alarcon, C., Col, S. and Massague, J. (2003). Distinct domain utilization by Smad3 and Smad4 for nucleoporin interaction and nuclear import. *J. Biol. Chem.* **278**, 42569-42577.
- Xu, L. and Massague, J. (2004). Nucleocytoplasmic shuttling of signal transducers. *Nat. Rev. Mol. Cell Biol.* **5**, 209-219.
- Xu, X., Sun, Y. L. and Hoey, T. (1996). Cooperative DNA binding and sequence-selective recognition conferred by the STAT amino-terminal domain. *Science* **273**, 794-797.
- Yamashita, H., Xu, J., Erwin, R. A., Farrar, W. L., Kirken, R. A. and Rui, H. (1998). Differential control of the phosphorylation state of proline-juxtaposed serine residues Ser725 of Stat5a and Ser730 of Stat5b in prolactin-sensitive cells. *J. Biol. Chem.* **273**, 30218-30224.
- Yokoya, F., Imamoto, N., Tachibana, T. and Yoneda, Y. (1999). beta-catenin can be transported into the nucleus in a Ran-unassisted manner. *Mol. Biol. Cell* **10**, 1119-1131.
- Yoo, J. Y., Huso, D. L., Nathans, D. and Desiderio, S. (2002). Specific ablation of Stat3beta distorts the pattern of Stat3-responsive gene expression and impairs recovery from endotoxic shock. *Cell* **108**, 331-344.
- You, M., Yu, D. H. and 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.

- Zakharova, N., Lymar, E. S., Yang, E., Malik, S., Zhang, J. J., Roeder, R. G. and Darnell, J. E., Jr. (2003). Distinct transcriptional activation functions of STAT1alpha and STAT1beta on DNA and chromatin templates. *J. Biol. Chem.* **278**, 43067-43073.
- Zeng, R., Aoki, Y., Yoshida, M., Arai, K. and Watanabe, S. (2002). Stat5B shuttles between cytoplasm and nucleus in a cytokine-dependent and -independent manner. *J. Immunol.* **168**, 4567-4575.
- Zhang, J. J., Vinkemeier, U., Gu, W., Chakravarti, D., Horvath, C. M. and Darnell, J. E., Jr. (1996). Two contact regions between Stat1 and CBP/p300 in interferon gamma signaling. *Proc. Natl. Acad. Sci. U. S. A* **93**, 15092-15096.
- Zhang, J. J., Zhao, Y., Chait, B. T., Lathem, W. W., Ritzi, M., Knippers, R. and Darnell, J. E., Jr. (1998). Ser727-dependent recruitment of MCM5 by Stat1alpha in IFN-gamma-induced transcriptional activation. *EMBO J.* **17**, 6963-6971.
- Zhang, T., Kee, W. H., Seow, K. T., Fung, W. and Cao, X. (2000). The coiled-coil domain of Stat3 is essential for its SH2 domain-mediated receptor binding and subsequent activation induced by epidermal growth factor and interleukin-6. *Mol. Cell Biol.* **20**, 7132-7139.
- Zhu, J. and McKeon, F. (2000). Nucleocytoplasmic shuttling and the control of NF-AT signaling. *Cell Mol. Life Sci.* **57**, 411-420.
- Zhu, X., Wen, Z., Xu, L. Z. and Darnell, J. E., Jr. (1997). Stat1 serine phosphorylation occurs independently of tyrosine phosphorylation and requires an activated Jak2 kinase. *Mol. Cell Biol.* **17**, 6618-6623.
- Zi, Z., Cho, K. H., Sung, M. H., Xia, X., Zheng, J. and Sun, Z. (2005). In silico identification of the key components and steps in IFN-gamma induced JAK-STAT signaling pathway. *FEBS Lett.* **579**, 1101-1108.
- Zong, C., Yan, R., August, A., Darnell, J. E., Jr. and Hanafusa, H. (1996). Unique signal transduction of Eyk: constitutive stimulation of the JAK-STAT pathway by an oncogenic receptor-type tyrosine kinase. *EMBO J.* **15**, 4515-4525.