6. Anhang

6.1 Literaturverzeichnis

Aalberse R.C. (2000) Structual biology of allergens. J. Allergy Clin. Immunol. 106:228-238

Aderem A., and Ulevitch R.J. (2000) Toll-like receptors in the induction of the innate immune response. Nature 406:782-787

Aman M.J., and Leonard W.J. (1997) Cytokine signaling: cytokine-inducible signaling inhibitors. Curr. Biol. 7:R84-R88

Bacharier L.B., and Geha R.S. (2000) Molecular mechanisms of IgE regulation. J. Allergy Clin. Immunol. 105:S547-S558

Bachmann M.F., McKall-Faienza K. Schmits R., Bouchard D., Beach J., Speiser D.E., Mak T.W., Ohashi P.S. (1997) Distinct roles for LFA1 and CD28 during activation of naive T cells: adhesion versus costimulation. Immunity 7:549-457

Barnes P.J. (2000) New directions in allergic diseases: mechanism-based anti-inflammatory therapies. J. Allergy Clin Immunol. 106:5-16

Bazan J.F. (1990) Haemopoetic receptors and helical cytokines. Immunol. Today 11:350-354

Beading C., Guschin D., Witthuhn B.A., Ziemiecki A., Ihle J.N., Kerr M., and Cantrell D.A. (1994) Activation of Jak kinases and Stat proteins by IL-2 and IFNα, but not the T cell antigen receptor, in human T lymphocytes. EMBO J. 13:5605-5613

Becker S., Groner B., and Muller C.W. (1998) Three-dimensional structure of the Stat3β homodimer bound to DNA. Nature 394:145-151

Bendelac A., Rivera M.N., Park S.H., and Roak J.H. (1997) Mouse CD1-specific NK1 T cells: development, specificity and function. Annu. Rev. Immunol. 15: 535-562

Bhattacharya S., Eckner R., Grossman S., Oldread E., Arany Z., D´Andrea A., and Livingston D.M. (1996) Cooperation of Stat2 and p300/CBP in signalling induced by interferon-alpha. Nature 383:344-347

Björksten B. (1999) Environment and infant immunity. Proc. Nutr. Soc. 58(3):729-732

von Boehmer H. (1994) Positive selection of lymphocytes. Cell 76:219-228

Boehncke W.H., Dressel D., Zollner T.M., and Kaufmann R. (1996) Pulling the trigger on psoriasis. Nature 379(6568):777

Brombacher F. (2000) The role of IL-13 in infectious diseases and allergy. Bioassays 22:646-656

Borst J., Jacobs., and Brouns G. (1996) Composition and function of T-cell receptor and B-cell receptor complexes on precursor lymphocytes. Curr. Opin. Imunol.8:181-190

Bowman T.S., Garcia R., Turkson J., and Jove R. (2000) Stats in oncogenesis. Oncogene 19(21):2474-2488

Bravo J., and Heath J.K. (2000) Receptor recognition by gp130 cytokines. EMBO J. 19:2399-2411

Buday L. (1999) Membrane-targeting of signalling molecules by SH2/SH3 domain-containing adaptor proteins. Biochim.Biophys Acta 1422:187-204

Caldenhoven E., van Djik T.B., Armstrong J., Raaijmakers J.A.M., Lammers J.W.J., Koenderman L., and de Groot R.P. (1996) Stat3β, a splice variant of transcription factor Stat3, is a dominant negative regulator of transcription. J. Biol. Chem. 271:13221-13227

Chambers C.A. (2001) The expanding world of co-stimulation: the two-signal model revisited. Trends Immuol. 22 (4):217-223

Christophers E. (1996) The immunophatology of psoriasis. Int. Arch. Allergy Immunol. 110:199-206

Chung, J., Uchida E., Grammer T.C., and Blenis J. (1997) Stat3 serine phosphorylation by ERK-dependent and -independent pathways negatively modulates its tyrosine phosphorylation. Mol. Cell. Biol.17:6508-6516

Conrad B., Weissmahr R.N., Boni J., Arcari R., Schupbach J., and Mach B. (1997) A human endogenous retroviral superantigen as candidate autoimmune gene in type I diabetes. Cell 90:303-313

Corry D.B., and Kheradmand F. (1999) Induction and regulation of the IgE response. Nature 402:B18-B22

Damaj B., Mourad W., and Naccache P.H. (1992) Superantigen-mediated human monocyte-T lymphocyte interactions are associated with an MHC class II-, TcR/CD3, and CD4-dependent mobilization of calcium in monpcytes. J. Immunol. 149(5):1497-1503

Danial N.N., Pernis A., and Rothman P.B. (1995) Jak-STAT signaling induced by the v-abl oncogene. Science 269:1875-1877

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

Darnell J.E. (1999) Stats and gene regulation. Science 277:1630-1635

Debets R., Hegmans J.P., Deleuran M., Hooft S., Benner R., and Prens E.P. (1996) Expression of cytokines and their receptors by psoriatic fibroblasts. Altered IL-6 synthesis. Cytokine8:70-79

Dustin M.L., and Cooper J.A. (2000) The immunological synapse and the actin cytoskeleton: molecular hardware for T cell signaling. Nature Immunol. 1:23-29

Emmel E.A., Verweij C.L., Durand D.B., Higgins K.M., Lacey E., and Crabtree G.R. (1989) Cyclosporin A specifically inhibits function of nuclear proteins involved in T cell activation. Science 1246:1617-1620

Ezekowitz (1998) Innate Immunity. Curr. Opin. Immunol.10: 9-53

Fayon M., Just J., Vu Thien H., Chiba T., Pascal L., Sandouk G., and Grimfeld A. (1999) Bacterial flora of the lower respiratory tract in children with broncial asthma. Acta Paediatr. 88:1216-1222

Fecteau S., Basadonna G.P., Freitas A., Ariyan C., Sayegh M.H., and Rothstein D.M. (2001) CTLA-4 up-regulation plays a role in tolerance mediated by CD45. Nature Immunol. 2(1): 58-63

Fields B.A., Malchiodi E.L., Ysern X., Stauffacher C.V., Schliefert P.M., Karjalainen K., and Mariuzza R.A. (1996) Crystal structre of a T cell receptor β chain complexed with a superantigen. Nature 384:188-192

Ford J.G., Rennick D., Donaldson D.D., Venkaya R., McArthur C., Hansell E., Kurup V.P., Warnock M., and Grunig G. (2001) IL-13 und IFNγ: interactions in lung inflammation. J. Immunol. 167(3):1769-1777

Fortner K.A., Russell J.Q., and Budd R.C. (1998) Down-modulated of CD2 deplays deletion of superantigen-responsive T cells. Eur. J. Immunol. 28:70-79

Foster P.S. (1999) Stat6: an intracellular target for the inhibition of allergic disease. Clin. Exp. Allergy 29:12-16

Fraser J., Arcus V., Kong P., Baker E., and Proft T. (2000) Superantigens - powerful modifiers of the immune system. Mol. Med. Today 6:125-132.

Fu X.Y., and Zhang J.J. (1993) Transcription factor p91 interacts with the epidermal groth factor and mediates activation of the c-fos gene promotor. Cell 74:1135-1145

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

Fuleihan R., Trede N., Chatila T., and Geha R.S. (1994) Superantigens activate HIV-1 gene expression in monocytic cells. Clin Immunol. Immunopathol. 72(3):357-361

Furmonaviciene R., and Shakib F. (2001) The molecular basis of allergenicity: comparative analysis of the three dimensional structures of diverse allergens reveals a common structural motif. J. Clin. Pathol. 54:155-159

Gallucci S. and Matzinger P. (2001) Danger signals: SOS to the immune system. Curr. Opin. Immunol. 13:114-119

Germain R.N. (1997) T-cell signaling: the importance of receptor clustering Curr. Biol 7:R640-R644

Gerwien J., Kaltoft K., Nielsen M., Nielsen M-B., Svejgaard A., Geisler C., Röpke C., and Ødum N. (1998) Staphylococcus enterotoxin A modulates IL-15-induced signaling and mitogenesis in human T cells. Tissue Antigens 51:164-173

Gerwien J., Nielsen M., Labuda T., Nissen M.H., Svejgaard A., Geisler C., Röpke C., and Ødum N. (1999) Cutting Edge: TcR Stimulation by antibody and bacterial superantigen induces Stat3 activation in human T cells. J. Immunol. 163:1742-1745

Gomez J., Gonzales A., Martinez C.A., and Rebollo A. (1998) IL-2-induced cellular events. Critical Rev. Immunol. 18:185-220

Gonzalo J.A., Tian J., Delaney T., Corcoran J., Rottman J.B., Lora J., Al-Garawi A., Kroczek R., Gutierrez-Ramos J.C., and Coyle A.J. (2001) ICOS is critical for T helper cell-mediated lung mucosal inflammatory responses. Nature Immunol. 2(7):597-603

Gouilleux-Gruart V., Gouilleux F., Desaint C., Claisse J.F., Capiod J.C., Delobel J., Weber-Nordt R., Dusant-Fourt I., Dreyfuss F., Groner B., anf Prin L. (1999) Stat-related transcription factors are constitutively activated in peripheral blood cells from acute leukemia patients. Blood 87:1692-1697

Grakoui A., Bromley S.K., Summen C., Davis M.M., Shaw A.S., Allen P.M., and Dustin M.L. (1999) The immunological synapse: a molecular machine controlling T cell activation. Science 285:221-227

Griffiths G.M. (1995) The cell biology of CTL killing. Curr. Opin. Immunol. 7:343-348

Grogan J.L., Mohrs M., Harmon B., Lacy D.A., Sedat J.W., and Locksley R.M. (2001) Early transcription and silencing of cytokine genes underlie polarization of T helper cell subsets. Immunity 14:205-215

Grünig G., Warnock M., Wakil A.E. et al. (1999) Requirement for IL-13 independly of IL-4 in experimental asthma. Science 282:2261-2263

Haque S.J., Harbor P., Tabrizi M., Yi T., and Williams B.R. (1998) Protein-tyrosine phosphatase Shp-1 is a negative regulator of IL-4 and IL-13-dependent signal transduction. J. Biol. Chem. 273:33893-33896

Haselden B.M., Kay A.B., and Larche´ M. (2000) Peptide-mediated immune responses in specific immunotherapy. Int. Arch. Allergy Immunol. 122:229-237

Hauk P.J., Wenzel S.E., Trumble A.E., Szefler S.J., Leung D.Y.M. (1999) Increased T-cell receptor Vβ8+ T cells in bronchoalveolar lavage fluid of subjects with poorly controlled asthma: a potential role for microbial superantigens. J. Allergy Clin. Immunol. 103:37-45

Havran W.L., and Boismenu R. (1994) Activation and function of γδ T cells. Curr. Opin. Immunol 6: 442-446

Henttinen, T., Levy D.E., Silvennoinen O., and Hurme M. (1995) Activation of the signal transducer and transcription (STAT) signaling pathway in a primary T cell response. Critical role for IL-6. J. Immunol. 155(10):4582-4587

Herman A., Kappler J.W., Marrack P., and Allen P.M. (1991) Superantigens: mechanism of T cell stimulation and role in immune responses. Annu. Rev. Immunol. 9:745-772

Herrmann T., Baschierri S., Lees R.K., and MacDonald H.R. (1992) In vivo responses of $CD4^+$ and $CD8^+$ cells to bacterial superantigens. Eur.J. Immunol. 22:1935-1938

Herz U., Bunikowski R., Mielke M., and Renz H. (1999) Contribution of bacterial superantigens to atopic dermatitis. Int Arch Allergy Immunol. 118:240-241.

Hibi M., and Hirano T. (1998) Signal transduction through cytokine receptors. Int. Rev. Immunol.17:75-102

Hilton D.J. (1999) Negative regulators of cytokine signal transduction. Cell Mol. Life Sci. 55:1568-1577

Huber B.T., Hsu P.N., Sutkowski N. (1996) Virus-encoded superantigens. Microbiol. Rev. 60:473-484

Hunter T. (1995) Protein kinases and phosphatases: the yin and yan of protein phosphorylation and signaling. Cell 80:225-236

Hunter C.A., and Reiner S.L. (2000) Cytokines and T cells in host defense. Curr. Opin. Immunol. 12:413-418

Ihle J.N. (1995) Cytokine receptor signaling. Nature 377:591-594

Ihle J.N. (2001) The Stat family in cytokine signaling. Curr. Opin. Cell Biol. 13:211-217

Irie-Sasaki J., Sasaki T., Matsumoto W., Opavsky A., Cheng M., Welstead G., Griffiths E., Krawczyk C., Richardson C.D., Aitken K., Iscove N., Koretzky G., Johnson P., Liu P., Rothstein D.M., and Penninger J.M. (2001) CD45 is a JAK phosphatase and negatively regulates cytokine receptor signalling. Nature 409(6818):349-354

Jain N., Zhang T., Fong S.L., Lim C.P., and Cao X. (1998) Repression of Stat3 activity by activation of mitogen-activated protein kinase (MAPK). Oncogene 17:3157-3167

Janeway (2001) Immunobiology. 5th edition

Janeway C.A., and Bottomly K. (1994) Signals and signs for lymphocyte responses. Cell 76:275-285

Jankovic D., Kullberg M.C., Noben-Trauth N., Caspar P., Paul W.E., Sher A. (2000) Single cell analysis reveals that IL-4/Stat6 signaling is not required for the in vivo or in vitro development of CD4+ lymphocytes with a Th2 cytokine profile. J. Immunol. 164:3047-3055

Jardetzky T.S., Brown J.H., Gorga J.C., Stern L.J., Urban R.G., Chi Y.I., Stauffacher C., Strominger J.L., and Wiley D.C. (1994) Three-dimensional structure of a human class-II major histokompatibility molecule complexed with a superantigen. Nature 386:711-718

Jember A.G-H., Zuberi R., Liu F-T., and Croft M. (2001) Development of allergic inflammation in a murine model of asthma is dependent on the costimulatory receprtor Ox40. J. Exp. Med. 193(3):387-392

Jiang H., Harris M.B., and Rothman P. (2000) IL-4/IL-13 signaling beyond Jak/Stat. J. Allergy Clin. Immunol. 105(6):1063-1070

Johnson L.R., McCormack S.A., Yang C-H., Peffer S.R., and Peffer L.M. (1999) EGF inducesnuclear translocation of Stat2 without tyrosine phosphorylation in intestinal epithelial cells. Am. Phys. Soc. C-419-C425

Johnston J.A., Bacon C.M., Riedy M.C., and O´Shea J.J. (1996) Signaling by IL-2 and related cytokines: Jaks, STATs and relationship to immunodeficiency. J. Leuko. Biol. 60:441-452

Jones C.A., Holloway J.A., and Warner J.O. (2000) Does atopic disease start in foetal life? Allergy 55:2-10

Kaltoft K., Hansen B.H., Pedersen C.B., Pedersen S., Thestrup-Pedersen K.(1995) Common clonal chromosome aberrations in cytokine-dependent continuous human T-lymphocyte cell lines. Cancer Gen.Cytogen.85:68-71

Kanner S.B., Odum N., Grosmaire L., Masewicz S., Svejgaard A., and Ledbetter J.A. (1992) Superantigen and HLA-DR ligation induce phospholipase-C gamma 1 activation in class II^+ T cells. J. Immunol. 149:3482-3488

Kanner S.B., Grosmaire L.S., Blake J., Schieven G.L., Masewicz S., Ødum N.L., and Ledbetter J.A. (1995) ZAP-70 and p72syk are signaling response elements through MHC class II molecules. Tissue Antigens 46:145-154

Kappler J, Kotzin B, Herron L (1989) Vβ-specific stimulation of human T cells by staphylococcal toxins. Science 244:811-813

Khandehar S.S., Brauer P.P., Naylor J.W., Chang H-C., Kern P., Newcomb J.R., LeClair K.P., Stump H.S., Bettencourt B.M., Kawasaki E., Banerji J., Profy A.T., and Jones B. (1997) Affinity and kinetics of the interaction between an ab T-cell receptor and its superantigen and class II-MHC/peptide ligands. Mol. Immunol. 34:493-503

Kilian M, Husby S, Host A, Halken S. Increased proportions of bacteria capable of cleaving IgA1 in the pharynx of infants with atopic disease. Pediatr Res 1995;38:182-186.

Kim T.K., and Maniatis T. (1996) Regulation of interferon-gamma-activated Stat1 by the ubiquitin-proteosome pathway. Science 273:1717-1719

Kotzin B.L., Leung D.Y., Kappler J., and Marrack P. (1993) Superantigens and their potential role in human disease. Advan. Immunol. 54:99-166

Krakauer T. (1999) Immune resonse to staphylococcal superantigens. Immunol. Res. 20:163-173

Krebs D.L., and Hilton D.J. (2000) SOCS: physiological suppressors of cytokine signaling. J. Cell Sci 113:2813-2819

Kreideweiß S., Ahlers C., Nordheim A., and Rühlmann A. (1999) Ca^{2+}-induced p38/SAPK signalling by the immunosupressant cyclosporin A in human peripheral blood mononuclear cells. Eur. J. Biochem. 265:1075-1084

Kon O.M., and Kay A.B. (1999) T cells and chronic asthma. Int. Arch. Allergy Immunol. 118:133-135

Krutzik S.R., Sieling P.A., and Modlin R.L. (2001) The role of Toll-like receptors in host defense against microbial infection. Curr. Opin. Immunol. 13:104-108

Kundig T.M., Schorle H., Bachmann M.F., Hengartner H., Zinkernagel R.M., and Horak I. (1993) Immune responses in IL-2-deficient mice. Science 262:1059-1061

Lacronique V., Boureux A., Valle V.D., Poirel H., Quang C.T., Mauchauffe M., Berthou C., Lessard M., Berger R., Ghysdael J., and Bernard O.A. (1997) A Tel-Jak2 fusion protein with constitutive kinase activity in human leukemia. Science 278:1309-1312

Lafont V., Decker T., and Cantrell D. (2000) Antigen receptor signal transduction: activating and inhibitory antigen receptors regulate Stat1 serine phosphorylation. Eur. J. Immunol. 30:1851-1860

Lamphear J.G., Stevens K.R., and Rich R.R. (1998) ICAM1 and LFA3 provide costimulation for superantigen-induced T lymphocyte proliferation in the absence of a specific presenting molecule. J. Immunol. 160:615-623

Lando P.A., Olsson., Kalland T., Newton D., Kotb M., and Dohlsten M. (1996) regulation of superantigen-induced T cell activation in the absence and in the presence of MHC class II. J. Immunol. 157:2857-63

Lanzavecchia A., and Sallusto F. (2000) Dynamics of T Lymphocyte Responses: Intermediates, Effectors and Memory Cells. Science 290: 92-97

Lanzavecchia A., and Sallusto F. (2001) Antigen decoding by T lymphocytes: from synapses to the fate determination. Nature Immunol. 2(6):487-492

Lavoie P.M., Thibodeau J., Cloutier I., Busch R., Sékaly R-P. (1997) Selective binding of bacterial toxins to MHC class II-expressing cells is controlled by invariant chain and HLA-DM. PNAS 94:6892-6897

Lavoie P.M., McGrath H., Shoukry N.H., Cazenave P-A., Sekaly R-P., and Thibodeau J. (2001) Quantitave relationship between MHC class II-superantigen complexes and the balance of T cell activation versus death. J. Immunol. 166:7229-7237

Leder L., Llera A., lavoie P.M., Lebedeva M.I., Li H., Sekaly R-P., Bohach G.A., Gahr P.J., Schlievert p.M., Karjalainen K., and Mariuzza R.A. (1998)A mutational analysis of the binding of staphylococcal enterotoxin B and C3 to the T cell receptor β chain and major histocompatibility complex II. J. Exp. Med 187:823-833

Leonard W.J. Kronke M., Peffer N.J., Depper J.M., and Greene W.C. (1985) Interleukin 2 receptor gene expression in normal human T lymphocytes. PNAS 82:6281-6285

Leonard W.J., and O´Shea J.J. (1998) Jaks and Stats: biological implications. Annu. Rev. Immunol.16:293-322

Leung D.Y., Travers J.B., Giorno R., Norris D.A., Skinner R., Aelion J.K., Kim M.H., Trumble A.E., Kotb M. (1995) Evidence for a streptoccocal superantigen-driven process in acute guttate psoriasis. J. Clin. Invest. 96:2106-12

Levings M.K., and Roncarolo M.G. (2000) T-regulatory 1 cells: a novel subset of CD4 T cells with immunoregulatory properties. J. Allergy Clin. Immunol. 106:109-112

Lewis H.M., Baker B.S., Bokth S., Powles A.V., Garioch J.J., and Valdimarsson H.F. (1993) Restricted T-cell receptor Vβ gene usage in the skin of patients with guttate and chronic plaque psoriasis. Brit. J. Dermat. 129:514-520

Li H., Llera A., Malchiodi E.L., and Mariuzza R.A. (1999) The structural basis of T cell activation by superantigens. Annu. Rev. Immunol. 17:435-466

Li H., Llera A., and Mariuzza R.A. (1998) Structure-function studies of T cell receptor-superantigen interactions basis of T cell activation. Immunol. Rev. 163:177-186

Li X-D., Essayan D.M., Liu M.C., Beaty T.M., and Huang S-K. (2001) Profiling of differential gene expression in activated, allergen-specific Th2 cells. Genes Immunity 2:88-98

Lim C.P., und Cao X. (1999) Serine phosphorylation and negative regulation of Stat3 by JNK. J. Biol. Chem. 274(43):31055-31061

Lin J-X., and Leonard W.J. (1997) Signaling from the IL-2 receptor to the nucleus. Cyt. Groth Fac. Rev. 8(4):313-332

Lin J-X., Migone T.S., Tsang M., Friedmann M., Weatherbee J.A., Zhou L., Yamauchi A., Bloom E.T., Mietz J., and John S. (1995) The role of shared receptor motifs and common Stat proteins in the generation of cytokine pleiotropy and redundancy by IL-2, IL-4, IL-7, IL-13, and IL-15. Immunity 2:331-339

Lin J., and Weiss A. (2001) T cell receptor signalling J. Cell Sci. 114:243-244

Lui K.D., Gaffen S.L., and Goldsmith M.A. (1998) Jak/Stat signaling by cytokine receptors. Curr. Opin. Immuol. 10:271-278

Liu K.D., Greene W.C., and Goldsmith M.A. (1996) The alpha chain of the IL-2 receptor determines the species specificity of high affinity IL-2 binding. Cytokine 8:613-621

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. PNAS 95:10626-10631

Lord G.M., Lechler R.I., George A.J.T. (1999) A kinetic differentiation model for the action of altered TcR ligands. Immnuol. Today 20(1):33-39

MacDonald T.T. (1998) T cell immunity to oral allergens. Curr. Opin. Immunol. 10:620-627

Malchiodi E.L., Eisenstein E., Fields B.A., Ohlendorf D.H., Schlievert P.M., Karjalainen K., and Mariuzza R.A. (1995) Superantigen binding to a T cell receptor β chain of known three-dimensional structure. J. Exp Med. 182:1833-1845

Maloy K.J., and Powrie F. (2001) Regulatory T cells in the control of immune pathology. Nature Immunol. 2 (9):816-822

Marone G. (1998) Asthma:recent advances. Immunol. Today 19(1):5-9

Marshall C.J. (1995) Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. Cell 80:179-185

Masewicz S., Ledbetter J.A., Martin P., Mickelson E., Hansen J.A., and Ødum N. (1993) Inhibition of allostimulated HLA-DQ and DP-specific T cells by staphylococcal enterotoxin A. Human Immunol. 36:142-149

Matsuda S., and Koyasu S. (2000) Mechanismims of action of cyclosporine. Immunopharmacology 47(2-3):119-125

Matzinger P. (1994) Tolerance, danger and the extended family. Annu. Rev. Immunol. 12:991-1045

McAdam A.J., Greenwald R.J., Levin M.A., Chernova T., Malenkovich N., Ling V., Freeman G., and Sharpe A.H. (2001) ICOS is critical for CD40-mediated antibody class switching. Nature 409:102-105

McKenzie G.J., Fallon P.G., Emson C.L., Grencis R.K., and McKenzie A.N. (1999) Simultaneous disruption of interleukin (IL)-4 and IL-13 defines individual roles in T helper cell type 2-mediated responses. J. Exp. Med. 189:1565-1572.

Mehindate K., Thibodeau J., Dohlsten M., Kalland T., Sékalv R.P., and Mourad W. (1995) Cross-linking of MHC class II molecules by staphylococal enterotoxin A superantigen is a requirement for inflammatory cytokine gene expression J. Exp. Med. 182: 1573-1577

Mehindate K., al-Daccak R., Damdoumi F., and Mourad W. (1996) Synergistic effeckt between CD40 and class II signals overcome the requirement for class II dimerization in superantigen-induced cytokine gene expression. Eur. J. Immunol. 26:2075-2080

Miyazaka T., Kawahara A., Fujii H., Nakagawa Y., Minami Y., Liu Z.J., Oishi I., Silvennoinen O., Witthuhn B.A., and Ihle J.N. (1994) Functional activation of Jak1 and Jak3 by selective association with IL-2 receptor subunits. Science 266:1045-1047

Miyazaki T., Liu Z.J., Kawahara A., Minami Y., Yamada K., Tsujimoto Y.B., Perlmutter R.M., and Taniguchi T. (1995) Three distinct IL-2 signaling pathways mediated by bcl-2, c-myc, and lck cooperate in hematopoietic cell proliferation. Cell 81:223-231

Monks C.R.F., Freiberg B., Kupfer H., Sciaky N., and Kupfer A. (1998) Three-dimensional segregation of supramolecular activation clusters in T cells. Nature 395:82-86

Moriggl R., Kristofic C., Kinzel B., Volarevic S., Groner B., and Brinkmann V. (1999) Activation of Stat proteins and cztokine genes in human Th1 and Th2 cells generated in the abscence of IL-12 and IL-4. J. Immunol. 160:3385-3392

Morita C.T., Li H., Lamphear J.G., Rich R.R., Fraser J.D., Mariuzza R.A., and Lee H.K. (2001) Superantigen recognition by γδ T cells: SEA recognition site for human Vγ2 T cell receptors. Immunity 14:331-344

Moser M., and Murphy K.M., (2000) Dendritic cell regulation of T_H1-T_H2 development. Nature Immunol. 1:199-205

Murata T., Obiri N.I., and Puri R.K. (1998) Structure and signal transduction through IL-4 and IL-13 receptors. Int. J. Mol. Med. 1:551-557

von Mutius E., Martinez F.D., Fritsch C., Nicolai T., Roell G., and Thiemann H.H. (1994) Prevalence of asthma and atopy in two areas of west and east germany. Am. J. Respir. Crit. Care Med. 149:358-364

Naclerio R., and Solomon W. (1997) Rhinitis and inhalant allergens. JAMA 278:1842-1848

Nakarai T., Robertson M.J., Streubli M., Wu Z., Ciardelli T.L., Smith K.A., and Ritz J. (1994) Interleukin 2 receptor gamma chain expression on resting and activated lymphoid cells. J.Exp. Med. 180 (1):241-245

Newton D.W., Dohlsten M., Olsson C., Segren S., Lundin K.E.A., Lando P.A., Kalland T., and Kotb M. (1996) Mutations in the MHC class II binding domains of staphylococcal enterotoxin A differentially affect T cell receptor Vbeta specificity. J. Immunol. 157:3988-3994

Ng, J., and Cantrell D. (1997) STAT3 is a serine kinase target in T lymphocytes. Interleukin 2 and T cell antigen receptor signals converge upon serine 727. J. Biol. Chem. 272(39):24542-24549

Niedergang F., Dautry-Varsat A., and Alcover A. (1998) Cooperative activation of TcRs by enterotoxin superantigens. J. Immunol. 161:6054-6058

Nielsen M., Ødum N., Bendtzen K., Ryder L.P., Jacobsen B.K., Svejgaard A.(1994) MHC Class II Molecules Regulate Growth in Human T Cells. Exp. Clin. Immunogen. 11:23-32

Nielsen M., Svejgaard A., Ropke C., Nordahl M., and Ødum N. (1995) Staphylococcal enterotoxins modulate interleukin 2 receptor expression and ligand-induced tyrosine phosphorylation of the Janus protein-tyrosine kinase 3 (Jak3) and signal transducers and activators of transcription (Stat proteins). PNAS 92:10995-10999

Noble A., Thomas M.J., and Kemeny D.M. (2001) Early Th1/Th2 cell polarization in the absence of IL-4 and IL-12: T cell receptor signaling regulates the response to cytokines in CD4 and CD8 T cells. Eur. J. Immunol. 31(7):2227-2235

Nossal G.J.V. (1994) Negative selection of lymphocytes Cell 76:229-239

Ødum N., Hartzman R., Jakobsen B.K., Morling N., Platz P., Robbins F.M., Ryder L.P., and Svejgaard A. (1986) The HLA-DP polymorphism in Denmark investigated by local and international PLT reagents: Definition of two new DP antigens. Tissue Antigens 28:105-118

Ødum N., Kanner S.B., Ledbetter J.A., Svejgaard A.(1993) MHC class II molecules deliver costimulatory signals in human T cells through a functional linkage with IL-2-receptors. J. Immunol. 150:5289-5298

O´Gara A. (1998) Cytokines induce the development of functionally heterogeneous T helper cell subsets. Immunity 8:275-283

Ohshima Y., Yang L-P., Uchiyama T., Tanaka Y., Baum P., Sergerie M., Hermann P., and Delespesse G. (1998) Ox40 costimulation enhances IL-4 expression at priming and promotes the differentiation of naive human $CD4^+$ T cells into high IL-4-producing effectors. Blood 92(9):3338-3345

O´Shea J.J. (1997) Jaks, Stats, cytokine signal transduction, and immunoregulation: are we there yet ? (Immunity) 7:1-11

Paliard X., West S.G., Lafferty A.J., Clements J.R., Kappler J.W., Marrack P., and Kotzin B.L. (1991) Evidence for the effect of a superantigen in rheumatoid arthritis. Science 253:325-329

Platts-Mills T.A. (1998) The role of allergens in allergic airway diseases. J. Allergy Clin. Immunol. 101:S364-S366

Papageorgiou A.C., and Acharya K.R. (2000) Microbial superantigens: from structure to function. Trends Microbiol. 8(8):369-375

Paul W.E., and Seder R.A. (1994) Lymphocyte resonses and cytokines. Cell 76:241-251

Paul W.E. (1999) Fundamental Immunology. 4th edition

Pawson T. (1995) Protein modules and signalling networks. Nature 373:573-580

Pearlman D.S. (1999) Pathophysiology of the inflammatory response. J. Allergy Clin. Immunol. 104:S132-S37

Peterson E.J., Clements J.L., Fang N., and Koretzky G.A. (1998) Adaptor Proteins in lymphocyte antigen receptor signaling. Curr. Opin. Immunol. 10:337-344

Picker L.J. (1994) Control of lymphocyte homing Curr. Opin. Immunol. 6:394-406

Pieters J. (2000) MHC class II-restricted antigen processing and presentation. Adv. Immunol. 75:159-208

Redpath S., Alam S.M., Lin C.M., O´Rouke A.M., and Gascoigne N.R.J. (1999) Trimolecular interaction of the TcR with MHC class II and bacterial superantigen shows a similar affinity to MHC/peptide ligands. J. Immunol. 163:6-10

Renauld J-C. (2001) New insights into the role of cytokines in asthma. J. Clin. Pathol. 54:577-589

Rengarajan J., Szabo S.J., and Glimcher L.H. (2000) Transcriptional regulation of Th1/Th2 polarization. Immunol. Today 21(10): 479-483

Ring J. (1997) Allergy and modern society: does 'Western life style' promote the development of allergies? Int Arch Allergy Immunol. 113:7-10.

Rink L., Luhm J., Koester M., and Kirchner H. (1996) Induction of a cytokine network by superantigens with parallel Th1 and Th2 stimulation. J. Interfer. Cytokine Res. 16:41-47

Rogers P.R., and Croft M. (1999) Peptide dose, affinity and time of differentiation can contribute to the Th1/Th2 balance. J. Immunol. 163:1205-1213

Rogers P.R., and Croft M. (2000) CD28, Ox-40, LFA1, and CD4 modulation of Th1/Th2 differentiation is directly dependent on the peptide dose. J. Immunol. 164:2955-2963

Rolland J., and O´Hehir R. (1998) Immunotherapy of allergy: anergy, deletion, and immune deviation. Curr. Opin. Immunol. 10:640-645

Romagnani S., Parronchi P., D´Elios M.M., Romagnani P., Annunziato F., Piccini M.P., Manetti R., Sampognaro S., Mavillia C., De-Carli M., Maggi E., and Del-Prete D.F. (1997) An update on Th1 and Th2 cells. Int. Arch. Allergy Immunol. 113:153156

Romagnani S. (2000) T cell subsets (Th1 versus Th2). Annal. Aller. Asth. Immunol. 85:9-18

Romagnani S. (2000b) The role of lymphocytes in allergic disease. J. Allergy Clin. Immunol. 2000;105:399-408.

Rothenberg E.V. (1996) How T cells count. Science 273:78-79

Sampson A.P., and Rorke S. (1996) Combination therapy with anti-mediator drugs in allergic disease. Clin. Exp. Allergy 31:11-17

Sayama K., Midorikawa K., Hanakawa Y., Sugai M., and Hashimoto K. (1998) Superantigen produktion by staphylococcus aureus in psoriassis. Dermatology 196:194-198

Schad E.M., Zaitseva I., Zaitseva V.N., Dohlsten M., Kalland T., Schlievert P.M., Ohlendorf D.H., Svensson L.A. (1995) Crystal structure of the superantigen staphylococcal enterotoxin type A. EMBO Journal 14:3292-3301

Schiffenbauer J., Johnson H.M., Butfiloski E.J., Weggryzn L., and Soos J.M. (1993) Staphylococcal enterotoxins can reactivate experimental allergic encephalomyelitis. PNAS 90:8543-8546

Schiffenbauer J., Soos J., and Johnson H. (1998) The possible role of bacterial superantigens in the pathogenesis of autoimmune disorders. Immuol. Today 19(3):117-120

Schindler C., and Darnell J.E. (1995) Transcriptional responses to polypeptid ligands: the Jak/Stat pathway. Annu. Rev. Biochem. 64:621-651

Schindler C. (1999) Cytokines and Jak-Stat signaling. Exp. Cell Res. 253:7-14

Schraven B., Marie-Cardine A., Hübener C., Bruyns E., and Ding I. (1999) Integration of receptor-mediated signals in T cells by transmembrane adaptor proteins. Immunol. Today 20(10):431-434

Schwartz R.H., Mueller D.L., Jenkins M.K., and Quill H. (1989) Cold Spring Habor Symp. Quant. Biol. 54:605-610

Seidel H.M., Miloco L.H., Lamb. P., Darnell J.E.J., Stein R.B., and Yoneda (1995) Spacing of palindromic half sites as a determinant of selective Stat DNA binding and transcriptional. PNAS 92:3041-3045

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

Seth A., Stern L.S., Ottenhoff T.H.M., Engel I., Owen M.L., Lamb J.R., KlausnerR.D., and Wiley D.C. (1994) Binary and ternary complexes between T-cell receptor, class II MHC and superantigen in vitro. Nature 369:324-327

Shaw A.S., and Dustin M.L. (1997) Making the T cell receptor go the distance: a topological view of T cell activation. Immunity 6:361-369

Shiomori T., Yoshida S., Miyamoto H., and Makishima K. (2000) Relationship of nasal carriage of Staphylococcus aureus to pathogenesis of perennial allergic rhinitis. J Allergy. Clin. Immunol. 105:449-454.

Showkat M.A., Sayeski P.P., and Berstein K. (2000) Jak2 acts as a Stat1 kinase and a molecular bridge linking Stat1 to the angiotensin II AT1 receptor. J. Biol. Chem. 275(20):15586-15593

Silvennoinen O., Ihle J.N., Schlessinger J., and Levy D.E. (1993) Interferon-induced nuclear signalling by Jak protein tyrosine kinases. Nature 366:583-585

Singer A., Bosselut R., and Bhandoola A. (1999) Signals involved in CD4/CD8 lineage commitment: current concepts and potential mechanisms. Sem. Immunol. 11: 273-281

Sparholt S.H., Larsen J.N., Ipsen H., Schou C., and van Neerven R.J. (1997) Crossreactivity and T-cell epitope specificity of Bet v 1-specific T cells suggest the involvement of multiple isoallergens in sensitization to birch pollen. Clin. Exp. Allergy 27:932-941.

Sperling A.I., and Bluestone J.A. (2001) ICOS costimulation: it´snot just for Th2 cells anymore. Nature Immunol. 2(7):573-574

Stange P., Skov L., and Baadsgaard O. (1994) Interferon γ-treated kertinocytes activate T cells in the presence of superantigens: involvment of major histocompatibility complex class II molecules. J. Invest. Dermatol. 102:150-154

Strasser A. (1995) Life and death during lymphocyte development and function:evidence of two distinct killing mechanisms. Curr. Opin. Immunol. 7: 228-234

Swaminathan S., Furey W., Pletcher J., Sax M.(1992) Crystal structure of staphylococcal enterotoxin type B, a superantigen. Nature 359:801-806

Taniguchi T. (1995) Cytokine signaling through nonreceptor protein kinases. Science 268:251-255

Taniguchi T., Miyazaki T., Minami Y. et al. (1995b) IL-2 signaling involves recruitment and activation of multiple protein tyrosine kinases by the IL-2 receptor. Annals N.Y. Acad. Sci. 766:235-244

Taskapan M.O., and Kumar P. (2000) Role of staphylococcal superantigens in atopic dermatitis: from colonization to inflammation. Ann Allergy Asthma Immunol. 84:3-10.

Tiedeman R.E., and Fraser J.D. (1996) Cross-linking of MHC class II molecules by SEA is essential for antigen-presenting cell and T cell activation. J. Immunol. 157:3958-3966

Uchiyama T., Yan X.J., Imanishi K., and Yagi J. (1994) Bacterial superantigens--mechanism of T cell activation by the superantigens and their role in the pathogenesis of infectious diseases. Microbiol Immunol. 38:245-256.

Uebel S., and Tampe R. (1999) Specificity of the proteosome and the TAP transporter. Curr. Opin. Immunol. 11: 203-208

Valitutti S., and Lanzavecchia A. (1997) Serial triggering of the TcRs: a basis for sensitivity and specificity of antigen recognition. Immnuol. Today 18:299-304

Viola A., and Lanzavecchia A. (1996) T cell activation determined by T cell receptor number and tunable thresholds. Science 273:104-106

Viola A., Schroeder S., Sakakibara Y., and Lanzavecchia A. (1999) T lymphocytes costimulation mediated by reorganization of membrane microdomains. Science 283: 680

Visco C., Magistrelli G., Boscotti R., Perego R., Rusconi L., Toma S., Zamai M., Acuto O., and Isacchi A. (2000) Activation of Zap-70 tyrosine kinase is due to a structural rearrangment induced by tyrosine phosphorylation and/or ITAM binding. Biochemistry 39:2784-2791

de Vries J.E., and Zurawski G. (1995) Immunoregulatory properties of IL-13: its potential role in atopic disease. Int. Arch. Allergy Immunol. 106:175-179.

de Vries J.E., Carballido J.M., and Aversa G. (1999) Receptors and cytokines involved in allergic Th2 cell responses. J. Allergy Clin. Immunol. 103:S492-S496

Vukmanovic-Stejic M., Vyas B., Gorak-Stolinska P., Noble A., and Kemeny D.M. (2000) Human Tc1 and Tc2/Tc0 CD8 T-cell clones display distinct cell surface functional phenotypes. Blood 95(1):231-240

Waldmann H., and Cobbold S. (2001) Regulating the immune response to transplants: a role for $CD4^+$ regulatory cells. Immunity 14:399-406

Wang R., Abrams S.I., Loh D.Y., Hsieh C.S., Murphy K.M., and Russell J.H. (1993) Separation of $CD4^+$ functional responses by peptide dose in T_H1 and T_H2 subsets expressing the same transgenic receptor. Cell Immunol. 148: 357-370

Ward A.C., Touw I., and Yoshimura A. (2000) The Jak-Stat pathwaz in normal and perturbed hematopoiesis. Blood 95:19-26

Watts T.H., and DeBenedette M.A. (1999) T cell co-stimulatory molecules other than CD28. Curr. Opin. Immunol. 11:286-293

Webb D.C., McKenzie A.N., Koskinen A.M., Yang M., Mattes J., and Foster P.S. Integrated signals between IL-13, IL-4, and IL-5 regulate airways hyperreactivity. J. Immunol. 165:108-113.

Welte T., Leitenberg D., Dittel B.N., al-Ramadi B.K., Xie B., Chin Y.E, Janeway C.A.,Bothwell A.L.M., Bottomly K, and Fu X.Y. (1999) STAT5 interaction with the T cell receptor complex and stimulation of T cell proliferation. Science 283:222-225

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

Wen R., Cole G.A., Surman S., Blackman M.A., Woodland D.L. (1996) MHC class II associated peptides control the presentation of bacterial superantigens to T cells. J. Exp. Med. 183(3):1083-1092

White J., Herman A., Pullen A.M., Kubo R., Kappler J.W., and Marrack P. (1989) The V beta-specific superantigen staphylococcal enterotoxin B: stimulation of mature T cells and clonal deletion in neonatal mice. Cell 56:27-35.

Williams C.M., and Galli S.J. (2000) The diverse potential effector and immuno regulatory roles of mast cells in allergic diseases. J. Allergy Clin Immunol. 105:847-859

Winther L., Malling H-J., and Mosbech H. (2000) Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. II. Side-effects. Allergy 55:827-835

Woodland DL, Blackman MA (1993) How do T-cell receptors, MHC molecules and superantigens get together ? Immunol. Today 14:208-212

Xu X., Sun Y.L., and Hoey T. (1996) Cooperative DNA binding and sequence-selective recognition conferrred by the Stat amino-terminal domain. Science 273:794-797

Yeh T.C., and Pellegrini S. (1999) The janus kinase family of protein tyrosine kinases and their role in signaling. Cell. Mol. Life Sci. 55:1523-1534

York I.A., Goldberg A.L., Mo X.Y., and Rock K.L. (1999) Proteolysis and class I major histocompatibility complex antigen presentation. Immunol. Rev. 172: 49-66

Yu C-L., Meyer D.J., Campell G.S., Larner A.C., Carter-Su C., Schwartz J., and Jove R. (1995) Enhanced DNA-binding activity of a Stat3-related protein in cells transformed by Src oncoprotein. Science 269:1875-1877

Yu C-L., Jove R., and Burakoff S.L. (1997) Constitutive activation of the janus kinase-stat pathway in T lymphoma overexpressing the Lck protein tyrosine kinase. J. Immunol. 159:5206-5210

Yu C-R., Kirken R.A., Malabarba G., Young H.A., and Ortaldo J.R. (1998) Differential regulation of Jak-Stat pathway and biologic function of IL-13 in primary human NK and T cells: A comparative study with IL-4. J. Immunol. 161:218-227

Zhang W., and Samelson L.E. (2000) The role of membrane-associated adaptors in T cell signalling. Semin. Immunol. 12:35-41

Zhu J., Guo L., Watson C.J., Hu-Li J., and Paul W.E. (2001) Stat6 is necessary and sufficient for IL-4s role in Th2 differentiation and cell expansion. J. Immunol. 166:7276-7281

Zuniga-Pflücker J.C., and Lenardo M.J. (1996) Regulation of thymocyte development from immature progenitors. Curr. Opin. Immunol. 8:215-224

6.2 Abkürzungsverzeichnis

Abb.	Abbildung
Ak	Antikörper
APC	Antigenpräsentierende Zelle
BcR	B-Zellen Rezeptor
bio.	biotinyliert
BSA	Rinderserum Albumin
CD	*Cluster of Differentiation,* Internationale Nomenklatur für Antigen
Cpm	Zähleinheiten pro Minute
CTL	Zytotoxische T-Zelle
EBV	Epstein-Barr Virus
ECL	verstärkte Chemilumineszens
EDTA	Ethylendiamintetraessigsäure
ER	Endoplasmatisches Riticulum
FACS	*Flourescence-activated Cell Sorter*
FCS	fötales Kälber Serum
Fc	konserviertes Fragment
GAS	IFNγ aktivierte Sequenz
ICAM-1	Intrazelluläres Adhäsionsmolekül-1
IFN	Interferon
Ig	Immunglobulin
IL	Interleukin
IL-2R	Interleukin-2 Rezeptor
in vivo	im lebenden Objekt
in vitro	im Reagenzglas
IP	Immunpräzipitation
ITAM	*immuno-receptor tyrosine based activation motifs*
Jak	Janus Kinase (*just another kinase*)
kDa	Kilo Dalton
LFA-1	*lymphocyte functions-associated antigen-1*
mAK	monoklonaler Antikörper

MAP	Mitogen aktivierte Proteinkinase
MFI	*mean fluorescence intensity*
MHC	Haupthistokompatibilitätskomplex (*major histocompatibility complex*)
min	Minuten
mRNA	*messanger Ribonucleic acid*
NCCLS	National Committee for Clinical Laboratory Standards
NFAT	*nuclear factor of activated T cells*
NK-cells	natural killer cells
NLS	Nukeus-Lokalisations-Sequenz
PBMC	*peripheral blood mononuclear cells*
phos.-ser.	Phosphorserin
phos.-tyr.	Phosphortyrosin
PMA	Phorbol-12-myristate-13-acetat
PMSF	Phenylmethylsulphonylflourid
RT	Raumtemperatur
SDS-PAGE	Natriumdodecylsuphat-Polyakrylamidgelelektophorese
SH2	*src-homology 2*
SH3	*src-homology 3*
SOCS	*suppressor of cytokine signaling*
Stat	*signal transducer and activator of transcription*
Tab.	Tabelle
TAP	Peptidtransporter (*transporter associated with antigen processing*)
TcR	T-Zellen Rezeptor
T_HC	T-Helfer Zelle
T_KC	T-Killer Zelle
TLR	*toll-like-receptors*
Tris	Tris-hydroxymethyl-aminomethan
WB	*Western Blot*
Zap	Zap70-Kinase (*zeta-associated protein*)

6. 3 Zusammenfassung

Bakterielle Enterotoxine oder Superantigene werden neben anderen Krankheiten mit Autoimmunerkrankungen, sowie mit Asthma und Allergie in Verbindung gebracht. Der genaue Mechanismus der durch Superantigene induzierten Signale in diesen Krankheiten ist jedoch noch nicht geklärt. Wir haben in der vorliegenden Arbeit versucht, die durch Superantigene induzierten Signale in humanen, alloaktivierten $CD4^+$ T-Zellen zu analysieren. Aktivierte humane T-Zellen besitzen MHC Klasse II Moleküle auf ihrer Oberfläche und machen damit die zusätzliche Anwendung von antigenpräsentierenden Zellen unnötig.

Superantigene induzieren eine, von Adhäsionsmolekülen abhängige Aggregation von humanen T-Zellen. Superantigene setzten die durch Zytokine induzierte Proliferation von T-Zellen herab. Die durch PMA induzierte Proliferation wurde jedoch verstärkt, sowie die Oberflächenexpression der einzelnen IL-2 Rezeptor Ketten regulativ verändert..

Die durch Superantigene induzierten Signale waren von Ca^{2+}-Signalen und src-Kinasen abhängig, da sie von Cyclosporin A und PP1 gehemmt werden konnten. Superantigene induzierten eine akkumulierende Phosphorylierung an Serin und Tyrosin von Stat3 und Stat6, in einigen T-Zelllinien sogar schon nach einigen Minuten. Die Aktivierung von Stat-Proteinen unterschied sich deutlich von der durch Zytokine induzierten Aktivierung von Stat-Proteinen. Durch Superantigene induziertes Stat3 war nicht nur phosphoryliert, sondern auch biologisch aktiv und band sich an verschiedene Promotorregionen.

Mittels Superantigenmutanten konnte keine funktionelle Abhängigkeit von einer der drei SEA-Bindungsstellen festgestellt werden, und die durch Superantigene induzierte Aktivierung von Stat-Proteinen erwies sich als abhängig von der Proteinbiosynthese.

Superantigene induzierten in verschiedenen T-Zellen Linien eine kräftige Produktion der T_H2-Zytokine IL-5 und IL-13. Außerdem konnte IL-13 mit einem IL-13 Rezeptor-Molekül als das Stat3- und Stat6-aktivierende Zytokin identifiziert werden.

Wir zeigten hier zum ersten Mal, dass humane $CD4^+$ T-Zellen nach Inkubation mit SEA und einer verstärkten Expression des IL-13 Rezeptors in der Lage waren, spezifisch auf IL-13 zu reagieren.

Neben den Zytokinen IL-5 und IL-13, sowie Stat6 induzierten Superantigene die Produktion des T_H2-spezifischen Transkriptionsfaktors Gata3 und der Kostimulations-moleküle Ox40 und ICOS in alloaktivierten humanen T-Zellen.

Die vorliegende Arbeit erweitert unser Wissen von der Funktionsweise der bakteriellen Enterotoxine. Die hier erzielten Ergebnisse lassen einige Fragen offen und werfen darüber hinaus neue Fragen auf. Die vorgestellten Daten können jedoch zur Erklärung der Funktionsweise von Superantigenen in verschiedenen pathologischen Reaktionen herangezogen werden. Die Ergebnisse weisen ebenfalls auch mögliche therapeutische Ansatzpunkte zur Bekämpfung von Krankheiten hin, in denen Superantigene eine Rolle spielen.

6. 4 Summary

Bacterial enterotoxins, or superantigens, have been implicated in the pathogenesis of autoimmune diseases and atopic disorders. Hence, the mechanism of how superantigens transmit their signals in those diseases is yet unknown. In the work presented here, we try to investigate the superantigen-induced signals in allo-activated, human $CD4^+$ T cells. As activated human T cells do express MHC II molecules, we were able to omit the usage of antigen presenting cells in our experimental setup.

The superantigen-induced T cell aggregation was found to be dependent on adhesion molecules. Superantigens down regulated the cytokine-induced T cell proliferation and up regulated the PMA-induced T cell proliferation, as well as modulated the expression of the IL-2 receptor chains.

The superantigen-induced reactions were sensitive to Ca^{2+}-signals and src-kinases, as cyclosporin A and PP1 inhibited those signals. We found an accumulating tyrosin and serin phosphorylation of Stat3 and Stat6, in some of the tested T cell lines all ready after 1 minute. The Stat activation observed here was different from an IL-2-induced Stat activation and resulted not only in phosphorylated Stat proteins but in Stat proteins that were able to bind different promoter regions and were biologic active.

By using superantigen mutants, we were unable to detect any significant functional differences between the three SEA binding sites. The superantigen-induced Stat activation was found to be dependent on *de novo* protein synthesis.

Superantigen induced a strong production of the T_H2-cytokines IL-5 and IL-13 in different T cell lines. By using a IL-13R-chimera, we identified IL-13 as the cytokine responsible for activating Stat3 and Stat6 after superantigen incubation.

Here, we give first evidence that incubation with superantigen induced a up regulation of the IL-13 receptor, resulting in a IL-13 responsiveness of human $CD4^+$ T cells.

Besides IL-5, IL-13 and Stat6, we found that superantigen induced activated human T cells to produce the T_H2-specific transcription factor Gata3, as well as the co-stimulatory molecules Ox-40 and ICOS.

We presented here some new evidence on the function of bacterial enterotoxins. Not all questions have been answered and new questions arose. The presented data could help to explain some of the pathologic reactions of superantigens. The results point to new therapeutic angles to strike on diseases were superantigens have been implicated.

6.5 Lebenslauf

Curriculum Vitae

Jens Gerwien

Ausbildung:	Dez. 1982 Abitur, Lily Braun Gymnasium, Berlin	
	Okt. 1986 Vordiplom in Chemie (1.0), F.U Berlin.	
	Dez. 1988 Vordiplom in Biochemie (1.0), F.U. Berlin	
	Mai 1991 Diplom in Biochemie (1.0), F.U. Berlin	
Diplomarbeit:	Reinigung und Charakterisierung der Serinprotease Akrosin	
Beschäftigungen:	**Juni 1991-Juli 1995 Assistent bei Prof. Dr. S. Buus**	
	1991-1993	Research Fellowship der Kommission der EU
	1993-1994	Stipendium des DAAD
	1994-1995	Stipendium der Daimler Benz Stiftung
	1995-2001	**Research Fellow bei Lektor Dr. N. Ødum**
	1995	Stipendium des dän. Forschungsforums
	1995-1998	Stipendium der Alfred Benzon´s Stiftung
	1998-2001	Stipendium der Stiftung von 17/12-1981
Arbeit an anderen Institutionen	1993	Olso Universität, bei Prof. O. Bakke, Ph.D
	1997	Wallenberg Lab., Lund, bei T. Labuda, Ph.D
	1999	Århus Universitet, bei Dr.med Keld Kaltoft
Auszeichnungen	2001	Dyssegaard-Preis für junge Forscher
Lehrerfahrung	1995-2000	Lehrer am Immunolkursus für Diplomanden der Universität Kopenhagen

Kurse und Kongresse (Poster/Abstrakt/Vortrag)

1992	FEBS Immunology Summer School, Greece
1992	AAI Summer School Immunoregulation, Colorado
1993	Immunology Conference on MHC, Les Embiez
1994	Erasmus Summer School: Immunology, Rotterdam
1995	Scan. Society for Immunology Meeting, Göteborg
1997	European Immunology Meeting, Amsterdam
1998	Scandinavian Immunology Congress
1999	Dansk Selskab for Allergi (Kolding)
1999	Nordisk Forsker Symposium (Tønder)
2000	Keystone Symp., T lymphocyte activation, Colorado
2000	European Allergy Congress, Lissabon
2001	AAAAI-Kongress, New Orleans
2001	ISI-Kongress, Stockhom

6.6 Publikationen

Publikationen von Jens Gerwien

1) U.Eberspächer, **J. Gerwien**, U.-F. Habenicht, W.-D Schleuning & P. Donner Mol. Reprod. Develop.; 30: 164-174 (1991)

2) L.Ø. Pedersen, A.S. Hansen, A.C. Olsen, **J. Gerwien**, M.H. Nissen & S. Buus Scand. J. Immunol.; 39: 64-72 (1994)

3) L.Ø. Pedersen, A.S. Hansen, T.L.Holte M.Etzerrodt, **J. Gerwien**, M.H. Nissen, H.C. Thøgersen & S. Buus Europ. J. Immunol; 25: 1609-16 (1995)

4) J. Gerwien, M. Nielsen, M. Nordahl, A. Svejgård, C. Röpke & N. Ødum Tissue Antigens; 51 (2): 164-173 (1998)

5) M.-B. Nielsen, **J. Gerwien**, M.Nielsen, C. Geisler, C. Röpke, A. Svejgård &N. Ødum Exp. Clin. Immunogenet. 15 (2):61-68 (1998)

6) M.-B. Nielsen, N. Ødum, **J. Gerwien**, A. Svejgård, K. Bendtzen, S. Bregenholt, C. Röpke, C. Geisler, M. Dohlsteen & K. Kaltoft Tissue Antigens 52: 530-538 (1998)

7) T. Labuda, **J. Gerwien**, N. Ødum & M. Dohlsteen Inter. Immunol. 11 (3) 427-433 (1999)

8) S. Thulesen, A. Jørgensen, **J**. **Gerwien,** M. Dohlsten, M. H. Nissen, N. Ødum & C. Röpke Exp. Clin Immunogenet. 1999, 16 (4):226-233

9) J. Gerwien, M. Nielsen, T. Labuda, M.H. Nissen, A. Svejgaard, C. Geisler, C. Röpke & N. Ødum J.Immunol 1999, cutting edge, 15;163 (4)1742-5

10) Nielsen, M., Nissen, M.H., **Gerwien, J**., Zocca, M., Rasmussen, HM., Nakajima, K., Ropke, C., Geisler, C., Kaltoft, K., and Odum, N. Blood, Submitted: 2001.

11) Gerwien J., Nissen M. H., Kristensen N., Kaltoft K., Nielsen M., Svejgaard A., Røpke C., and Ødum N. J. Allergy and Clin. Immunol. Submitted, 2001

6.7 Danksagung

Die vorliegende Arbeit habe ich im Labor von Dr. Niels Ødum an der Universität Kopenhagen durchgeführt. Ohne seine inspirierende Betreuung, seine menschlichen und fachlichen Qualitäten wäre die Durchführung der Arbeit nicht möglich gewesen. Dafür und für sein in mich gesetztes Vertrauen bin ich Niels aufrichtig dankbar.

Das gesamte Labor hatte natürlich großen Anteil am Gelingen dieses Forschungsprojektes. Besonders Mette Nielsen, Teis Jensen und Johannes Brockdorff seien hier für die zahllosen fruchtbaren Diskussionen im Labor und die Schaffung einer wunderbaren Arbeitsatmosphäre gedankt.

Ohne die vorbehaltslose Unterstützung und die gezeigte Geduld meiner Eltern und meiner zukünftigen Frau Rikke hätte ich dieses Projekt sicher nicht beenden können. Für diese Erfahrung, und für das Gefühl immer auf ihre Hilfe setzen zu können, werde ich ihnen immer dankbar sein.

Mein besonderer Dank geht an meine Freunde Nicolai, Bogdan, Sten und Reinhard und die Bitte mir zu verzeihen, dass ihnen durch meine Arbeit so oft wertvolle, gemeinsame Zeit vorenthalten wurde.

Vielen Dank auch an Tilo Schientek für die Korrektur dieser Arbeit.

Dem Dyssegård Fond danke für die Anerkennung meiner Arbeit durch die Verleihung ihres Forscher-Preises und die damit verbundene, zusätzliche Motivation.

Die Durchführung eines Forschungsprojektes ist nicht zeit-, sondern auch kostenaufwendig. Hiermit möchte ich den folgenden Institutionen für ihre finanzielle Unterstützung meines Projektes oder des Labors danken;

Alfred Benzon Fond, Fonden fra 17/12-1981, DARC, Forskningsrådet, Lundbeck Fonden, Toyota Fonden, Løvens Kemiske Fabriks Forskningsfonden, Hørslev Fonden, Daimler Benz Stiftung, DAAD;