
6. References

- Abramovich, C., Yakobson, B., Chebath, J. and Revel, M. (1997) A protein-arginine methyltransferase binds to the intracytoplasmic domain of the IFNAR1 chain in the type I interferon receptor. *EMBO J* **16**, 260-266.
- Adachi, Y. and Yanagida, M. (1989) Higher order chromosome structure is affected by cold-sensitive mutations in a *Schizosaccharomyces pombe* gene *crm1+* which encodes a 115-kD protein preferentially localized in the nucleus and its periphery. *J Cell Biol* **108**, 1195-1207.
- Akira, S. (1999) Functional roles of STAT family proteins: lessons from knockout mice. *Stem Cells* **17**, 138-146.
- Aoki, N. and Matsuda, T. (2000) A cytosolic protein-tyrosine phosphatase PTP1B specifically dephosphorylates and deactivates prolactin-activated STAT5a and STAT5b. *J Biol Chem* **275**, 39718-39726.
- Arenzana-Seisdedos, F., Turpin, P., Rodriguez, M., Thomas, D., Hay, R.T., Virelizier, J.L. and Dargemont, C. (1997) Nuclear localization of I kappa B alpha promotes active transport of NF-kappa B from the nucleus to the cytoplasm. *J Cell Sci* **110**, 369-378.
- Askjaer, P., Jensen, T.H., Nilsson, J., Englmeier, L. and Kjems, J. (1998) The specificity of the CRM1-Rev nuclear export signal interaction is mediated by RanGTP. *J Biol Chem* **273**, 33414-33422.
- Asscher, Y., Pleban, S., Ben-Shushan, M., Levin-Khalifa, M., Yao, Z. and Seger R. (2001) Leptomycin B: An Important Tool for the Study of Nuclear Export. *LifeScience, A technical application bulletin* **2**, 2
- Baden, H.A., Sarma, S.P., Kapust, R.B., Byrd, R.A. and Waugh, D.S. (1998) The amino-terminal domain of human STAT4. Overproduction, purification, and biophysical characterization. *J Biol Chem* **273**, 17109-17114.
- 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.
- Berenson, L.S., Ota, N. and Murphy, K.M. (2004) Issues in T-helper 1 development--resolved and unresolved. *Immunol Rev* **202**, 157-174.
- Bhatt, U., Christmann, M., Quitschalle, M., Claus, E. and Kalesse, M. (2001) The first total synthesis of +-ratjadone. *J Org Chem* **66**, 1885-1893.
- Bhattacharya, S. and Schindler, C. (2003) Regulation of Stat3 nuclear export. *J Clin Invest* **111**, 553-559.
- Birbach, A., Gold, P., Binder, B.R., Hofer, E., de Martin, R. and Schmid, J.A. (2002) Signaling molecules of the NF-kappa B pathway shuttle constitutively between cytoplasm and nucleus. *J Biol Chem* **277**, 10842-10851.

6. References

- Boisvert, F.M., Cote, J., Boulanger, M.C. and Richard, S. (2003) A proteomic analysis of arginine-methylated protein complexes. *Mol Cell Proteomics* **2**, 1319-1330.
- Burzlaff, A., Kalesse, M., Kasper, C. and Scheper, T. (2003) Multi parameter in vitro testing of ratjadone using flow cytometry. *Appl Microbiol Biotechnol* **62**, 174-179.
- Callanan, M., Kudo, N., Gout, S., Brocard, M., Yoshida, M., Dimitrov, S. and Khochbin, S. (2000) Developmentally regulated activity of CRM1/XPO1 during early Xenopus embryogenesis. *J Cell Sci* **113**, 451-459.
- Callard, R. and Gearing A. (1994) *The Cytokines and Their Receptors: IL-4*. Academic Press Limited. San Diego, CA. pp. 53-58.
- Carson, D.A., Nobori, T., Kajander, E.O., Carrera, C.J., Kubota, M. and Yamanaka, H. (1988) Methylthioadenosine (MeSAAdo) phosphorylase deficiency in malignancy. *Adv Exp Med Biol* **250**, 179-185.
- Chada, S., Ramesh, R. and Mhashilkar, A.M. (2003) Cytokine- and chemokine-based gene therapy for cancer. *Curr Opin Mol Ther* **5**, 463-474.
- Chang, H.C., Zhang, S., Oldham, I., Naeger, L., Hoey, T. and Kaplan, M.H. (2003) STAT4 requires the N-terminal domain for efficient phosphorylation. *J Biol Chem* **278**, 32471-32477.
- 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, W., Daines, M.O. and Hershey, G.K. (2004) Methylation of STAT6 modulates STAT6 phosphorylation, nuclear translocation, and DNA-binding activity. *J Immunol* **172**, 6744-6750.
- Chen, X., Bhandari, R., Vinkemeier, U., Van Den Akker, F., Darnell, J.E.J. and Kuriyan, J. (2003) A reinterpretation of the dimerization interface of the N-terminal domains of STATs. *Protein Sci* **12**, 361-365.
- Chen, X., Vinkemeier, U., Zhao, Y., Jeruzalmi, D., Darnell, J.E.J. and Kuriyan, J. (1998) Crystal structure of a tyrosine phosphorylated STAT-1 dimer bound to DNA. *Cell* **93**, 827-839.
- Chin, Y.E., Kitagawa, M., Kuida, K., Flavell, R.A. and Fu, X.Y. (1997) Activation of the STAT signaling pathway can cause expression of caspase 1 and apoptosis. *Mol Cell Biol* **17**, 5328-5337.
- Clarke, S. (1993) Protein methylation. *Curr Opin Cell Biol* **5**, 977-983.
- Cohen, S.N., Chang, A.C. and Hsu, L. (1972) Nonchromosomal antibiotic resistance in bacteria: genetic transformation of *Escherichia coli* by R-factor DNA. *Proc Natl Acad Sci U S A* **69**, 2110-2114.
- Conti, E., Uy, M., Leighton, L., Blobel, G. and Kuriyan, J. (1998) Crystallographic analysis of the recognition of a nuclear localization signal by the nuclear import factor karyopherin alpha. *Cell* **94**, 193-204.

- la Cour, T., Gupta, R., Rapacki, K., Skriver, K., Poulsen, F.M. and Brunak, S. (2003) NESbase version 1.0: a database of nuclear export signals. *Nucleic Acids Res* **31**, 393-396.
- Crooks, G.E., Hon, G., Chandonia, J.M. and Brenner, S.E. (2004) WebLogo: a sequence logo generator. *Genome Res* **14**, 1188-1190.
- Daelemans, D., Costes, S.V., Lockett, S. and Pavlakis, G.N. (2005) Kinetic and molecular analysis of nuclear export factor CRM1 association with its cargo *in vivo*. *Mol Cell Biol* **25**, 728-739.
- Darnell, J.E.J. (1997) STATs and gene regulation. *Science* **277**, 1630-1635.
- Darnell, J.E.J., 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.
- Decker, T. and Kovarik, P. (2000) Serine phosphorylation of STATs. *Oncogene* **19**, 2628-2637.
- Decker, T., Kovarik, P. and Meinke, A. (1997) GAS elements: a few nucleotides with a major impact on cytokine-induced. *J Interferon Cytokine Res* **17**, 121-134.
- Dingwall, C. and Laskey, R.A. (1991) Nuclear targeting sequences -a consensus? *Trends Biochem Sci* **16**, 478-481.
- Dingwall, C., Sharnick, S.V. and Laskey, R.A. (1982) A polypeptide domain that specifies migration of nucleoplasmin into the nucleus. *Cell* **30**, 449-458.
- Duong, F.H., Filipowicz, M., Tripodi, M., La Monica, N. and Heim, M.H. (2004) Hepatitis C virus inhibits interferon signaling through up-regulation of of protein phosphatase 2A. *Gastroenterology* **126**, 263-277.
- Dupuis, S., Jouanguy, E., Al-Hajjar, S., Fieschi, C., Al-Mohsen, I.Z., Al-Jumaah, S., Yang, K., Chapgier, A., Eidenschenk, C., Eid, P., Al Ghoniaim, A., Tufenkeji, H., Frayha, H., Al-Gazlan, S., Al-Rayes, H., Schreiber, R.D., Gresser, I. and Casanova, J.L. (2003) Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. *Nat Genet* **33**, 388-391.
- Dupuis, S., Dargemont, C., Fieschi, C., Thomassin, N., Rosenzweig, S., Harris, J., Holland, S.M., Schreiber, R.D. and Casanova, J.L. (2001) Impairment of mycobacterial but not viral immunity by a germline human STAT1 mutation. *Science* **293**, 300-303.
- 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.
- Fagerlund, R., Melen, 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.

6. References

- Fischer, U., Huber, J., Boelens, W.C., Mattaj, I.W. and Luhrmann, R. (1995) The HIV-1 Rev activation domain is a nuclear export signal that accesses an export pathway used by specific cellular RNAs. *Cell* **82**, 475-483.
- Fitch, J.H., Riscoe, M.K., Dana, B.W., Lawrence, H.J. and Ferro, A.J. (1986) Methylthioadenosine phosphorylase deficiency in human leukemias and solid tumors. *Cancer Res* **46**, 5409-5412.
- Fontes, M.R., Teh, T. and Kobe, B. (2000) Structural basis of recognition of monopartite and bipartite nuclear localization sequences by mammalian importin- α . *J Mol Biol* **297**, 1183-1194.
- Fornerod, M., Ohno, M., Yoshida, M. and Mattaj, I.W. (1997) CRM1 is an export receptor for leucine-rich nuclear export signals. *Cell* **90**, 1051-1060.
- Freedman, D.A. and Levine, A.J. (1998) Nuclear export is required for degradation of endogenous p53 by MDM2 and human papillomavirus E6. *Mol Cell Biol* **18**, 7288-7293.
- Fried, M. and Crothers, D.M. (1981) Equilibria and kinetics of lac repressor-operator interactions by polyacrylamide gel electrophoresis. *Nucleic Acids Res* **9**, 6505-6525.
- Fu, X.Y. and Zhang, J.J. (1993) Transcription factor p91 interacts with the epidermal growth factor receptor and mediates activation of the c-fos gene promoter. *Cell* **74**, 1135-1145.
- Fukuda, M., Asano, S., Nakamura, T., Adachi, M., Yoshida, M., Yanagida, M. and Nishida, E. (1997) CRM1 is responsible for intracellular transport mediated by the nuclear export signal. *Nature* **390**, 308-311.
- Fukuzawa, M., Abe, T. and Williams, J.G. (2003) The Dictyostelium prestalk cell inducer DIF regulates nuclear accumulation of a STAT protein by controlling its rate of export from the nucleus. *Development* **130**, 797-804.
- Garcia-Castellano, J.M., Villanueva, A., Healey, J.H., Sowers, R., Cordon-Cardo, C., Huvos, A., Bertino, J.R., Meyers, P. and Gorlick, R. (2002) Methylthioadenosine phosphorylase gene deletions are common in osteosarcoma. *Clin Cancer Res* **8**, 782-787.
- Gary, J.D. and Clarke, S. (1998) RNA and protein interactions modulated by protein arginine methylation. *Prog Nucleic Acid Res Mol Biol* **61**, 65-131.
- Gerth, K., Schummer, D., Höfle, G., Irschik, H. and Reichenbach, H. (1995) Ratjadon: a new antifungal compound from *Sorangium cellulosum* (myxobacteria) production, physicochemical and biological properties. *J Antibiot (Tokyo)* **48**, 973-976.
- Görlich, D. and Kutay, U. (1999) Transport between the cell nucleus and the cytoplasm. *Annu Rev Cell Dev Biol* **15**, 607-660.
- Görlich, D. and Mattaj, I.W. (1996) Nucleocytoplasmic transport. *Science* **271**, 1513-1518.

- 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.
- Hamamoto, T., Gunji, S., Tsuji, H. and Beppu, T. (1983a) Leptomycins A and B, new antifungal antibiotics. I. Taxonomy of the producing strain and their fermentation, purification and characterization. *J Antibiot (Tokyo)* **36**, 639-645.
- Hamamoto, T., Seto, H. and Beppu, T. (1983b) Leptomycins A and B, new antifungal antibiotics. II. Structure elucidation. *J Antibiot (Tokyo)* **36**, 646-650.
- Haspel, R.L. and Darnell, J.E.J. (1999) A nuclear protein tyrosine phosphatase is required for the inactivation of Stat1. *Proc Natl Acad Sci U S A* **96**, 10188-10193.
- Haspel, R.L., Salditt-Georgieff, M. and Darnell, J.E.J. (1996) The rapid inactivation of nuclear tyrosine phosphorylated Stat1 depends upon a protein tyrosine phosphatase. *EMBO J* **15**, 6262-6268.
- Henderson, B.R. and Eleftheriou, A. (2000) A comparison of the activity, sequence specificity, and CRM1-dependence of different nuclear export signals. *Exp Cell Res* **256**, 213-224.
- Henriksen, M.A., Betz, A., Fuccillo, M.V. and Darnell, J.E.J. (2002) Negative regulation of STAT92E by an N-terminally truncated STAT protein derived from an alternative promoter site. *Genes Dev* **16**, 2379-2389.
- 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.
- Holaska, J.M. and Paschal, B.M. (1998) A cytosolic activity distinct from crm1 mediates nuclear export of protein kinase inhibitor in permeabilized cells. *Proc Natl Acad Sci U S A* **95**, 14739-14744.
- Horvath, C.M. (2000) STAT proteins and transcriptional responses to extracellular signals. *Trends Biochem Sci* **25**, 496-502.
- Horvath, C.M. (2004) Weapons of STAT destruction. *Eur J Biochem* **271**, 4621-4628.
- Hou, S.X., Zheng, Z., Chen, X. and Perrimon, N. (2002) The Jak/STAT pathway in model organisms: emerging roles in cell movement. *Dev Cell* **3**, 765-778.
- Huang, T.T., Kudo, N., Yoshida, M. and Miyamoto, S. (2000) A nuclear export signal in the N-terminal regulatory domain of IkappaBalpha controls cytoplasmic localization of inactive NF-kappaB/IkappaBalpha complexes. *Proc Natl Acad Sci U S A* **97**, 1014-1019.
- Ihle, J.N. (2001) The Stat family in cytokine signaling. *Curr Opin Cell Biol* **13**, 211-217.
- Isaacs, A., Lindenmann, J. (1957) Virus interference. I. The interferon. *Proc. R. Soc. London Ser. B* **147**, 258-67.

6. References

- John, S., Vinkemeier, U., Soldaini, E., Darnell, J.E.J. and Leonard, W.J. (1999) The significance of tetramerization in promoter recruitment by Stat5. *Mol Cell Biol* **19**, 1910-1918.
- Johnson, C., Van Antwerp, D. and Hope, T.J. (1999) An N-terminal nuclear export signal is required for the nucleocytoplasmic shuttling of I κ B. *EMBO J* **18**, 6682-6693.
- Kalderon, D., Roberts, B.L., Richardson, W.D. and Smith, A.E. (1984) A short amino acid sequence able to specify nuclear location. *Cell* **39**, 499-509.
- Kalesse, M., Christmann, M., Bhatt, U., Quitschalle, M., Claus, E., Saeed, A., Burzlaff, A., Kasper, C., Haustedt, L.O., Hofer, E., Scheper, T. and Beil, W. (2001) The chemistry and biology of ratjadone. *Chembiochem* **2**, 709-714.
- Kamatani, N. and Carson, D.A. (1980) Abnormal regulation of methylthioadenosine and polyamine metabolism in methylthioadenosine phosphorylase-deficient human leukemic cell lines. *Cancer Res* **40**, 4178-4182.
- Kamatani, N., Nelson-Rees, W.A. and Carson, D.A. (1981) Selective killing of human malignant cell lines deficient in methylthioadenosine phosphorylase, a purine metabolic enzyme. *Proc Natl Acad Sci U S A* **78**, 1219-1223.
- Kamatani, N., Yu, A.L. and Carson, D.A. (1982) Deficiency of methylthioadenosine phosphorylase in human leukemic cells in vivo. *Blood* **60**, 1387-1391.
- 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.
- Kleuss, C. and Krause, E. (2003) Galpha(s) is palmitoylated at the N-terminal glycine. *EMBO J* **22**, 826-832.
- Koike, M., Kose, S., Furuta, M., Taniguchi, N., Yokoya, F., Yoneda, Y. and Imamoto, N. (2004) Beta-catenin shows an overlapping sequence requirement but distinct molecular interactions for its bidirectional passage through nuclear pores. *J Biol Chem* **279**, 34038-34047.
- Komeili, A. and O'Shea, E.K. (2001) New perspectives on nuclear transport. *Annu Rev Genet* **35**, 341-364.
- Koradi, R., Billeter, M. and Wuthrich, K. (1996) MOLMOL: a program for display and analysis of macromolecular structures. *J Mol Graph* **14**, 51-32.
- 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., Lykke-Andersen, S., Elnakady, Y.A., Gerth, K., Washausen, P., Höfle, G., Sasse, F., Kjems, J. and Hauser, H. (2003) Ratjadones inhibit nuclear export by blocking CRM1/exportin 1. *Exp Cell Res* **286**, 321-331.

- Kubota, M., Kajander, E.O. and Carson, D.A. (1985) Independent regulation of ornithine decarboxylase and S-adenosylmethionine decarboxylase in methylthioadenosine phosphorylase-deficient malignant murine lymphoblasts. *Cancer Res* **45**, 3567-3572.
- Kudo, N., Khochbin, S., Nishi, K., Kitano, K., Yanagida, M., Yoshida, M. and Horinouchi, S. (1997) Molecular cloning and cell cycle-dependent expression of mammalian CRM1, a protein involved in nuclear export of proteins. *J Biol Chem* **272**, 29742-29751.
- 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 USA* **96**, 9112-9117.
- Kudo, N., Wolff, B., Sekimoto, T., Schreiner, E.P., Yoneda, Y., Yanagida, M., Horinouchi, S. and Yoshida, M. (1998) Leptomycin B inhibition of signal-mediated nuclear export by direct binding to CRM1. *Exp Cell Res* **242**, 540-547.
- 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.
- Kumar, S., Tamura, K., Jakobsen, I.B. and Nei, M. (2001) MEGA2: molecular evolutionary genetics analysis software. *Bioinformatics* **17**, 1244-1245.
- Laemmli, U.K. (1970) Cleavage of structural proteins during the assembly of the head of bacteriophage T4. *Nature* **227**, 680-685.
- Lam, M.H., Michell, B.J., Fodero-Tavoletti, M.T., Kemp, B.E., Tonks, N.K. and Tiganis, T. (2001) Cellular stress regulates the nucleocytoplasmic distribution of the protein-tyrosine phosphatase TCPTP. *J Biol Chem* **276**, 37700-37707.
- Lanford, R.E. and Butel, J.S. (1984) Construction and characterization of an SV40 mutant defective in nuclear transport of T antigen. *Cell* **37**, 801-813.
- Laskey, R.A. and Mills, A.D. (1975) Quantitative film detection of ³H and ¹⁴C in polyacrylamide gels by fluorography. *Eur J Biochem* **56**, 335-341.
- Lathe, R. (1985) Synthetic oligonucleotide probes deduced from amino acid sequence data. *J Mol Biol* **183**, 1-12.
- Lens, M.B. and Dawes, M. (2002) Interferon alfa therapy for malignant melanoma: a systematic review of randomized controlled trials. *J Clin Oncol* **20**, 1818-1825.
- Levy, D.E. and Darnell, J.E.J. (2002) Stats: transcriptional control and biological impact. *Nat Rev Mol Cell Biol* **3**, 651-662.
- Levy, D.E., Kessler, D.S., Pine, R., Reich, N. and Darnell, J.E.J. (1988) Interferon-induced nuclear factors that bind a shared promoter element. *Genes Dev* **2**, 383-393.
- Li, X., Leung, S., Kerr, I.M. and Stark, G.R. (1997) Functional subdomains of STAT2 required for preassociation with the alpha interferon receptor and for signaling. *Mol Cell Biol* **17**, 2048-2056.

6. References

- Liao, J., Fu, Y. and Shuai, K. (2000) Distinct roles of the NH₂- and COOH-terminal domains of the protein inhibitor of activated signal transducer and activator of transcription (STAT) 1 (PIAS1) in cytokine-induced PIAS1-Stat1 interaction. *Proc Natl Acad Sci U S A* **97**, 5267-5272.
- Liu, B., Liao, J., Rao, X., Kushner, S.A., Chung, C.D., Chang, D.D. and Shuai, K. (1998) Inhibition of Stat1-mediated gene activation by PIAS1. *Proc Natl Acad Sci U S A* **95**, 10626-10631.
- Liu, Q. and Dreyfuss, G. (1995) In vivo and in vitro arginine methylation of RNA-binding proteins. *Mol Cell Biol* **15**, 2800-2808.
- Ma, J., Zhang, T., Novotny-Diermayr, V., Tan, A.L. and Cao, X. (2003) A novel sequence in the coiled-coil domain of Stat3 essential for its nuclear translocation. *J Biol Chem* **278**, 29252-29260.
- Macara, I.G. (2001) Transport into and out of the nucleus. *Microbiol Mol Biol Rev* **65**, 570-94, table.
- Maher, P.A. (1993) Inhibition of the tyrosine kinase activity of the fibroblast growth factor receptor by the methyltransferase inhibitor 5'-methylthioadenosine. *J Biol Chem* **268**, 4244-4249.
- 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.
- McBride, A.E. and Silver, P.A. (2001) State of the arg: protein methylation at arginine comes of age. *Cell* **106**, 5-8.
- McBride, K.M. and Reich, N.C. (2003) The ins and outs of STAT1 nuclear transport. *Sci STKE* **2003**, RE13
- 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.
- McBride, K.M., McDonald, C. and Reich, N.C. (2000) Nuclear export signal located within the DNA-binding domain of the STAT1 transcription factor. *EMBO J* **19**, 6196-6206.
- Meissner, T., Krause, E. and Vinkemeier, U. (2004a) Ratjadone and leptomyacin B block CRM1-dependent nuclear export by identical mechanisms. *FEBS Lett* **576**, 27-30.
- Meissner, T., Krause, E., Lödige, I. and Vinkemeier, U. (2004b) Arginine methylation of STAT1: a reassessment. *Cell* **119**, 587-589.
- Melen, K., Fagerlund, R., Franke, J., Köhler, M., Kinnunen, L. and Julkunen, I. (2003) Importin alpha nuclear localization signal binding sites for STAT1, STAT2, and influenza A virus nucleoprotein. *J Biol Chem* **278**, 28193-28200.

- Melen, K., Fagerlund, R., Nyqvist, M., Keskinen, P. and Julkunen, I. (2004) Expression of hepatitis C virus core protein inhibits interferon-induced nuclear import of STATs. *J Med Virol* **73**, 536-547.
- Melen, 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. and Vinkemeier, U. (2004) Nucleocytoplasmic shuttling of STAT transcription factors. *Eur J Biochem* **271**, 4606-4612.
- Meyer, T., Begitt, A., Lödige, I., van Rossum, M. and Vinkemeier, U. (2002a) Constitutive and IFN-gamma-induced nuclear import of STAT1 proceed through independent pathways. *EMBO J* **21**, 344-354.
- Meyer, T., Gavenis, K. and Vinkemeier, U. (2002b) Cell type-specific and tyrosine phosphorylation-independent nuclear presence of STAT1 and STAT3. *Exp Cell Res* **272**, 45-55.
- 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.
- 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.
- Mowen, K. and David, M. (2000) Regulation of STAT1 nuclear export by Jak1. *Mol Cell Biol* **20**, 7273-7281.
- Mowen, K.A. and David, M. (2001) Analysis of protein arginine methylation and protein arginine-methyltransferase activity. *Sci STKE* **2001**, L1
- Mowen, K.A., Tang, J., Zhu, W., Schurter, B.T., Shuai, K., Herschman, H.R. and David, M. (2001) Arginine methylation of STAT1 modulates IFNalpha/beta-induced transcription. *Cell* **104**, 731-741.
- Müller, M., Laxton, C., Briscoe, J., Schindler, C., Improta, T., Darnell, J.E.J., 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.
- Neville, M. and Rosbash, M. (1999) The NES-Crm1p export pathway is not a major mRNA export route in *Saccharomyces cerevisiae*. *EMBO J* **18**, 3746-3756.

6. References

- Newlands, E.S., Rustin, G.J. and Brampton, M.H. (1996) Phase I trial of elactocin. *Br J Cancer* **74**, 648-649.
- Nguyen, V.P., Saleh, A.Z., Arch, A.E., Yan, H., Piazza, F., Kim, J. and Krolewski, J.J. (2002) Stat2 binding to the interferon-alpha receptor 2 subunit is not required for interferon-alpha signaling. *J Biol Chem* **277**, 9713-9721.
- Nicola, N.A. (ed.) (1994) Guidebook to Cytokines and their Receptors, Oxford University Press, Oxford.
- Nobori, T., Takabayashi, K., Tran, P., Orvis, L., Batova, A., Yu, A.L. and Carson, D.A. (1996) Genomic cloning of methylthioadenosine phosphorylase: a purine metabolic enzyme deficient in multiple different cancers. *Proc Natl Acad Sci U S A* **93**, 6203-6208.
- Ossareh-Nazari, B. and Dargemont, C. (1999) Domains of Crm1 involved in the formation of the Crm1, RanGTP, and leucine-rich nuclear export sequences trimeric complex. *Exp Cell Res* **252**, 236-241.
- Ossareh-Nazari, B., Gwizdek, C. and Dargemont, C. (2001) Protein export from the nucleus. *Traffic* **2**, 684-689.
- Ota, N., Brett, T.J., Murphy, T.L., Fremont, D.H. and Murphy, K.M. (2004) N-domain-dependent nonphosphorylated STAT4 dimers required for cytokine-driven activation. *Nat Immunol* **5**, 208-215.
- Paine, P.L. and Feldherr, C.M. (1972) Nucleocytoplasmic exchange of macromolecules. *Exp Cell* **74**, 81-98.
- Pajula, R.L. and Raina, A. (1979) Methylthioadenosine, a potent inhibitor of spermine synthase from bovine brain. *FEBS Lett* **99**, 343-345.
- Patel, B.K., Pierce, J.H. and LaRoche, W.J. (1998) Regulation of interleukin 4-mediated signaling by naturally occurring dominant negative and attenuated forms of human Stat6. *Proc Natl Acad Sci U S A* **95**, 172-177.
- Pestka, S., Krause, C.D. and Walter, M.R. (2004) Interferons, interferon-like cytokines, and their receptors. *Immunol Rev* **202**, 8-32.
- Petosa, C., Schoehn, G., Askjaer, P., Bauer, U., Moulin, M., Steuerwald, U., Soler-Lopez, M., Baudin, F., Mattaj, I.W. and Müller, C.W. (2004) Architecture of CRM1/Exportin1 suggests how cooperativity is achieved during formation of a nuclear export complex. *Mol Cell* **16**, 761-775.
- Pollack, B.P., Kotenko, S.V., He, W., Izotova, L.S., Barnoski, B.L. and Pestka, S. (1999) The human homologue of the yeast proteins Skb1 and Hsl7p interacts with Jak kinases and contains protein methyltransferase activity. *J Biol Chem* **274**, 31531-31542.
- Pranada, A.L., Metz, S., Herrmann, A., Heinrich, P.C. and Müller-Newen, G. (2004) Real time analysis of STAT3 nucleocytoplasmic shuttling. *J Biol Chem* **279**, 15114-15123.
- Qureshi, S.A., Leung, S., Kerr, I.M., Stark, G.R. and Darnell, J.E.J. (1996) Function of Stat2 protein in transcriptional activation by alpha interferon. *Mol Cell Biol* **16**, 288-293.

- Ragimbeau, J., Dondi, E., Alcover, A., Eid, P., Uze, G. and Pellegrini, S. (2003) The tyrosine kinase Tyk2 controls IFNAR1 cell surface expression. *EMBO J* **22**, 537-547.
- Raina, A., Tuomi, K. and Pajula, R.L. (1982) Inhibition of the synthesis of polyamines and macromolecules by 5'-methylthioadenosine and 5'-alkylthiotubercidins in BHK21 cells. *Biochem J* **204**, 697-703.
- 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.
- Ramana, C.V., Gil, M.P., Schreiber, R.D. and Stark, G.R. (2002) Stat1-dependent and -independent pathways in IFN-gamma-dependent signaling. *Trends Immunol* **23**, 96-101.
- Rho, J., Choi, S., Seong, Y.R., Choi, J. and Im, D.S. (2001) The arginine-1493 residue in QRRGRTGR1493G motif IV of the hepatitis C virus NS3 helicase domain is essential for NS3 protein methylation by the protein arginine methyltransferase 1. *J Virol* **75**, 8031-8044.
- Rodriguez, J.J., Parisien, J.P. and Horvath, C.M. (2002) Nipah virus V protein evades alpha and gamma interferons by preventing STAT1 and STAT2 activation and nuclear accumulation. *J Virol* **76**, 11476-11483.
- Rodriguez, J.J., Wang, L.F. and Horvath, C.M. (2003) Hendra virus V protein inhibits interferon signaling by preventing STAT1 and STAT2 nuclear accumulation. *J Virol* **77**, 11842-11845.
- Ryan, K.J. and Wenthe, S.R. (2000) The nuclear pore complex: a protein machine bridging the nucleus and cytoplasm. *Curr Opin Cell Biol* **12**, 361-371.
- Sachdev, S. and Hannink, M. (1998) Loss of IkappaB alpha-mediated control over nuclear import and DNA binding enables oncogenic activation of c-Rel. *Mol Cell Biol* **18**, 5445-5456.
- Sambrook, J. and Russell, D.W. (2001) Molecular cloning: a laboratory manual. 3rd ed. CSHL Press, Cold Spring Harbor, New York.
- 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.
- Schindler, C., Shuai, K., Prezioso, V.R. and Darnell, J.E.J. (1992) Interferon-dependent tyrosine phosphorylation of a latent cytoplasmic transcription factor. *Science* **257**, 809-813.
- 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.
- 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.

6. References

- Shuai, K. (2000) Modulation of STAT signaling by STAT-interacting proteins. *Oncogene* **19**, 2638-2644.
- Shuai, K., Horvath, C.M., Huang, L.H., Qureshi, S.A., Cowburn, D. and Darnell, J.E.J. (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., Schindler, C., Prezioso, V.R. and Darnell, J.E.J. (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.J. (1993) A single phosphotyrosine residue of Stat91 required for gene activation by interferon-gamma. *Science* **261**, 1744-1746.
- Simoncic, P.D., Lee-Loy, A., Barber, D.L., Tremblay, M.L. and McGlade, C.J. (2002) The T cell protein tyrosine phosphatase is a negative regulator of janus family kinases 1 and 3. *Curr Biol* **12**, 446-453.
- Stade, K., Ford, C.S., Guthrie, C. and Weis, K. (1997) Exportin 1 (Crm1p) is an essential nuclear export factor. *Cell* **90**, 1041-1050.
- 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.
- Stommel, J.M., Marchenko, N.D., Jimenez, G.S., Moll, U.M., Hope, T.J. and Wahl, G.M. (1999) A leucine-rich nuclear export signal in the p53 tetramerization domain: regulation of subcellular localization and p53 activity by NES masking. *EMBO J* **18**, 1660-1672.
- 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.
- Strobl, B., Arulampalam, V., Is'harc, H., Newman, S.J., Schlaak, J.F., Watling, D., Costa-Pereira, A.P., Schaper, F., Behrmann, I., Sheehan, K.C., Schreiber, R.D., Horn, F., Heinrich, P.C. and Kerr, I.M. (2001) A completely foreign receptor can mediate an interferon-gamma-like response. *EMBO J* **20**, 5431-5442.
- Su, W.C., Kitagawa, M., Xue, N., Xie, B., Garofalo, S., Cho, J., Deng, C., Horton, W.A. and Fu, X.Y. (1997) Activation of Stat1 by mutant fibroblast growth-factor receptor in thanatophoric dysplasia type II dwarfism. *Nature* **386**, 288-292.
- Suntharalingam, M. and Wenthe, S.R. (2003) Peering through the pore: nuclear pore complex structure, assembly, and function. *Dev Cell* **4**, 775-789.
- 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.

- Toyoda, H., Ido, M., Hayashi, T., Gabazza, E.C., Suzuki, K., Bu, J., Tanaka, S., Nakano, T., Kamiya, H., Chipeta, J., Kisenge, R.R., Kang, J., Hori, H. and Komada, Y. (2004) Impairment of IL-12-dependent STAT4 nuclear translocation in a patient with recurrent *Mycobacterium avium* infection. *J Immunol* **172**, 3905-3912.
- 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.
- Vigneri, P. and Wang, J.Y. (2001) Induction of apoptosis in chronic myelogenous leukemia cells through nuclear entrapment of BCR-ABL tyrosine kinase. *Nat Med* **7**, 228-234.
- Vinkemeier, U. (2004) Getting the message across, STAT! Design principles of a molecular signaling circuit. *J Cell Biol* **167**, 197-201.
- Vinkemeier, U., Cohen, S.L., Moarefi, I., Chait, B.T., Kuriyan, J. and Darnell, J.E.J. (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.J. and Kuriyan, J. (1998) Structure of the amino-terminal protein interaction domain of STAT-4. *Science* **279**, 1048-1052.
- 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.
- Weis, K. (2003) Regulating access to the genome: nucleocytoplasmic transport throughout the cell cycle. *Cell* **112**, 441-451.
- Wen, Z., Zhong, Z. and Darnell, J.E.J. (1995a) Maximal activation of transcription by Stat1 and Stat3 requires both tyrosine and serine phosphorylation. *Cell* **82**, 241-250.
- Wen, W., Meinkoth, J.L., Tsien, R.Y. and Taylor, S.S. (1995b) Identification of a signal for rapid export of proteins from the nucleus. *Cell* **82**, 463-473.
- Williams-Ashman, H.G., Seidenfeld, J. and Galletti, P. (1982) Trends in the biochemical pharmacology of 5'-deoxy-5'-methylthioadenosine. *Biochem Pharmacol* **31**, 277-288.
- Wolff, B., Sanglier, J.J. and Wang, Y. (1997) Leptomycin B is an inhibitor of nuclear export: inhibition of nucleo-cytoplasmic translocation of the human immunodeficiency virus type 1 (HIV-1) Rev protein and Rev-dependent mRNA. *Chem Biol* **4**, 139-147.
- Wozniak, R.W., Rout, M.P. and Aitchison, J.D. (1998) Karyopherins and kissing cousins. *Trends Cell Biol* **8**, 184-188.
- 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. and 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.

6. References

- Xiao, Z., Watson, N., Rodriguez, C. and Lodish, H.F. (2001) Nucleocytoplasmic shuttling of Smad1 conferred by its nuclear localization and nuclear export signals. *J Biol Chem* **276**, 39404-39410.
- 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.
- Yang, J., Bardes, E.S., Moore, J.D., Brennan, J., Powers, M.A. and Kornbluth, S. (1998) Control of cyclin B1 localization through regulated binding of the nuclear export factor CRM1. *Genes Dev* **12**, 2131-2143.
- 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.
- 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.J. (1996) Two contact regions between Stat1 and CBP/p300 in interferon gamma signaling. *Proc Natl Acad Sci U S A* **93**, 15092-15096.
- 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.
- Zhang, X. and Darnell, J.E.J. (2001) Functional importance of Stat3 tetramerization in activation of the alpha 2-macroglobulin gene. *J Biol Chem* **276**, 33576-33581.
- Zhu, W., Mustelin, T. and David, M. (2002) Arginine methylation of STAT1 regulates its dephosphorylation by T cell protein tyrosine phosphatase. *J Biol Chem* **277**, 35787-35790.
- Zong, C., Yan, R., August, A., Darnell, J.E.J. 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.