

7 Literaturverzeichnis

- Agazie Y. M. und Hayman M. J. (2003)
Molecular mechanism for a role of SHP2 in epidermal growth factor receptor signaling; *Mol.Cell Biol.* (23), 7875-7886
- Arch J. R. (2005)
Central regulation of energy balance: inputs, outputs and leptin resistance; *Proc.Nutr.Soc.* (64), 39-46
- Bahrenberg G., Behrmann I., Barthel A., Hekerman P., Heinrich P. C., Joost H. G. und Becker W. (2002)
Identification of the critical sequence elements in the cytoplasmic domain of leptin receptor isoforms required for Janus kinase/signal transducer and activator of transcription activation by receptor heterodimers; *Mol.Endocrinol.* (16), 859-872
- Banks A. S., Davis S. M., Bates S. H. und Myers M. G., Jr. (2000)
Activation of downstream signals by the long form of the leptin receptor; *J.Biol.Chem.* (275), 14563-14572
- Barr V. A., Lane K. und Taylor S. I. (1999)
Subcellular localization and internalization of the four human leptin receptor isoforms; *J.Biol.Chem.* (274), 21416-21424
- Bates S. H., Stearns W. H., Dundon T. A., Schubert M., Tso A. W., Wang Y., Banks A. S., Lavery H. J., Haq A. K., Maratos-Flier E., Neel B. G., Schwartz M. W. und Myers M. G., Jr. (2003)
STAT3 signalling is required for leptin regulation of energy balance but not reproduction; *Nature* (421), 856-859
- Behrmann I., Smyczek T., Heinrich P. C., Schmitz-Van de L. H., Komyod W., Giese B., Mueller-Newen G., Haan S. und Haan C. (2004)
Janus kinase (Jak) subcellular localization revisited: the exclusive membrane localization of endogenous Janus kinase 1 by cytokine receptor interaction uncovers the Jak.receptor complex to be equivalent to a receptor tyrosine kinase; *J.Biol.Chem.* (279), 35486-35493
- Belouzard S., Delcroix D. und Rouille Y. (2004)
Low levels of expression of leptin receptor at the cell surface result from constitutive endocytosis and intracellular retention in the biosynthetic pathway; *J.Biol.Chem.* (279), 28499-28508
- Bence K. K., Delibegovic M., Xue B., Gorgun C. Z., Hotamisligil G. S., Neel B. G. und Kahn B. B. (2006)

- Neuronal PTP1B regulates body weight, adiposity and leptin action; Nat.Med. (12), 917-924
- Bjorbaek C., Buchholz R. M., Davis S. M., Bates S. H., Pierroz D. D., Gu H., Neel B. G., Myers M. G., Jr. und Flier J. S. (2001)
Divergent roles of SHP-2 in ERK activation by leptin receptors; J.Biol.Chem. (276), 4747-4755
- Bjorbaek C., El-Haschimi K., Frantz J. D. und Flier J. S. (1999)
The role of SOCS-3 in leptin signaling and leptin resistance; J.Biol.Chem. (274), 30059-30065
- Bjorbaek C., Elmquist J. K., Frantz J. D., Shoelson S. E. und Flier J. S. (1998)
Identification of SOCS-3 as a potential mediator of central leptin resistance; Mol.Cell (1), 619-625
- Bjorbaek C., Lavery H. J., Bates S. H., Olson R. K., Davis S. M., Flier J. S. und Myers M. G., Jr. (2000)
SOCS3 mediates feedback inhibition of the leptin receptor via Tyr985; J.Biol.Chem. (275), 40649-40657
- Bjorbaek C., Uotani S., da S. B. und Flier J. S. (1997)
Divergent signaling capacities of the long and short isoforms of the leptin receptor; J.Biol.Chem. (272), 32686-32695
- Bourette R. P., De S. P., Arnaud S., Dubreuil P., Rottapel R. und Mouchiroud G. (2001)
Suppressor of cytokine signaling 1 interacts with the macrophage colony-stimulating factor receptor and negatively regulates its proliferation signal; J.Biol.Chem. (276), 22133-22139
- Caro J. F., Kolaczynski J. W., Nyce M. R., Ohannesian J. P., Opentanova I., Goldman W. H., Lynn R. B., Zhang P. L., Sinha M. K. und Considine R. V. (1996)
Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance; Lancet (348), 159-161
- Carpenter L. R., Farruggella T. J., Symes A., Karow M. L., Yancopoulos G. D. und Stahl N. (1998)
Enhancing leptin response by preventing SH2-containing phosphatase 2 interaction with Ob receptor; Proc.Natl.Acad.Sci.U.S.A (95), 6061-6066
- Carter-Su C., Argetsinger L. S., Campbell G. S., Wang X., Ihle J. und Witthuhn B. (1994)
The identification of JAK2 tyrosine kinase as a signaling molecule for growth hormone; Proc.Soc.Exp.Biol.Med. (206), 210-215

- Chehab F. F., Lim M. E. und Lu R. (1996)
Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin; *Nat.Genet.* (12), 318-320
- Clement K., Vaisse C., Lahlou N., Cabrol S., Pelloux V., Cassuto D., Gormelen M., Dina C., Chambaz J., Lacorte J. M., Basdevant A., Bougneres P., Lebouc Y., Froguel P. und Guy-Grand B. (1998)
A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction; *Nature* (392), 398-401
- Considine R. V., Sinha M. K., Heiman M. L., Kriauciunas A., Stephens T. W., Nyce M. R., Ohannesian J. P., Marco C. C., McKee L. J. und Bauer T. L. (1996)
Serum immunoreactive-leptin concentrations in normal-weight and obese humans; *N.Engl.J.Med.* (334), 292-295
- Couturier C. und Jockers R. (2003)
Activation of the leptin receptor by a ligand-induced conformational change of constitutive receptor dimers; *J.Biol.Chem.* (278), 26604-26611
- Croker B. A., Krebs D. L., Zhang J. G., Wormald S., Willson T. A., Stanley E. G., Robb L., Greenhalgh C. J., Forster I., Clausen B. E., Nicola N. A., Metcalf D., Hilton D. J., Roberts A. W. und Alexander W. S. (2003)
SOCS3 negatively regulates IL-6 signaling in vivo; *Nat.Immunol.* (4), 540-545
- Darnell J. E., Kerr I. M. und Stark G. R. (1994)
Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins; *Science* (264), 1415-1421
- de Luca C., Kowalski T. J., Zhang Y., Elmquist J. K., Lee C., Kilimann M. W., Ludwig T., Liu S. M. und Chua S. C., Jr. (2005)
Complete rescue of obesity, diabetes, and infertility in db/db mice by neuron-specific LEPR-B transgenes; *J.Clin.Invest* (115), 3484-3493
- De Vos J., Jourdan M., Tarte K., Jasmin C. und 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
- Devos R., Guisez Y., Van der H. J., White D. W., Kalai M., Fountoulakis M. und Plaetinck G. (1997)
Ligand-independent dimerization of the extracellular domain of the leptin receptor and determination of the stoichiometry of leptin binding; *J.Biol.Chem.* (272), 18304-18310

- Dittrich E., Haft C. R., Muys L., Heinrich P. C. und Graeve L. (1996)
A di-leucine motif and an upstream serine in the interleukin-6 (IL-6) signal transducer gp130 mediate ligand-induced endocytosis and down-regulation of the IL-6 receptor; *J.Biol.Chem.* (271), 5487-5494
- Ducy P., Amling M., Takeda S., Priemel M., Schilling A. F., Beil F. T., Shen J., Vinson C., Rueger J. M. und Karsenty G. (2000)
Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass; *Cell* (100), 197-207
- Dunn S. L., Bjornholm M., Bates S. H., Chen Z., Seifert M. und Myers M. G., Jr. (2005)
Feedback inhibition of leptin receptor/Jak2 signaling via Tyr1138 of the leptin receptor and suppressor of cytokine signaling 3; *Mol.Endocrinol.* (19), 925-938
- El-Haschimi K., Pierroz D. D., Hileman S. M., Bjorbaek C. und Flier J. S. (2000)
Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity; *J.Clin.Invest* (105), 1827-1832
- Elbashir S. M., Lendeckel W. und Tuschl T. (2001)
RNA interference is mediated by 21- and 22-nucleotide RNAs; *Genes Dev.* (15), 188-200
- Elchebly M., Payette P., Michaliszyn E., Cromlish W., Collins S., Loy A. L., Normandin D., Cheng A., Himms-Hagen J., Chan C. C., Ramachandran C., Gresser M. J., Tremblay M. L. und Kennedy B. P. (1999)
Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene; *Science* (283), 1544-1548
- Emilsson V., Arch J. R., de Groot R. P., Lister C. A. und Cawthorne M. A. (1999)
Leptin treatment increases suppressors of cytokine signaling in central and peripheral tissues; *FEBS Lett.* (455), 170-174
- Endo T. A., Masuhara M., Yokouchi M., Suzuki R., Sakamoto H., Mitsui K., Matsumoto A., Tanimura S., Ohtsubo M., Misawa H., Miyazaki T., Leonor N., Taniguchi T., Fujita T., Kanakura Y., Komiya S. und Yoshimura A. (1997)
A new protein containing an SH2 domain that inhibits JAK kinases; *Nature* (387), 921-924
- Eyckerman S., Broekaert D., Verhee A., Vandekerckhove J. und Tavernier J. (2000)
Identification of the Y985 and Y1077 motifs as SOCS3 recruitment sites in the murine leptin receptor; *FEBS Lett.* (486), 33-37
- Eyckerman S., Waelput W., Verhee A., Broekaert D., Vandekerckhove J. und Tavernier J. (1999)

- Analysis of Tyr to Phe and fa/fa leptin receptor mutations in the PC12 cell line; Eur.Cytokine Netw. (10), 549-556
- Farooqi I. S., Jebb S. A., Langmack G., Lawrence E., Cheetham C. H., Prentice A. M., Hughes I. A., McCamish M. A. und O'Rahilly S. (1999)
Effects of recombinant leptin therapy in a child with congenital leptin deficiency; N.Engl.J.Med. (341), 879-884
- Feinberg A. P. und Vogelstein B. (1983)
A technique for radiolabeling DNA restriction endonuclease fragments to high specific activity; Anal.Biochem. (132), 6-13
- Ferguson S. S., Downey W. E., III, Colapietro A. M., Barak L. S., Menard L. und Caron M. G. (1996)
Role of beta-arrestin in mediating agonist-promoted G protein-coupled receptor internalization; Science (271), 363-366
- Fischer P., Lehmann U., Sobota R. M., Schmitz J., Niemand C., Linnemann S., Haan S., Behrmann I., Yoshimura A., Johnston J. A., Muller-Newen G., Heinrich P. C. und Schaper F. (2004)
The role of the inhibitors of interleukin-6 signal transduction SHP2 and SOCS3 for desensitization of interleukin-6 signalling; Biochem.J. (378), 449-460
- Frangioni J. V., Beahm P. H., Shifrin V., Jost C. A. und Neel B. G. (1992)
The nontransmembrane tyrosine phosphatase PTP-1B localizes to the endoplasmic reticulum via its 35 amino acid C-terminal sequence; Cell (68), 545-560
- Frank S., Stallmeyer B., Kampfer H., Kolb N. und Pfeilschifter J. (2000)
Leptin enhances wound re-epithelialization and constitutes a direct function of leptin in skin repair; J.Clin.Invest (106), 501-509
- Frantsve J., Schwaller J., Sternberg D. W., Kutok J. und Gilliland D. G. (2001)
Socs-1 inhibits TEL-JAK2-mediated transformation of hematopoietic cells through inhibition of JAK2 kinase activity and induction of proteasome-mediated degradation; Mol.Cell Biol. (21), 3547-3557
- Frederich R. C., Hamann A., Anderson S., Lollmann B., Lowell B. B. und Flier J. S. (1995)
Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action; Nat.Med. (1), 1311-1314
- Fukamachi H., Tojo A., Saito T., Kitamura T., Nakata M., Urabe A. und Takaku F. (1987)

- Internalization of radioiodinated erythropoietin and the ligand-induced modulation of its receptor in murine erythroleukemia cells; *Int.J.Cell Cloning* (5), 209-219
- Gao Q., Wolfgang M. J., Neschen S., Morino K., Horvath T. L., Shulman G. I. und Fu X. Y. (2004)
Disruption of neural signal transducer and activator of transcription 3 causes obesity, diabetes, infertility, and thermal dysregulation; *Proc.Natl.Acad.Sci.U.S.A* (101), 4661-4666
- Gaunitz F. und Papke M. (1998)
Gene transfer and expression; *Methods Mol.Biol.* (107), 361-370
- Ge H., Huang L., Pourbahrami T. und Li C. (2002)
Generation of soluble leptin receptor by ectodomain shedding of membrane-spanning receptors in vitro and in vivo; *J.Biol.Chem.* (277), 45898-45903
- Ghilardi N. und Skoda R. C. (1997)
The leptin receptor activates janus kinase 2 and signals for proliferation in a factor-dependent cell line; *Mol.Endocrinol.* (11), 393-399
- Giese B., Au-Yeung C. K., Herrmann A., Diefenbach S., Haan C., Kuster A., Wortmann S. B., Roderburg C., Heinrich P. C., Behrmann I. und Muller-Newen G. (2003)
Long term association of the cytokine receptor gp130 and the Janus kinase Jak1 revealed by FRAP analysis; *J.Biol.Chem.* (278), 39205-39213
- Greenhalgh C. J., Rico-Bautista E., Lorentzon M., Thaus A. L., Morgan P. O., Willson T. A., Zervoudakis P., Metcalf D., Street I., Nicola N. A., Nash A. D., Fabri L. J., Norstedt G., Ohlsson C., Flores-Morales A., Alexander W. S. und Hilton D. J. (2005)
SOCS2 negatively regulates growth hormone action in vitro and in vivo; *J.Clin.Invest* (115), 397-406
- Gura T. (1999)
Obesity research. Leptin not impressive in clinical trial; *Science* (286), 881-882
- Gurniak C. B. und Berg L. J. (1996)
Murine JAK3 is preferentially expressed in hematopoietic tissues and lymphocyte precursor cells; *Blood* (87), 3151-3160
- Guschin D., Rogers N., Briscoe J., Witthuhn B., Watling D., Horn F., Pellegrini S., Yasukawa K., Heinrich P. und Stark G. R. (1995)
A major role for the protein tyrosine kinase JAK1 in the JAK/STAT signal transduction pathway in response to interleukin-6; *EMBO J.* (14), 1421-1429

- Halaas J. L., Gajiwala K. S., Maffei M., Cohen S. L., Chait B. T., Rabinowitz D., Lallone R. L., Burley S. K. und Friedman J. M. (1995)
Weight-reducing effects of the plasma protein encoded by the obese gene;
Science (269), 543-546
- Han Y., Watling D., Rogers N. C. und Stark G. R. (1997)
JAK2 and STAT5, but not JAK1 and STAT1, are required for prolactin-induced
beta-lactoglobulin transcription; Mol.Endocrinol. (11), 1180-1188
- Hanahan D. (1983)
Studies on transformation of Escherichia coli with plasmids; J.Mol.Biol. (166),
557-580
- Heinrich P. C., Behrmann I., Haan S., Hermanns H. M., Mueller-Newen G. und
Schaper F. (2003)
Principles of interleukin (IL)-6-type cytokine signalling and its regulation;
Biochem.J. (374), 1-20
- Hekerman P. (2004)
Differentielle Genexpression in der Insulinoma-Zelllinie RINm5F nach Stimulation
mit Leptin;
- Hekerman P., Zeidler J., Bamberg-Lemper S., Knobelspies H., Lavens D., Tavernier
J., Joost H. G. und Becker W. (2005)
Pleiotropy of leptin receptor signalling is defined by distinct roles of the
intracellular tyrosines; FEBS J. (272), 109-119
- Heymsfield S. B., Greenberg A. S., Fujioka K., Dixon R. M., Kushner R., Hunt T.,
Lubina J. A., Patane J., Self B., Hunt P. und McCamish M. (1999)
Recombinant leptin for weight loss in obese and lean adults: a randomized,
controlled, dose-escalation trial; JAMA (282), 1568-1575
- Hilkens C. M., Is'harc H., Lillemeier B. F., Strobl B., Bates P. A., Behrmann I. und
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
- Hilton D. J., Richardson R. T., Alexander W. S., Viney E. M., Willson T. A., Sprigg N.
S., Starr R., Nicholson S. E., Metcalf D. und Nicola N. A. (1998)
Twenty proteins containing a C-terminal SOCS box form five structural classes;
Proc.Natl.Acad.Sci.U.S.A (95), 114-119
- Hou X. S., Melnick M. B. und Perrimon N. (1996)
Marelle acts downstream of the Drosophila HOP/JAK kinase and encodes a
protein similar to the mammalian STATs; Cell (84), 411-419

- Howard J. K., Cave B. J., Oksanen L. J., Tzameli I., Bjorbaek C. und Flier J. S. (2004)
Enhanced leptin sensitivity and attenuation of diet-induced obesity in mice with haploinsufficiency of Socs3; *Nat.Med.* (10), 734-738
- Hubbard S. R., Mohammadi M. und Schlessinger J. (1998)
Autoregulatory mechanisms in protein-tyrosine kinases; *J.Biol.Chem.* (273), 11987-11990
- Hummel K. P., Dickie M. M. und Coleman D. L. (1966)
Diabetes, a new mutation in the mouse; *Science* (153), 1127-1128
- Ihle J. N. (1995)
The Janus protein tyrosine kinase family and its role in cytokine signaling; *Adv.Immunol.* (60), 1-35
- Ihle J. N. und Kerr I. M. (1995)
Jaks and Stats in signaling by the cytokine receptor superfamily; *Trends Genet.* (11), 69-74
- Ingalls A. M., Dickie M. M. und Snell G. D. (1950)
Obese, a new mutation in the house mouse; *J.Hered.* (41), 317-318
- Johnson L. N., Noble M. E. und Owen D. J. (1996)
Active and inactive protein kinases: structural basis for regulation; *Cell* (85), 149-158
- Karlsson C., Lindell K., Svensson E., Bergh C., Lind P., Billig H., Carlsson L. M. und Carlsson B. (1997)
Expression of functional leptin receptors in the human ovary; *J.Clin.Endocrinol.Metab* (82), 4144-4148
- Kaszubska W., Falls H. D., Schaefer V. G., Haasch D., Frost L., Hessler P., Kroeger P. E., White D. W., Jirousek M. R. und Trevillyan J. M. (2002)
Protein tyrosine phosphatase 1B negatively regulates leptin signaling in a hypothalamic cell line; *Mol.Cell Endocrinol.* (195), 109-118
- Kawazoe Y., Naka T., Fujimoto M., Kohzaki H., Morita Y., Narazaki M., Okumura K., Saitoh H., Nakagawa R., Uchiyama Y., Akira S. und Kishimoto T. (2001)
Signal transducer and activator of transcription (STAT)-induced STAT inhibitor 1 (SSI-1)/suppressor of cytokine signaling 1 (SOCS1) inhibits insulin signal transduction pathway through modulating insulin receptor substrate 1 (IRS-1) phosphorylation; *J.Exp.Med.* (193), 263-269

- Kieffer T. J., Heller R. S. und Habener J. F. (1996)
Leptin receptors expressed on pancreatic beta-cells;
Biochem.Biophys.Res.Commun. (224), 522-527
- Kim H., Hawley T. S., Hawley R. G. und Baumann H. (1998)
Protein tyrosine phosphatase 2 (SHP-2) moderates signaling by gp130 but is not required for the induction of acute-phase plasma protein genes in hepatic cells;
Mol.Cell Biol. (18), 1525-1533
- Kline A. D., Becker G. W., Churgay L. M., Landen B. E., Martin D. K., Muth W. L., Rathnachalam R., Richardson J. M., Schoner B., Ulmer M. und Hale J. E. (1997)
Leptin is a four-helix bundle: secondary structure by NMR; *FEBS Lett.* (407), 239-242
- Kloek C., Haq A. K., Dunn S. L., Lavery H. J., Banks A. S. und Myers M. G., Jr. (2002)
Regulation of Jak kinases by intracellular leptin receptor sequences;
J.Biol.Chem. (277), 41547-41555
- Korner J., Savontaus E., Chua S. C., Jr., Leibel R. L. und Wardlaw S. L. (2001)
Leptin regulation of Agrp and Npy mRNA in the rat hypothalamus;
J.Neuroendocrinol. (13), 959-966
- Kristensen P., Judge M. E., Thim L., Ribel U., Christjansen K. N., Wulff B. S., Clausen J. T., Jensen P. B., Madsen O. D., Vrang N., Larsen P. J. und Hastrup S. (1998)
Hypothalamic CART is a new anorectic peptide regulated by leptin; *Nature* (393), 72-76
- Kutoh E., Boss O., Levasseur F. und Giacobino J. P. (1998)
Quantification of the full length leptin receptor (OB-Rb) in human brown and white adipose tissue; *Life Sci.* (62), 445-451
- Lammert A., Kiess W., Bottner A., Glasow A. und Kratzsch J. (2001)
Soluble leptin receptor represents the main leptin binding activity in human blood;
Biochem.Biophys.Res.Commun. (283), 982-988
- Lee G. H., Proenca R., Montez J. M., Carroll K. M., Darvishzadeh J. G., Lee J. I. und Friedman J. M. (1996)
Abnormal splicing of the leptin receptor in diabetic mice; *Nature* (379), 632-635
- Li C. und Friedman J. M. (1999)
Leptin receptor activation of SH2 domain containing protein tyrosine phosphatase 2 modulates Ob receptor signal transduction; *Proc.Natl.Acad.Sci.U.S.A* (96), 9677-9682

- Loffreda S., Yang S. Q., Lin H. Z., Karp C. L., Brengman M. L., Wang D. J., Klein A. S., Bulkley G. B., Bao C., Noble P. W., Lane M. D. und Diehl A. M. (1998)
Leptin regulates proinflammatory immune responses; *FASEB J.* (12), 57-65
- Lothgren A., McCartney M., Rupp T. E. und James S. R. (2001)
A model of activation of the protein tyrosine phosphatase SHP-2 by the human leptin receptor; *Biochim.Biophys.Acta* (1545), 20-29
- Lund I. K., Hansen J. A., Andersen H. S., Moller N. P. und Billestrup N. (2005)
Mechanism of protein tyrosine phosphatase 1B-mediated inhibition of leptin signalling; *J.Mol.Endocrinol.* (34), 339-351
- May P., Gerhartz C., Heesel B., Welte T., Doppler W., Graeve L., Horn F. und Heinrich P. C. (1996)
Comparative study on the phosphotyrosine motifs of different cytokine receptors involved in STAT5 activation; *FEBS Lett.* (394), 221-226
- Meydan N., Grunberger T., Dadi H., Shahar M., Arpaia E., Lapidot Z., Leeder J. S., Freedman M., Cohen A., Gazit A., Levitzki A. und Roifman C. M. (1996)
Inhibition of acute lymphoblastic leukaemia by a Jak-2 inhibitor; *Nature* (379), 645-648
- Mix H., Widjaja A., Jandl O., Cornberg M., Kaul A., Goke M., Beil W., Kuske M., Brabant G., Manns M. P. und Wagner S. (2000)
Expression of leptin and leptin receptor isoforms in the human stomach; *Gut* (47), 481-486
- Miyamoto N., Sugita K., Goi K., Inukai T., Lijima K., Tezuka T., Kojika S., Nakamura M., Kagami K. und Nakazawa S. (2001)
The JAK2 inhibitor AG490 predominantly abrogates the growth of human B-precursor leukemic cells with 11q23 translocation or Philadelphia chromosome; *Leukemia* (15), 1758-1768
- Montague C. T., Farooqi I. S., Whitehead J. P., Soos M. A., Rau H., Wareham N. J., Sewter C. P., Digby J. E., Mohammed S. N., Hurst J. A., Cheetham C. H., Earley A. R., Barnett A. H., Prins J. B. und O'Rahilly S. (1997)
Congenital leptin deficiency is associated with severe early-onset obesity in humans; *Nature* (387), 903-908
- Mori H., Hanada R., Hanada T., Aki D., Mashima R., Nishinakamura H., Torisu T., Chien K. R., Yasukawa H. und Yoshimura A. (2004)
Socs3 deficiency in the brain elevates leptin sensitivity and confers resistance to diet-induced obesity; *Nat.Med.* (10), 739-743

- Morton N. M., Emilsson V., de G. P., Pallett A. L. und Cawthorne M. A. (1999)
Leptin signalling in pancreatic islets and clonal insulin-secreting cells;
J.Mol.Endocrinol. (22), 173-184
- Mueller M., Briscoe J., Laxton C., Guschin D., Ziemiecki A., Silvennoinen O., Harpur A. G., Barbieri G., Witthuhn B. A. und Schindler C. (1993)
The protein tyrosine kinase JAK1 complements defects in interferon-alpha/beta and -gamma signal transduction; *Nature* (366), 129-135
- Muenzberg H., Bjornholm M., Bates S. H. und Myers M. G., Jr. (2005)
Leptin receptor action and mechanisms of leptin resistance; *Cell Mol.Life Sci.* (62), 642-652
- Muenzberg H., Flier J. S. und Bjorbaek C. (2004)
Region-specific leptin resistance within the hypothalamus of diet-induced obese mice; *Endocrinology* (145), 4880-4889
- Murakami M., Narazaki M., Hibi M., Yawata H., Yasukawa K., Hamaguchi M., Taga T. und Kishimoto T. (1991)
Critical cytoplasmic region of the interleukin 6 signal transducer gp130 is conserved in the cytokine receptor family; *Proc.Natl.Acad.Sci.U.S.A* (88), 11349-11353
- Muraoka O., Xu B., Tsurumaki T., Akira S., Yamaguchi T. und Higuchi H. (2003)
Leptin-induced transactivation of NPY gene promoter mediated by JAK1, JAK2 and STAT3 in the neural cell lines; *Neurochem.Int.* (42), 591-601
- Myers M. P., Andersen J. N., Cheng A., Tremblay M. L., Horvath C. M., Parisien J. P., Salmeen A., Barford D. und Tonks N. K. (2001)
TYK2 and JAK2 are substrates of protein-tyrosine phosphatase 1B; *J.Biol.Chem.* (276), 47771-47774
- Naka T., Narazaki M., Hirata M., Matsumoto T., Minamoto S., Aono A., Nishimoto N., Kajita T., Taga T., Yoshizaki K., Akira S. und Kishimoto T. (1997)
Structure and function of a new STAT-induced STAT inhibitor; *Nature* (387), 924-929
- Nicholson S. E., Novak U., Ziegler S. F. und Layton J. E. (1995)
Distinct regions of the granulocyte colony-stimulating factor receptor are required for tyrosine phosphorylation of the signaling molecules JAK2, Stat3, and p42, p44MAPK; *Blood* (86), 3698-3704
- Nicholson S. E., Willson T. A., Farley A., Starr R., Zhang J. G., Baca M., Alexander W. S., Metcalf D., Hilton D. J. und Nicola N. A. (1999)
Mutational analyses of the SOCS proteins suggest a dual domain requirement

- but distinct mechanisms for inhibition of LIF and IL-6 signal transduction; *EMBO J.* (18), 375-385
- Niemand C., Nimmegern A., Haan S., Fischer P., Schaper F., Rossaint R., Heinrich P. C. und Muller-Newen G. (2003)
Activation of STAT3 by IL-6 and IL-10 in primary human macrophages is differentially modulated by suppressor of cytokine signaling 3; *J.Immunol.* (170), 3263-3272
- Niswender K. D., Gallis B., Blevins J. E., Corson M. A., Schwartz M. W. und Baskin D. G. (2003)
Immunocytochemical detection of phosphatidylinositol 3-kinase activation by insulin and leptin; *J.Histochem.Cytochem.* (51), 275-283
- Ollmann M. M., Wilson B. D., Yang Y. K., Kerns J. A., Chen Y., Gantz I. und Barsh G. S. (1997)
Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein; *Science* (278), 135-138
- Oral E. A., Simha V., Ruiz E., Andewelt A., Premkumar A., Snell P., Wagner A. J., DePaoli A. M., Reitman M. L., Taylor S. I., Gorden P. und Garg A. (2002)
Leptin-replacement therapy for lipodystrophy; *N.Engl.J.Med.* (346), 570-578
- Perrimon N. und Mahowald A. P. (1986)
l(1)hopscotch, A larval-pupal zygotic lethal with a specific maternal effect on segmentation in *Drosophila*; *Dev.Biol.* (118), 28-41
- Petersen K. F., Oral E. A., Dufour S., Befroy D., Ariyan C., Yu C., Cline G. W., DePaoli A. M., Taylor S. I., Gorden P. und Shulman G. I. (2002)
Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy; *J.Clin.Invest* (109), 1345-1350
- Pezet A., Ferrag F., Kelly P. A. und Edery M. (1997)
Tyrosine docking sites of the rat prolactin receptor required for association and activation of stat5; *J.Biol.Chem.* (272), 25043-25050
- Radtke S., Haan S., Jorissen A., Hermanns H. M., Diefenbach S., Smyczek T., Schmitz-Vandeleur H., Heinrich P. C., Behrmann I. und Haan C. (2005)
The Jak1 SH2 domain does not fulfill a classical SH2 function in Jak/STAT signaling but plays a structural role for receptor interaction and up-regulation of receptor surface expression; *J.Biol.Chem.* (280), 25760-25768
- Rui H., Kirken R. A. und Farrar W. L. (1994)
Activation of receptor-associated tyrosine kinase JAK2 by prolactin; *J.Biol.Chem.* (269), 5364-5368

- Saharinen P., Takaluoma K. und Silvennoinen O. (2000)
Regulation of the Jak2 tyrosine kinase by its pseudokinase domain; *Mol.Cell Biol.* (20), 3387-3395
- Sambrook J. und Russell D. W. (1989)
Molecular cloning: A Laboratory Manual;
- Sanger F., Nicklen S. und Coulson A. R. (1992)
DNA sequencing with chain-terminating inhibitors. 1977; *Biotechnology* (24), 104-108
- Sasaki A., Yasukawa H., Shouda T., Kitamura T., Dikic I. und Yoshimura A. (2000)
CIS3/SOCS-3 suppresses erythropoietin (EPO) signaling by binding the EPO receptor and JAK2; *J.Biol.Chem.* (275), 29338-29347
- Satoh N., Ogawa Y., Katsuura G., Numata Y., Masuzaki H., Yoshimasa Y. und Nakao K. (1998)
Satiety effect and sympathetic activation of leptin are mediated by hypothalamic melanocortin system; *Neurosci.Lett.* (249), 107-110
- Schaper F., Gendo C., Eck M., Schmitz J., Grimm C., Anhuf D., Kerr I. M. und Heinrich P. C. (1998)
Activation of the protein tyrosine phosphatase SHP2 via the interleukin-6 signal transducing receptor protein gp130 requires tyrosine kinase Jak1 and limits acute-phase protein expression; *Biochem.J.* (335 (Pt 3)), 557-565
- Schindler C. und Darnell J. E. (1995)
Transcriptional responses to polypeptide ligands: the JAK-STAT pathway; *Annu.Rev.Biochem.* (64), 621-651
- Schwartz M. W., Baskin D. G., Bukowski T. R., Kuijper J. L., Foster D., Lasser G., Prunkard D. E., Porte D., Jr., Woods S. C., Seeley R. J. und Weigle D. S. (1996)
Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice; *Diabetes* (45), 531-535
- Seufert J., Kieffer T. J., Leech C. A., Holz G. G., Moritz W., Ricordi C. und Habener J. F. (1999)
Leptin suppression of insulin secretion and gene expression in human pancreatic islets: implications for the development of adipogenic diabetes mellitus; *J.Clin.Endocrinol.Metab* (84), 670-676
- Simoncic P. D., Lee-Loy A., Barber D. L., Tremblay M. L. und 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

- Song M. M. und Shuai K. (1998)
The suppressor of cytokine signaling (SOCS) 1 and SOCS3 but not SOCS2 proteins inhibit interferon-mediated antiviral and antiproliferative activities; *J.Biol.Chem.* (273), 35056-35062
- Sporri B., Kovanen P. E., Sasaki A., Yoshimura A. und Leonard W. J. (2001)
JAB/SOCS1/SSI-1 is an interleukin-2-induced inhibitor of IL-2 signaling; *Blood* (97), 221-226
- Stahl N., Farruggella T. J., Boulton T. G., Zhong Z., Darnell J. E., Jr. und Yancopoulos G. D. (1995)
Choice of STATs and other substrates specified by modular tyrosine-based motifs in cytokine receptors; *Science* (267), 1349-1353
- Stanley B. G., Kyrkouli S. E., Lampert S. und Leibowitz S. F. (1986)
Neuropeptide Y chronically injected into the hypothalamus: a powerful neurochemical inducer of hyperphagia and obesity; *Peptides* (7), 1189-1192
- Starr R., Willson T. A., Viney E. M., Murray L. J., Rayner J. R., Jenkins B. J., Gonda T. J., Alexander W. S., Metcalf D., Nicola N. A. und Hilton D. J. (1997)
A family of cytokine-inducible inhibitors of signalling; *Nature* (387), 917-921
- Stoiber D., Kovarik P., Cohnen S., Johnston J. A., Steinlein P. und Decker T. (1999)
Lipopolysaccharide induces in macrophages the synthesis of the suppressor of cytokine signaling 3 and suppresses signal transduction in response to the activating factor IFN-gamma; *J.Immunol.* (163), 2640-2647
- Strous G. J., van K. P., Govers R., Ciechanover A. und Schwartz A. L. (1996)
The ubiquitin conjugation system is required for ligand-induced endocytosis and degradation of the growth hormone receptor; *EMBO J.* (15), 3806-3812
- Sui G., Soohoo C., Affar e. B., Gay F., Shi Y., Forrester W. C. und Shi Y. (2002)
A DNA vector-based RNAi technology to suppress gene expression in mammalian cells; *Proc.Natl.Acad.Sci.U.S.A* (99), 5515-5520
- Suzuki K., Nakajima H., Saito Y., Saito T., Leonard W. J. und Iwamoto I. (2000)
Janus kinase 3 (Jak3) is essential for common cytokine receptor gamma chain (gamma(c))-dependent signaling: comparative analysis of gamma(c), Jak3, and gamma(c) and Jak3 double-deficient mice; *Int.Immunol.* (12), 123-132
- Tanner J. W., Chen W., Young R. L., Longmore G. D. und Shaw A. S. (1995)
The conserved box 1 motif of cytokine receptors is required for association with JAK kinases; *J.Biol.Chem.* (270), 6523-6530

- Tartaglia L. A. (1997)
The leptin receptor; *J.Biol.Chem.* (272), 6093-6096
- Tartaglia L. A., Dembski M., Weng X., Deng N., Culpepper J., Devos R., Richards G. J., Campfield L. A., Clark F. T., Deeds J., Muir C., Sanker S., Moriarty A., Moore K. J., Smutko J. S., Mays G. G., Wool E. A., Monroe C. A. und Tepper R. I. (1995)
Identification and expression cloning of a leptin receptor, OB-R; *Cell* (83), 1263-1271
- Thiel S., Behrmann I., Timmermann A., Dahmen H., Muller-Newen G., Schaper F., Tavernier J., Pitard V., Heinrich P. C. und Graeve L. (1999)
Identification of a Leu-Ile internalization motif within the cytoplasmic domain of the leukaemia inhibitory factor receptor; *Biochem.J.* (339 (Pt 1)), 15-19
- Uotani S., Bjorbaek C., Tornoe J. und Flier J. S. (1999)
Functional properties of leptin receptor isoforms: internalization and degradation of leptin and ligand-induced receptor downregulation; *Diabetes* (48), 279-286
- Verdier F., Chretien S., Muller O., Varlet P., Yoshimura A., Gisselbrecht S., Lacombe C. und Mayeux P. (1998)
Proteasomes regulate erythropoietin receptor and signal transducer and activator of transcription 5 (STAT5) activation. Possible involvement of the ubiquitinated Cis protein; *J.Biol.Chem.* (273), 28185-28190
- Watling D., Guschin D., Muller M., Silvennoinen O., Witthuhn B. A., Quelle F. W., Rogers N. C., Schindler C., Stark G. R. und Ihle J. N. (1993)
Complementation by the protein tyrosine kinase JAK2 of a mutant cell line defective in the interferon-gamma signal transduction pathway; *Nature* (366), 166-170
- Wei S. H., Ming-Lum A., Liu Y., Wallach D., Ong C. J., Chung S. W., Moore K. W. und Mui A. L. (2006)
Proteasome-mediated proteolysis of the interleukin-10 receptor is important for signal downregulation; *J.Interferon Cytokine Res.* (26), 281-290
- Witthuhn B. A., Quelle F. W., Silvennoinen O., Yi T., Tang B., Miura O. und Ihle J. N. (1993)
JAK2 associates with the erythropoietin receptor and is tyrosine phosphorylated and activated following stimulation with erythropoietin; *Cell* (74), 227-236
- Xia L., Wang L., Chung A. S., Ivanov S. S., Ling M. Y., Dragoi A. M., Platt A., Gilmer T. M., Fu X. Y. und Chin Y. E. (2002)
Identification of both positive and negative domains within the epidermal growth factor receptor COOH-terminal region for signal transducer and activator of transcription (STAT) activation; *J.Biol.Chem.* (277), 30716-30723

- Xu X., Sun Y. L. und Hoey T. (1996)
Cooperative DNA binding and sequence-selective recognition conferred by the STAT amino-terminal domain; *Science* (273), 794-797
- Yamasaki K., Naito S., Anaguchi H., Ohkubo T. und Ota Y. (1997)
Solution structure of an extracellular domain containing the WSxWS motif of the granulocyte colony-stimulating factor receptor and its interaction with ligand; *Nat.Struct.Biol.* (4), 498-504
- Yang X. P., Albrecht U., Zakowski V., Sobota R. M., Haussinger D., Heinrich P. C., Ludwig S., Bode J. G. und Schaper F. (2004)
Dual function of interleukin-1beta for the regulation of interleukin-6-induced suppressor of cytokine signaling 3 expression; *J.Biol.Chem.* (279), 45279-45289
- Yasukawa H., Misawa H., Sakamoto H., Masuhara M., Sasaki A., Wakioka T., Ohtsuka S., Imaizumi T., Matsuda T., Ihle J. N. und Yoshimura A. (1999)
The JAK-binding protein JAB inhibits Janus tyrosine kinase activity through binding in the activation loop; *EMBO J.* (18), 1309-1320
- Yoshimura A., Ohkubo T., Kiguchi T., Jenkins N. A., Gilbert D. J., Copeland N. G., Hara T. und Miyajima A. (1995)
A novel cytokine-inducible gene CIS encodes an SH2-containing protein that binds to tyrosine-phosphorylated interleukin 3 and erythropoietin receptors; *EMBO J.* (14), 2816-2826
- Zeidler J. (2006)
Bedeutung der intrazellulären Tyrosinreste für die Desensitivierung der Leptinrezeptor-Signaltransduktion;
- Zhang E. E., Chapeau E., Hagihara K. und Feng G. S. (2004)
Neuronal Shp2 tyrosine phosphatase controls energy balance and metabolism; *Proc.Natl.Acad.Sci.U.S.A* (101), 16064-16069
- Zhang J., Ferguson S. S., Barak L. S., Menard L. und Caron M. G. (1996)
Dynamin and beta-arrestin reveal distinct mechanisms for G protein-coupled receptor internalization; *J.Biol.Chem.* (271), 18302-18305
- Zhang J. G., Farley A., Nicholson S. E., Willson T. A., Zugaro L. M., Simpson R. J., Moritz R. L., Cary D., Richardson R., Hausmann G., Kile B. J., Kent S. B., Alexander W. S., Metcalf D., Hilton D. J., Nicola N. A. und Baca M. (1999)
The conserved SOCS box motif in suppressors of cytokine signaling binds to elongins B and C and may couple bound proteins to proteasomal degradation; *Proc.Natl.Acad.Sci.U.S.A* (96), 2071-2076

Zhang Y., Proenca R., Maffei M., Barone M., Leopold L. und Friedman J. M. (1994)
Positional cloning of the mouse obese gene and its human homologue; Nature
(372), 425-432

Zhang Y. und Scarpace P. J. (2006)
The role of leptin in leptin resistance and obesity; Physiol Behav. (88), 249-256

Zhang Y., Turkson J., Carter-Su C., Smithgall T., Levitzki A., Kraker A., Krolewski J.
J., Medveczky P. und Jove R. (2000)
Activation of Stat3 in v-Src-transformed fibroblasts requires cooperation of Jak1
kinase activity; J.Biol.Chem. (275), 24935-24944

Zhou Y. J., Chen M., Cusack N. A., Kimmel L. H., Magnuson K. S., Boyd J. G., Lin
W., Roberts J. L., Lengi A., Buckley R. H., Geahlen R. L., Candotti F., Gadina M.,
Changelian P. S. und O'Shea J. J. (2001)
Unexpected effects of FERM domain mutations on catalytic activity of Jak3:
structural implication for Janus kinases; Mol.Cell (8), 959-969