ZUSAMMENFASSUNG

Bisher sind Etiologie und Pathogenese chronisch entzündlicher Darmerkrankungen (CED), Colitis ulcerosa und Morbus Crohn, nicht vollständig geklärt. Derzeit geht man von einem Zusammenspiel dreier Faktoren aus, die an der Entstehung und der Chronizität der Entzündung beteiligt sind: der genetischen Prädisposition, Umwelteinflüssen und immunologischen Faktoren. Da γδ T-Zellen immun-regulatorisches Potential besitzen und im Tiermodell protektive Effekte bei anderen entzündlichen Erkrankungen wie Arthritis, Diabetes und Lupus zeigten, wurde ihre Rolle bei CED näher untersucht.

In verschiedenen CED-Tiermodellen (induzierbare und genetische) konnte in einem ersten Schritt gezeigt werden, dass sich eine Depletion/Defizienz der γδ T-Zellen negativ auf die Entstehung und den Verlauf einer intestinalen Entzündung auswirkt. Infolge dieser γδ T-Zelldepletion/defizienz wiesen die Tiere eine schwerwiegende Schädigung der intestinalen Mukosa auf, zeigten eine erhöhte Sekretion proinflammatorischer und eine erniedrigte Sekretion antiinflammatorischer Zytokine sowie in einigen Fällen eine erhöhte Mortalität.

In einem zweiten Schritt wurde der Einfluss eines γδ T-Zelltransfers auf die Entstehung und den Verlauf der CED in einem chemisch-induzierten Tiermodell untersucht. Die transferierten γδ T-Zellen stammten entweder von Wildtyp Mäusen oder wurden aus Interleukin-10 transgenen Tieren isoliert. Unabhängig vom Spender wirkten sich die transferierten γδ T-Zellen protektiv auf die Entstehung und den Verlauf einer chemisch-induzierten Colitis aus. Die Tiere zeigten ein verlängertes Überleben, eine verminderte intestinale Schädigung und eine erhöhte Sekretion antiinflammatorischer Zytokine sowie eine erniedrigte Sekretion proinflammatorischer Zytokine. Der γδ T-Zelltransfer bei etablierter Colitis zeigte zwar keinen Einfluss auf die Mortalität, das mukosale Epithel der Tiere war jedoch weniger geschädigt als das untransferierter Tiere. Gleichzeitig war die Sekretion antiinflammatorischer Zytokine erhöht, die proinflammatorischer Zytokine erniedrigt.

Da sich im Tiermodell die Depletion/Defizienz von γδ T-Zellen auf das Entzündungsgeschehen bei CED negativ und der Transfer positiv bzw. protektiv auswirkt, scheinen γδ T-Zellen einen protektiven Effekt auf das mukosale Epithel sowie einen regulatorischen Effekt auf das intestinale Immunsystem auszuüben. Diese Effekte vermitteln sie vermutlich über die Regulation der Zytokindisbalance, die

Suppression von unkontrolliert proliferierenden Entzündungszellen und ihre Beteiligung an der epithelialen Regeneration. Dieses Potenzial wurde *in vitro* näher untersucht. Es zeigte sich, dass humane γδ T-Zellen anerg sind und das Wachstum von $CD4^+$ T-Zellen supprimieren. Diese Suppression üben sie schon in geringen Zellverhältnissen aus. Ferner sezernieren sie vernachlässigbar geringe Mengen an IL-2, jedoch große Mengen an IL-4, IL-10, TGF-β und IFN-γ. So konnte erstmals gezeigt werden, dass γδ T-Zellen sowohl protektives als auch regulatorisches Potenzial besitzen. Diese Eigenschaften machen sie für den therapeutischen Einsatz zur Behandlung von CED interessant. Einerseits proliferieren γδ T-Zellen aufgrund ihrer Anergie nicht unkontrolliert, andererseits können sie die unkontrollierte Ausbreitung autoreaktiver Entzündungszellen hemmen. Durch die Sekretion von Th2-Zytokinen und des Wachstumsfaktors TGF-β sind sie an der epithelialen Regeneration beteiligt und wirken antiinflammatorisch. Die Sekretion von IFN-γ sowie die Regulation der IFN-γ-Produktion durch αβ T-Zellen befähigt sie gleichzeitig zur Infekt- und Tumorabwehr. Daher wurde eine Anreicherung der γδ T-Zellen aus humanen Blutlymphozyten durch verschiedene Stimulationen getestet. Dabei erwiesen sich zwei Stimulationsansätze mit synthetischen Phospho-Antigenen als erfolgversprechend. Zum einen die Stimulation mit Isopentenylpyrophosphat, zum anderen die Stimulation mit Alendronat unter Th2-„priming“ Bedingungen. In beiden Ansätzen war für eine erfolgreiche Anreicherung die Zugabe von rekombinantem IL-2 essentiell. Allerdings müssen diese Anreicherungsansätze noch optimiert werden. Zusätzlich sollte geklärt werden, ob die angereicherten γδ T-Zellen unter der Kultivierung ihren regulatorischen Phänotyp beibehalten haben.

Zusammenfassend wird festgestellt, dass γδ T-Zellen einen neuen Ansatzpunkt für die Therapie von CED darstellen, jedoch weiterführende Untersuchungen hinsichtlich ihrer Generierung und ihres therapeutischen Einsatzes erforderlich sind.

Summary

So far, the etiology and pathogenesis of inflammatory bowel disease (IBD), ulcerative Colitis and Crohn´s Disease, is unclear. At present, three factors, that is genetic predisposition, environmental influences, and immunological factors seem responsible for the development and perpetuation of intestinal inflammation. As γδ T cells possess immunoregulatory potential as well as protective effects in other animal models of inflammatory diseases e.g., arthritis, diabetes und lupus, their role in IBD was examined.

First, it was shown in various IBD animal models (inducible and genetic), that the depletion of and deficiency in γδ T cells affected the development and the course of intestinal inflammation negatively. Due to γδ T cell depletion/deficiency the animals displayed a severely damaged intestinal mucosa and increased secretion of proinflammatory as well as decreased secretion of antiinflammatory cytokines with increased mortality in some cases.

Second, the influence of γδ T cell transfer on the development and the course of IBD was examined in a chemically induced animal model. The γδ T cells transferred were isolated from wildtype mice or from interleukin-10 transgene animals. These γδ T cells acted independently from their origin protectively on the development and the course of chemically induced colitis. The animals showed increased survival, diminished intestinal injury, and an increased secretion of antiinflammatory cytokines as well as a decreased secretion of proinflammatory cytokines. The γδ T cell transfer at established colitis though not influencing the mortality, resulted in less damaged mucosal epithelium. Simultaneously, the secretion of antiinflammatory cytokines was increased, while the secretion of proinflammatory cytokines was decreased.

As the depletion of and the deficiency in γδ cells affected the inflammation in IBD negatively, while the transfer of γδ T cells had a positive and protective effect, respectively, it seems likely, that γδ T cells have a protective effect on the mucosal epithelium as well as a regulatory effect on the intestinal immune system. These effects seem to be mediated by the regulation of the cytokine dysbalance, the suppression of uncontrolled proliferating inflammatory cells, and their involvement in epithelial regeneration. This potential was examined more closely in *in vitro* experiments. The *in vitro* data showed, that human γδ T cells are anergic and suppress the growth of $CD4^+$ T cells. They mediate this suppressive effect even at

low cell ratios. Additionally, they secrete low amounts of IL-2, but high quantities of IL-4, IL-10, TGF-β, and IFN-γ. The data presented herein showed for the first time, that γδ T cells possess both, protective and regulatory potential. These properties of γδ T cells make them an interesting candidate for IBD immunotherapy. On the one hand, due to their anergy γδ T cells do not proliferate in an autocrine fashion and are able to suppress growth of autoreactive inflammatory cells. Due to their secretion of Th2 cytokines and the growth factor TGF-β, they are involved in epithelial regeneration and act antiinflammatorily. Further, they are able to prevent infections and tumor formation due to their secretion of IFN-γ as well as their regulation of IFN-γ production by αβ T cells. Therefore, various stimulations for the enrichment of γδ T cells from human peripheral blood lymphocytes were tested. Two approaches employing synthetic phosphoantigens seem promising; the stimulation with Isopentenylpyrophosphate and the stimulation with Alendronate under Th2-priming conditions. The addition of endogenous IL-2 was essential for successful enrichment using both methods. Still, the expansion process needs further optimization. Additionally, it is necessary to clarify if the γδ T cells maintain their regulatory phenotype under these culture conditions.

In summary, γδ T cells exhibit a new therapeutical approach in treatment of IBD, while further experiments regarding their generation and their therapeutical application are necessary.

Bibliographie

1. Neurath MF, Schurmann G. [Immunopathogenesis of inflammatory bowel diseases]. Chirurg 2000;71:30-40.
2. Sartor RB. Pathogenesis and immune mechanisms of chronic inflammatory bowel diseases. Am J Gastroenterol 1997;92:5S-11S.
3. Rogler G, Andus T. Cytokines in inflammatory bowel disease. World J Surg 1998;22:382-9.
4. Boirivant M, Marini M, Di Felice G, et al. Lamina propria T cells in Crohn's disease and other gastrointestinal inflammation show defective CD2 pathway-induced apoptosis. Gastroenterology 1999;116:557-65.
5. Neurath MF, Finotto S, Fuss I, et al. Regulation of T-cell apoptosis in inflammatory bowel disease: to die or not to die, that is the mucosal question. Trends Immunol 2001;22:21-6.
6. ten Hove T, van Montfrans C, Peppelenbosch MP, van Deventer SJ. Infliximab treatment induces apoptosis of lamina propria T lymphocytes in Crohn's disease. Gut 2002;50:206-11.
7. Steeber DA, Tedder TF. Adhesion molecule cascades direct lymphocyte recirculation and leukocyte migration during inflammation. Immunol Res 2000;22:299-317.
8. Picarella D, Hurlbut P, Rottman J, et al. Monoclonal antibodies specific for beta 7 integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) reduce inflammation in the colon of scid mice reconstituted with CD45RBhigh CD4+ T cells. J Immunol 1997;158:2099-106.
9. Sydora BC, Wagner N, Lohler J, et al. beta7 Integrin expression is not required for the localization of T cells to the intestine and colitis pathogenesis. Clin Exp Immunol 2002;129:35-42.
10. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. N Engl J Med 2003;348:24-32.
11. Shevach EM. Regulatory T cells in autoimmmunity*. Annu Rev Immunol 2000;18:423-49.
12. Roncarolo MG, Bacchetta R, Bordignon C, Narula S, Levings MK. Type 1 T regulatory cells. Immunol Rev 2001;182:68-79.
13. Dieckmann D, Plottner H, Berchtold S, Berger T, Schuler G. Ex vivo isolation and characterization of CD4(+)CD25(+) T cells with regulatory properties from human blood. J Exp Med 2001;193:1303-10.
14. Papiernik M, de Moraes ML, Pontoux C, Vasseur F, Penit C. Regulatory CD4 T cells: expression of IL-2R alpha chain, resistance to clonal deletion and IL-2 dependency. Int Immunol 1998;10:371-8.
15. Jonuleit H, Schmitt E, Stassen M, et al. Identification and functional characterization of human CD4(+)CD25(+) T cells with regulatory properties isolated from peripheral blood. J Exp Med 2001;193:1285-94.
16. Asseman C, Mauze S, Leach MW, Coffman RL, Powrie F. An essential role for interleukin 10 in the function of regulatory T cells that inhibit intestinal inflammation. J Exp Med 1999;190:995-1004.
17. Levings MK, Bacchetta R, Schulz U, Roncarolo MG. The role of IL-10 and TGF-beta in the differentiation and effector function of T regulatory cells. Int Arch Allergy Immunol 2002;129:263-76.

18. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. Science 2003;299:1057-61.
19. Groux H, O'Garra A, Bigler M, et al. A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature 1997;389:737-42.
20. Singh B, Read S, Asseman C, et al. Control of intestinal inflammation by regulatory T cells. Immunol Rev 2001;182:190-200.
21. Asseman C, Fowler S, Powrie F. Control of experimental inflammatory bowel disease by regulatory T cells. Am J Respir Crit Care Med 2000;162:S185-9.
22. Levings MK, Sangregorio R, Roncarolo MG. Human cd25(+)cd4(+) t regulatory cells suppress naive and memory T cell proliferation and can be expanded in vitro without loss of function. J Exp Med 2001;193:1295-302.
23. Groux H. An overview of regulatory T cells. Microbes Infect 2001;3:883-9.
24. Levings MK, Sangregorio R, Sartirana C, et al. Human CD25+CD4+ T suppressor cell clones produce transforming growth factor beta, but not interleukin 10, and are distinct from type 1 T regulatory cells. J Exp Med 2002;196:1335-46.
25. Mendel I, Shevach EM. The IL-10-producing competence of Th2 cells generated in vitro is IL-4 dependent. Eur J Immunol 2002;32:3216-24.
26. Lehmann J, Huehn J, de la Rosa M, et al. Expression of the integrin alpha Ebeta 7 identifies unique subsets of CD25+ as well as CD25- regulatory T cells. Proc Natl Acad Sci U S A 2002;99:13031-6.
27. Annacker O, Pimenta-Araujo R, Burlen-Defranoux O, et al. CD25+ CD4+ T cells regulate the expansion of peripheral CD4 T cells through the production of IL-10. J Immunol 2001;166:3008-18.
28. Stephens LA, Mason D. CD25 is a marker for CD4+ thymocytes that prevent autoimmune diabetes in rats, but peripheral T cells with this function are found in both CD25+ and CD25- subpopulations. J Immunol 2000;165:3105-10.
29. Bank I, DePinho RA, Brenner MB, et al. A functional T3 molecule associated with a novel heterodimer on the surface of immature human thymocytes. Nature 1986;322:179-81.
30. Brenner MB, McLean J, Dialynas DP, et al. Identification of a putative second T-cell receptor. Nature 1986;322:145-9.
31. Allison JP, Havran WL. The immunobiology of T cells with invariant gamma delta antigen receptors. Annu Rev Immunol 1991;9:679-705.
32. Hayday AC. [gamma][delta] cells: a right time and a right place for a conserved third way of protection. Annu Rev Immunol 2000;18:975-1026.
33. Kaufmann SH. gamma/delta and other unconventional T lymphocytes: what do they see and what do they do? Proc Natl Acad Sci U S A 1996;93:2272-9.
34. Kabelitz D, Glatzel A, Wesch D. Antigen recognition by human gammadelta T lymphocytes. Int Arch Allergy Immunol 2000;122:1-7.
35. Kabelitz D, Marischen L, Oberg HH, Holtmeier W, Wesch D. Epithelial Defence by gammadelta T Cells. Int Arch Allergy Immunol 2005;137:73-81.
36. Haas W, Pereira P, Tonegawa S. Gamma/delta cells. Annu Rev Immunol 1993;11:637-85.
37. Kagnoff MF. Current concepts in mucosal immunity. III. Ontogeny and function of gamma delta T cells in the intestine. Am J Physiol 1998;274:G455-8.
38. Hayday A, Theodoridis E, Ramsburg E, Shires J. Intraepithelial lymphocytes: exploring the Third Way in immunology. Nat Immunol 2001;2:997-1003.
39. Andrew EM, Carding SR. Murine gammadelta T cells in infections: beneficial or deleterious? Microbes Infect 2005.

40. Ferrick DA, Schrenzel MD, Mulvania T, et al. Differential production of interferon-gamma and interleukin-4 in response to Th1- and Th2-stimulating pathogens by gamma delta T cells in vivo. Nature 1995;373:255-7.
41. Weintraub BC, Jackson MR, Hedrick SM. Gamma delta T cells can recognize nonclassical MHC in the absence of conventional antigenic peptides. J Immunol 1994;153:3051-8.
42. Guehler SR, Bluestone JA, Barrett TA. Activation and peripheral expansion of murine T-cell receptor gamma delta intraepithelial lymphocytes. Gastroenterology 1999;116:327-34.
43. Kunzmann V, Bauer E, Feurle J, et al. Stimulation of gammadelta T cells by aminobisphosphonates and induction of antiplasma cell activity in multiple myeloma. Blood 2000;96:384-92.
44. Bonneville M, Fournie JJ. Sensing cell stress and transformation through Vgamma9Vdelta2 T cell-mediated recognition of the isoprenoid pathway metabolites. Microbes Infect 2005;7:503-9.
45. Bukowski JF, Morita CT, Brenner MB. Human gamma delta T cells recognize alkylamines derived from microbes, edible plants, and tea: implications for innate immunity. Immunity 1999;11:57-65.
46. Morita CT, Lee HK, Wang H, et al. Structural features of nonpeptide prenyl pyrophosphates that determine their antigenicity for human gamma delta T cells. J Immunol 2001;167:36-41.
47. Allison TJ, Garboczi DN. Structure of gammadelta T cell receptors and their recognition of non-peptide antigens. Mol Immunol 2002;38:1051-61.
48. Havran WL, Chien YH, Allison JP. Recognition of self antigens by skin-derived T cells with invariant gamma delta antigen receptors. Science 1991;252:1430-2.
49. Hayday A, Geng L. Gamma delta cells regulate autoimmunity. Curr Opin Immunol 1997;9:884-9.
50. Boismenu R, Chen Y, Havran WL. The role of intraepithelial gammadelta T cells: a gut-feeling. Microbes Infect 1999;1:235-40.
51. Lopez RD. Human gammadelta-T cells in adoptive immunotherapy of malignant and infectious diseases. Immunol Res 2002;26:207-21.
52. Burns J, Lobo S, Bartholomew B. Requirement for CD4+ T cells in the gammadelta T cell proliferative response to Daudi Burkitt's lymphoma. Cell Immunol 1996;174:19-24.
53. Fayen JD, Tykocinski ML. The expansion of human gammadelta T cells in response to Daudi cells requires the participation of CD4+ T cells. Immunology 1999;97:272-9.
54. Zocchi MR, Poggi A. Role of gammadelta T lymphocytes in tumor defense. Front Biosci 2004;9:2588-604.
55. Spada FM, Grant EP, Peters PJ, et al. Self-recognition of CD1 by gamma/delta T cells: implications for innate immunity. J Exp Med 2000;191:937-48.
56. Aydintug MK, Roark CL, Yin X, et al. Detection of cell surface ligands for the gamma delta TCR using soluble TCRs. J Immunol 2004;172:4167-75.
57. Havran WL. A role for epithelial gammadelta T cells in tissue repair. Immunol Res 2000;21:63-9.
58. Jameson JM, Cauvi G, Sharp LL, Witherden DA, Havran WL. {gamma}{delta} T cell-induced hyaluronan production by epithelial cells regulates inflammation. J Exp Med 2005;201:1269-79.

59. Born WK, O'Brien RL. The healing touch of epidermal T cells. Nat Med 2002;8:560-1.
60. King DP, Hyde DM, Jackson KA, et al. Cutting edge: protective response to pulmonary injury requires gamma delta T lymphocytes. J Immunol 1999;162:5033-6.
61. Boismenu R. Function of intestinal gammadelta T cells. Immunol Res 2000;21:123-7.
62. Chen Y, Chou K, Fuchs E, Havran WL, Boismenu R. Protection of the intestinal mucosa by intraepithelial gamma delta T cells. Proc Natl Acad Sci U S A 2002;99:14338-43.
63. Makita S, Kanai T, Matsumoto S, et al. The role of cryptopatch-derived intraepithelial lymphocytes in the development of chronic ileocecitis. Scand J Immunol 2003;58:428-35.
64. Boismenu R, Havran WL. Modulation of epithelial cell growth by intraepithelial gamma delta T cells. Science 1994;266:1253-5.
65. Workalemahu G, Foerster M, Kroegel C, Braun RK. Human gamma delta-T lymphocytes express and synthesize connective tissue growth factor: effect of IL-15 and TGF-beta 1 and comparison with alpha beta-T lymphocytes. J Immunol 2003;170:153-7.
66. Workalemahu G, Foerster M, Kroegel C. Expression and synthesis of fibroblast growth factor-9 in human gammadelta T-lymphocytes. Response to isopentenyl pyrophosphate and TGF-beta1/IL-15. J Leukoc Biol 2004;75:657-63.
67. Born W, Cady C, Jones-Carson J, et al. Immunoregulatory functions of gamma delta T cells. Adv Immunol 1999;71:77-144.
68. Tsukaguchi K, de Lange B, Boom WH. Differential regulation of IFN-gamma, TNF-alpha, and IL-10 production by CD4(+) alphabetaTCR+ T cells and vdelta2(+) gammadelta T cells in response to monocytes infected with Mycobacterium tuberculosis-H37Ra. Cell Immunol 1999;194:12-20.
69. Skeen MJ, Rix EP, Freeman MM, Ziegler HK. Exaggerated proinflammatory and Th1 responses in the absence of gamma/delta T cells after infection with Listeria monocytogenes. Infect Immun 2001;69:7213-23.
70. O'Brien RL, Yin X, Huber SA, Ikuta K, Born WK. Depletion of a gamma delta T cell subset can increase host resistance to a bacterial infection. J Immunol 2000;165:6472-9.
71. Diaz-Bardales BM, Novaski SM, Goes AE, et al. Modulation of the severity of experimental autoimmune encephalomyelitis by gammadelta T lymphocytes activated by mycobacterial antigens. Immunol Invest 2001;30:245-58.
72. Inagaki-Ohara K, Chinen T, Matsuzaki G, et al. Mucosal T Cells Bearing TCRgammadelta Play a Protective Role in Intestinal Inflammation. J Immunol 2004;173:1390-1398.
73. Kaufmann SH, Blum C, Yamamoto S. Crosstalk between alpha/beta T cells and gamma/delta T cells in vivo: activation of alpha/beta T-cell responses after gamma/delta T-cell modulation with the monoclonal antibody GL3. Proc Natl Acad Sci U S A 1993;90:9620-4.
74. Roberts SJ, Smith AL, West AB, et al. T-cell alpha beta + and gamma delta + deficient mice display abnormal but distinct phenotypes toward a natural, widespread infection of the intestinal epithelium. Proc Natl Acad Sci U S A 1996;93:11774-9.

75. Egan PJ, Carding SR. Downmodulation of the inflammatory response to bacterial infection by gammadelta T cells cytotoxic for activated macrophages. J Exp Med 2000;191:2145-58.
76. Dalton JE, Howell G, Pearson J, Scott P, Carding SR. Fas-Fas ligand interactions are essential for the binding to and killing of activated macrophages by gamma delta T cells. J Immunol 2004;173:3660-7.
77. Born WK, Lahn M, Takeda K, et al. Role of gammadelta T cells in protecting normal airway function. Respir Res 2000;1:151-8.
78. Lahn M, Kanehiro A, Takeda K, et al. gammadelta T cells as regulators of airway hyperresponsiveness. Int Arch Allergy Immunol 2001;125:203-10.
79. Simpson SJ, Hollander GA, Mizoguchi E, et al. Expression of pro-inflammatory cytokines by TCR alpha beta+ and TCR gamma delta+ T cells in an experimental model of colitis. Eur J Immunol 1997;27:17-25.
80. Pennington DJ, Silva-Santos B, Shires J, et al. The inter-relatedness and interdependence of mouse T cell receptor gammadelta+ and alphabeta+ cells. Nat Immunol 2003;4:991-8.
81. Kawaguchi-Miyashita M, Shimada S, Kurosu H, et al. An accessory role of TCRgammadelta (+) cells in the exacerbation of inflammatory bowel disease in TCRalpha mutant mice. Eur J Immunol 2001;31:980-8.
82. Szczepanik M, Gryglewski A, Bryniarski K, Stachura J, Ptak W. Experimental inflammatory bowel disease--role of T cells. J Physiol Pharmacol 2000;51:333-46.
83. Inagaki-Ohara K, Sawaguchi A, Suganuma T, Matsuzaki G, Nawa Y. Intraepithelial lymphocytes express junctional molecules in murine small intestine. Biochem Biophys Res Commun 2005;331:977-83.
84. Tsuchiya T, Fukuda S, Hamada H, et al. Role of gamma delta T cells in the inflammatory response of experimental colitis mice. J Immunol 2003;171:5507-13.
85. Leung FW, Heng MC, Allen S, et al. Involvement of luminal bacteria, heat shock protein 60, macrophages and gammadelta T cells in dextran sulfate sodium-induced colitis in rats. Dig Dis Sci 2000;45:1472-9.
86. Hoffmann JC, Peters K, Henschke S, et al. Role of T lymphocytes in rat 2,4,6-trinitrobenzene sulphonic acid (TNBS) induced colitis: increased mortality after gammadelta T cell depletion and no effect of alphabeta T cell depletion. Gut 2001;48:489-95.
87. Poussier P, Julius M. Thymus independent T cell development and selection in the intestinal epithelium. Annu Rev Immunol 1994;12:521-53.
88. Shires J, Theodoridis E, Hayday AC. Biological insights into TCRgammadelta+ and TCRalphabeta+ intraepithelial lymphocytes provided by serial analysis of gene expression (SAGE). Immunity 2001;15:419-34.
89. Yeung MM, Melgar S, Baranov V, et al. Characterisation of mucosal lymphoid aggregates in ulcerative colitis: immune cell phenotype and TcR-gammadelta expression. Gut 2000;47:215-27.
90. Kanazawa H, Ishiguro Y, Munakata A, Morita T. Multiple accumulation of Vdelta2+ gammadelta T-cell clonotypes in intestinal mucosa from patients with Crohn's disease. Dig Dis Sci 2001;46:410-6.
91. McVay LD, Li B, Biancaniello R, et al. Changes in human mucosal gamma delta T cell repertoire and function associated with the disease process in inflammatory bowel disease. Mol Med 1997;3:183-203.

92. Kirsner JB. Experimental "colitis" with particular reference to hypersensitivity reactions in the colon. Gastroenterology 1961;40:307-12.
93. Hoffmann JC, Pawlowski NN, Kuhl AA, Hohne W, Zeitz M. Animal models of inflammatory bowel disease: an overview. Pathobiology 2002;70:121-30.
94. Elson CO, Sartor RB, Tennyson GS, Riddell RH. Experimental models of inflammatory bowel disease. Gastroenterology 1995;109:1344-67.
95. Cooper HS, Murthy SN, Shah RS, Sedergran DJ. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. Lab Invest 1993;69:238-49.
96. Okayasu I, Hatakeyama S, Yamada M, et al. A novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. Gastroenterology 1990;98:694-702.
97. Mahler M, Bristol IJ, Sundberg JP, et al. Genetic analysis of susceptibility to dextran sulfate sodium-induced colitis in mice. Genomics 1999;55:147-56.
98. Renes IB, Verburg M, Van Nispen DJ, et al. Epithelial proliferation, cell death, and gene expression in experimental colitis: alterations in carbonic anhydrase I, mucin MUC2, and trefoil factor 3 expression. Int J Colorectal Dis 2002;17:317-26.
99. Dieleman LA, Palmen MJ, Akol H, et al. Chronic experimental colitis induced by dextran sulphate sodium (DSS) is characterized by Th1 and Th2 cytokines. Clin Exp Immunol 1998;114:385-91.
100. Okayasu I, Ohkusa T, Kajiura K, Kanno J, Sakamoto S. Promotion of colorectal neoplasia in experimental murine ulcerative colitis. Gut 1996;39:87-92.
101. Tanaka T, Kohno H, Suzuki R, et al. A novel inflammation-related mouse colon carcinogenesis model induced by azoxymethane and dextran sodium sulfate. Cancer Sci 2003;94:965-73.
102. Morris GP, Beck PL, Herridge MS, et al. Hapten-induced model of chronic inflammation and ulceration in the rat colon. Gastroenterology 1989;96:795-803.
103. Neurath MF, Fuss I, Kelsall BL, Stuber E, Strober W. Antibodies to interleukin 12 abrogate established experimental colitis in mice. J Exp Med 1995;182:1281-90.
104. Dohi T, Fujihashi K, Rennert PD, et al. Hapten-induced colitis is associated with colonic patch hypertrophy and T helper cell 2-type responses. J Exp Med 1999;189:1169-80.
105. Wirtz S, Neurath MF. Animal models of intestinal inflammation: new insights into the molecular pathogenesis and immunotherapy of inflammatory bowel disease. Int J Colorectal Dis 2000;15:144-60.
106. Iijima H, Neurath MF, Nagaishi T, et al. Specific Regulation of T Helper Cell 1-mediated Murine Colitis by CEACAM1. J Exp Med 2004;199:471-82.
107. Wallace JL, Le T, Carter L, Appleyard CB, Beck PL. Hapten-induced chronic colitis in the rat: alternatives to trinitrobenzene sulfonic acid. J Pharmacol Toxicol Methods 1995;33:237-9.
108. Boismenu R, Chen Y. Insights from mouse models of colitis. J Leukoc Biol 2000;67:267-78.
109. Fuss IJ, Neurath M, Boirivant M, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative

colitis LP cells manifest increased secretion of IL-5. J Immunol 1996;157:1261-70.
110. Kuhn R, Lohler J, Rennick D, Rajewsky K, Muller W. Interleukin-10-deficient mice develop chronic enterocolitis. Cell 1993;75:263-74.
111. Sadlack B, Merz H, Schorle H, et al. Ulcerative colitis-like disease in mice with a disrupted interleukin-2 gene. Cell 1993;75:253-61.
112. Mombaerts P, Mizoguchi E, Grusby MJ, et al. Spontaneous development of inflammatory bowel disease in T cell receptor mutant mice. Cell 1993;75:274-82.
113. Autenrieth IB, Bucheler N, Bohn E, Heinze G, Horak I. Cytokine mRNA expression in intestinal tissue of interleukin-2 deficient mice with bowel inflammation. Gut 1997;41:793-800.
114. Horak I, Lohler J, Ma A, Smith KA. Interleukin-2 deficient mice: a new model to study autoimmunity and self-tolerance. Immunol Rev 1995;148:35-44.
115. Simpson SJ, Mizoguchi E, Allen D, Bhan AK, Terhorst C. Evidence that CD4+, but not CD8+ T cells are responsible for murine interleukin-2-deficient colitis. Eur J Immunol 1995;25:2618-25.
116. Ma A, Datta M, Margosian E, Chen J, Horak I. T cells, but not B cells, are required for bowel inflammation in interleukin 2-deficient mice. J Exp Med 1995;182:1567-72.
117. Schultz M, Clarke SH, Arnold LW, Sartor RB, Tonkonogy SL. Disrupted B-lymphocyte development and survival in interleukin-2-deficient mice. Immunology 2001;104:127-34.
118. Ehrhardt RO, Ludviksson BR, Gray B, Neurath M, Strober W. Induction and prevention of colonic inflammation in IL-2-deficient mice. J Immunol 1997;158:566-73.
119. Schultz M, Tonkonogy SL, Sellon RK, et al. IL-2-deficient mice raised under germfree conditions develop delayed mild focal intestinal inflammation. Am J Physiol 1999;276:G1461-72.
120. Baumgart DC, Olivier WA, Reya T, et al. Mechanisms of intestinal epithelial cell injury and colitis in interleukin 2 (IL2)-deficient mice. Cell Immunol 1998;187:52-66.
121. Meijssen MA, Brandwein SL, Reinecker HC, Bhan AK, Podolsky DK. Alteration of gene expression by intestinal epithelial cells precedes colitis in interleukin-2-deficient mice. Am J Physiol 1998;274:G472-9.
122. Waidmann M, Allemand Y, Lehmann J, et al. Microflora reactive IL-10 producing regulatory T cells are present in the colon of IL-2 deficient mice but lack efficacious inhibition of IFN-gamma and TNF-alpha production. Gut 2002;50:170-9.
123. Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut-associated immunopathologies. Immunity 1999;10:387-98.
124. Pizarro TT, Arseneau KO, Cominelli F. Lessons from genetically engineered animal models XI. Novel mouse models to study pathogenic mechanisms of Crohn's disease. Am J Physiol Gastrointest Liver Physiol 2000;278:G665-9.
125. Matsumoto S, Okabe Y, Setoyama H, et al. Inflammatory bowel disease-like enteritis and caecitis in a senescence accelerated mouse P1/Yit strain. Gut 1998;43:71-8.

126. Podolsky DK. Inflammatory bowel disease (1). N Engl J Med 1991;325:928-37.
127. Van Deventer SJ. Tumour necrosis factor and Crohn's disease. Gut 1997;40:443-8.
128. Neurath MF, Fuss I, Pasparakis M, et al. Predominant pathogenic role of tumor necrosis factor in experimental colitis in mice. Eur J Immunol 1997;27:1743-50.
129. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029-35.
130. Ke Y, Pearce K, Lake JP, Ziegler HK, Kapp JA. Gamma delta T lymphocytes regulate the induction and maintenance of oral tolerance. J Immunol 1997;158:3610-8.
131. Kanai T, Watanabe M, Okazawa A, et al. Macrophage-derived IL-18-mediated intestinal inflammation in the murine model of Crohn's disease. Gastroenterology 2001;121:875-88.
132. Siegmund B, Fantuzzi G, Rieder F, et al. Neutralization of interleukin-18 reduces severity in murine colitis and intestinal IFN-gamma and TNF-alpha production. Am J Physiol Regul Integr Comp Physiol 2001;281:R1264-73.
133. Strober W, Kelsall B, Fuss I, et al. Reciprocal IFN-gamma and TGF-beta responses regulate the occurrence of mucosal inflammation. Immunol Today 1997;18:61-4.
134. Ginzberg HH, Cherapanov V, Dong Q, et al. Neutrophil-mediated epithelial injury during transmigration: role of elastase. Am J Physiol Gastrointest Liver Physiol 2001;281:G705-17.
135. Hurley BP, McCormick BA. Intestinal epithelial defense systems protect against bacterial threats. Curr Gastroenterol Rep 2004;6:355-61.
136. Tazuke Y, Drongowski RA, Teitelbaum DH, Coran AG. Interleukin-6 changes tight junction permeability and intracellular phospholipid content in a human enterocyte cell culture model. Pediatr Surg Int 2003;19:321-5.
137. Wang L, Walia B, Evans J, et al. IL-6 induces NF-kappa B activation in the intestinal epithelia. J Immunol 2003;171:3194-201.
138. Atreya R, Neurath MF. Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. Clin Rev Allergy Immunol 2005;28:187-96.
139. Ito H. IL-6 and Crohn's disease. Curr Drug Targets Inflamm Allergy 2003;2:125-30.
140. Murata Y, Ishiguro Y, Itoh J, Munakata A, Yoshida Y. The role of proinflammatory and immunoregulatory cytokines in the pathogenesis of ulcerative colitis. J Gastroenterol 1995;30 Suppl 8:56-60.
141. Gross V, Andus T, Caesar I, Roth M, Scholmerich J. Evidence for continuous stimulation of interleukin-6 production in Crohn's disease. Gastroenterology 1992;102:514-9.
142. Mudter J, Wirtz S, Galle PR, Neurath MF. A new model of chronic colitis in SCID mice induced by adoptive transfer of CD62L+ CD4+ T cells: insights into the regulatory role of interleukin-6 on apoptosis. Pathobiology 2002;70:170-6.
143. Ito H. Treatment of Crohn's disease with anti-IL-6 receptor antibody. J Gastroenterol 2005;40 Suppl 16:32-4.
144. Siegmund B, Lehr HA, Fantuzzi G. Leptin: a pivotal mediator of intestinal inflammation in mice. Gastroenterology 2002;122:2011-25.

145. Melgar S, Yeung MM, Bas A, et al. Over-expression of interleukin 10 in mucosal T cells of patients with active ulcerative colitis. Clin Exp Immunol 2003;134:127-37.
146. Hahm KB, Im YH, Parks TW, et al. Loss of transforming growth factor beta signalling in the intestine contributes to tissue injury in inflammatory bowel disease. Gut 2001;49:190-8.
147. Beck PL, Rosenberg IM, Xavier RJ, et al. Transforming growth factor-beta mediates intestinal healing and susceptibility to injury in vitro and in vivo through epithelial cells. Am J Pathol 2003;162:597-608.
148. Mammen JM, Matthews JB. Mucosal repair in the gastrointestinal tract. Crit Care Med 2003;31:S532-7.
149. Dignass AU. Mechanisms and modulation of intestinal epithelial repair. Inflamm Bowel Dis 2001;7:68-77.
150. Babyatsky MW, Rossiter G, Podolsky DK. Expression of transforming growth factors alpha and beta in colonic mucosa in inflammatory bowel disease. Gastroenterology 1996;110:975-84.
151. Thompson JS, Saxena SK, Sharp JG. Regulation of intestinal regeneration: new insights. Microsc Res Tech 2000;51:129-37.
152. Kulkarni AB, Huh CG, Becker D, et al. Transforming growth factor beta 1 null mutation in mice causes excessive inflammatory response and early death. Proc Natl Acad Sci U S A 1993;90:770-4.
153. Andus T, Targan SR, Deem R, Toyoda H. Measurement of tumor necrosis factor alpha mRNA in small numbers of cells by quantitative polymerase chain reaction. Reg Immunol 1993;5:11-7.
154. Reinecker HC, Steffen M, Witthoeft T, et al. Enhanced secretion of tumour necrosis factor-alpha, IL-6, and IL-1 beta by isolated lamina propria mononuclear cells from patients with ulcerative colitis and Crohn's disease. Clin Exp Immunol 1993;94:174-81.
155. Gratz R, Becker S, Sokolowski N, et al. Murine monoclonal anti-tNF antibody administration has a beneficial effect on inflammatory bowel disease that develops in IL-10 knockout mice. Dig Dis Sci 2002;47:1723-7.
156. Schaffer M, Fuchs N, Volker J, et al. Differential effect of tacrolimus on dermal and intestinal wound healing. J Invest Surg 2005;18:71-9.
157. Mori R, Kondo T, Ohshima T, Ishida Y, Mukaida N. Accelerated wound healing in tumor necrosis factor receptor p55-deficient mice with reduced leukocyte infiltration. Faseb J 2002;16:963-74.
158. Loncar MB, Al-azzeh ED, Sommer PS, et al. Tumour necrosis factor alpha and nuclear factor kappaB inhibit transcription of human TFF3 encoding a gastrointestinal healing peptide. Gut 2003;52:1297-303.
159. Itoh H, Beck PL, Inoue N, Xavier R, Podolsky DK. A paradoxical reduction in susceptibility to colonic injury upon targeted transgenic ablation of goblet cells. J Clin Invest 1999;104:1539-47.
160. Kinoshita K, Taupin DR, Itoh H, Podolsky DK. Distinct pathways of cell migration and antiapoptotic response to epithelial injury: structure-function analysis of human intestinal trefoil factor. Mol Cell Biol 2000;20:4680-90.
161. Kojouharoff G, Hans W, Obermeier F, et al. Neutralization of tumour necrosis factor (TNF) but not of IL-1 reduces inflammation in chronic dextran sulphate sodium-induced colitis in mice. Clin Exp Immunol 1997;107:353-8.
162. Brannigan AE, O'Connell PR, Hurley H, et al. Neutrophil apoptosis is delayed in patients with inflammatory bowel disease. Shock 2000;13:361-6.

163. Carter L, Wallace JL. Alterations in rat peripheral blood neutrophil function as a consequence of colitis. Dig Dis Sci 1995;40:192-7.
164. Palmen MJ, Dieleman LA, van der Ende MB, et al. Non-lymphoid and lymphoid cells in acute, chronic and relapsing experimental colitis. Clin Exp Immunol 1995;99:226-32.
165. Leibovich SJ, Ross R. The role of the macrophage in wound repair. A study with hydrocortisone and antimacrophage serum. Am J Pathol 1975;78:71-100.
166. Sylvia CJ. The role of neutrophil apoptosis in influencing tissue repair. J Wound Care 2003;12:13-6.
167. Park JE, Barbul A. Understanding the role of immune regulation in wound healing. Am J Surg 2004;187:11S-16S.
168. Canturk NZ, Esen N, Vural B, et al. The relationship between neutrophils and incisional wound healing. Skin Pharmacol Appl Skin Physiol 2001;14:108-16.
169. Dignass AU, Podolsky DK. Interleukin 2 modulates intestinal epithelial cell function in vitro. Exp Cell Res 1996;225:422-9.
170. Cua DJ, Groux H, Hinton DR, Stohlman SA, Coffman RL. Transgenic interleukin 10 prevents induction of experimental autoimmune encephalomyelitis. J Exp Med 1999;189:1005-10.
171. Papadakis KA, Targan SR. Role of cytokines in the pathogenesis of inflammatory bowel disease. Annu Rev Med 2000;51:289-98.
172. Fuss IJ, Boirivant M, Lacy B, Strober W. The interrelated roles of TGF-beta and IL-10 in the regulation of experimental colitis. J Immunol 2002;168:900-8.
173. Kucharzik T, Stoll R, Lugering N, Domschke W. Circulating antiinflammatory cytokine IL-10 in patients with inflammatory bowel disease (IBD). Clin Exp Immunol 1995;100:452-6.
174. Schreiber S, Fedorak RN, Nielsen OH, et al. Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's Disease IL-10 Cooperative Study Group. Gastroenterology 2000;119:1461-72.
175. Fedorak RN, Gangl A, Elson CO, et al. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. Gastroenterology 2000;119:1473-82.
176. Fiorucci S, Distrutti E, Mencarelli A, et al. Inhibition of intestinal bacterial translocation with rifaximin modulates lamina propria monocytic cells reactivity and protects against inflammation in a rodent model of colitis. Digestion 2002;66:246-56.
177. Gardiner KR, Erwin PJ, Anderson NH, et al. Colonic bacteria and bacterial translocation in experimental colitis. Br J Surg 1993;80:512-6.
178. Clark E, Hoare C, Tanianis-Hughes J, Carlson GL, Warhurst G. Interferon gamma induces translocation of commensal Escherichia coli across gut epithelial cells via a lipid raft-mediated process. Gastroenterology 2005;128:1258-67.
179. Shen B, Zuccaro G, Gramlich TL, et al. Ex vivo histology-correlated optical coherence tomography in the detection of transmural inflammation in Crohn's disease. Clin Gastroenterol Hepatol 2004;2:754-60.
180. Rivera-Nieves J, Bamias G, Vidrich A, et al. Emergence of perianal fistulizing disease in the SAMP1/YitFc mouse, a spontaneous model of chronic ileitis. Gastroenterology 2003;124:972-82.
181. Hagenbaugh A, Sharma S, Dubinett SM, et al. Altered immune responses in interleukin 10 transgenic mice. J Exp Med 1997;185:2101-10.

182. Huang S, Hendriks W, Althage A, et al. Immune response in mice that lack the interferon-gamma receptor. Science 1993;259:1742-5.
183. Kamijo R, Le J, Shapiro D, et al. Mice that lack the interferon-gamma receptor have profoundly altered responses to infection with Bacillus Calmette-Guerin and subsequent challenge with lipopolysaccharide. J Exp Med 1993;178:1435-40.
184. Camoglio L, te Velde AA, de Boer A, et al. Hapten-induced colitis associated with maintained Th1 and inflammatory responses in IFN-gamma receptor-deficient mice. Eur J Immunol 2000;30:1486-95.
185. Bregenholt S, Brimnes J, Nissen MH, Claesson MH. In vitro activated CD4+ T cells from interferon-gamma (IFN-gamma)-deficient mice induce intestinal inflammation in immunodeficient hosts. Clin Exp Immunol 1999;118:228-34.
186. Tozawa K, Hanai H, Sugimoto K, et al. Evidence for the critical role of interleukin-12 but not interferon-gamma in the pathogenesis of experimental colitis in mice. J Gastroenterol Hepatol 2003;18:578-87.
187. Shevach EM. CD4+ CD25+ suppressor T cells: more questions than answers. Nat Rev Immunol 2002;2:389-400.
188. Stephens LA, Mottet C, Mason D, Powrie F. Human CD4(+)CD25(+) thymocytes and peripheral T cells have immune suppressive activity in vitro. Eur J Immunol 2001;31:1247-54.
189. Vieira PL, Christensen JR, Minaee S, et al. IL-10-secreting regulatory T cells do not express Foxp3 but have comparable regulatory function to naturally occurring CD4+CD25+ regulatory T cells. J Immunol 2004;172:5986-93.
190. Dieckmann D, Bruett CH, Ploettner H, Lutz MB, Schuler G. Human CD4(+)CD25(+) regulatory, contact-dependent T cells induce interleukin 10-producing, contact-independent type 1-like regulatory T cells [corrected]. J Exp Med 2002;196:247-53.
191. Jonuleit H, Schmitt E, Kakirman H, et al. Infectious tolerance: human CD25(+) regulatory T cells convey suppressor activity to conventional CD4(+) T helper cells. J Exp Med 2002;196:255-60.
192. Ferrarini M, Ferrero E, Dagna L, Poggi A, Zocchi MR. Human gammadelta T cells: a nonredundant system in the immune-surveillance against cancer. Trends Immunol 2002;23:14-8.
193. Gao Y, Yang W, Pan M, et al. Gamma delta T cells provide an early source of interferon gamma in tumor immunity. J Exp Med 2003;198:433-42.
194. Matsuda S, Kudoh S, Katayama S. Enhanced formation of azoxymethane-induced colorectal adenocarcinoma in gammadelta T lymphocyte-deficient mice. Jpn J Cancer Res 2001;92:880-5.
195. Girardi M, Oppenheim DE, Steele CR, et al. Regulation of cutaneous malignancy by gammadelta T cells. Science 2001;294:605-9.
196. Belmant C, Espinosa E, Poupot R, et al. 3-Formyl-1-butyl pyrophosphate A novel mycobacterial metabolite-activating human gammadelta T cells. J Biol Chem 1999;274:32079-84.
197. Kabelitz D, Holtmeier W. gammadelta T Cells Link Innate and Adaptive Immune Responses. Chem Immunol Allergy 2005;86:151-83.
198. Wilhelm M, Kunzmann V, Eckstein S, et al. Gammadelta T cells for immune therapy of patients with lymphoid malignancies. Blood 2003;102:200-6.
199. Sato K, Kimura S, Segawa H, et al. Cytotoxic effects of gammadelta T cells expanded ex vivo by a third generation bisphosphonate for cancer immunotherapy. Int J Cancer 2005.

Abkürzungen

BSA	*Bovine Serum Albumin*, Rinderserumalbumin
CD	*Cluster of Differentiation*, Differenzierungskomplex
CDI	*Cell Division Index*, Zellteilungsindex
CED	Chronisch entzündliche Darmerkrankungen
CFSE	Carboxyfluorescein
Ci	Curie
CO_2	Kohlendioxid
CTGF	*connective tissue growth factor*, Bindegewebswachstumsfaktor
CU	Colitis ulcerosa
DETC	*Dendritic Epidermal T Cells*, dendritische epidermale T-Zellen
DMSO	Dimethylsulfoxid
DNA	*Deoxyribonucleic acid*, Desoxyribonukleinsäure
ds	Doppelstrang
DSS	*Dextran Sulfate Sodium*, Dextransulfat
DTT	Dithiothreitol
EDTA	Ethylendiamintetraessigsäure
ELISA	*Enzyme-linked Immunosorbent Assay*, enzymgekoppelter Immunadsorptionstest
Fas/FasL	Fibroblasten-assoziiertes Antigen/Fas-Ligand
FACS	*Fluorescence Activated Cell Sorting*, Durchflusszytometrie
Fc	*Fragment crystallizable*, konstante Immunglobulin-Region
FCS	*Fetal Calf Serum*, fetales Kälberserum
FGF	*Fibroblast Growth Factor*, Fibroblasten Wachstumsfaktor
FITC	Fluoresceinisothiocyanat
GaM	*Goat-anti-Mouse*, Ziege-anti-Maus
GF	*germfree*, keimfrei
HBSS	*Hank´s Balanced Salt Solution*, ausgewogene Salzlösung nach Hank
HCl	Salzsäure
HEPES	N-2-Hydroxyethylpiperazin-N´-2-Ethan-Sulfonsäure
HRP	*Horseradish Peroxidase*, Peroxidase (Hämprotein) aus der Meerettichwurzel
hsp	*heat shock protein*, Hitzeschockprotein

iLPL	ileale Lamina propria Lymphozyten
i.p.	intraperitoneal
IEL	intraepitheliale Lymphozyten
IFN	Interferon
Ig	Immunglobulin
IL	Interleukin
ko	*knockout*, defizient
LPL	Lamina propria Lymphozyten
LPS	Lipopolysaccharid
MACS	*Magnetic Activated Cell Sorting*, magnetisch aktivierte Zellsortierung
mAk	monoklonaler Antikörper
MC	Morbus Crohn
MHC	*Major Histocompatibility Complex*, Haupthistokompatibilitätskomplex
MICA/B	stressinduzierte MHC-I-verwandte Moleküle A bzw. B
MG	Molekulargewicht
mLKL	mesenteriale Lymphknotenlymphozyten
MW	Mittelwert
n	Stichprobenzahl, Tierzahl
Na_2CO_3	Dinatriumcarbonat
NaCl	Natriumchlorid
$NaHCO_3$	Natriumhydrogencarbonat
NaN_3	Natriumazid
NaOH	Natronlauge
n.d.	nicht detektiert
n.s.	nicht signifikant
P	*P*-Wert
PBL	periphere Blutlymphozyten
PBS	*Phosphate Buffered Saline*, Phosphat-gepufferte Salzlösung
PCR	*Polymerase Chain Reaction*, Polymerasekettenreaktion
PE	Phycoerythryin
PI	Proliferationsindex
PLT	*platelets*, Thrombozyten
rpm	*rounds per minute*, Umdrehungen pro Minute
RPMI	Rose Park Institute-Medium

RT	Raumtemperatur
Sav	Streptavidin
SPF	*Specific Pathogene Free*, pathogenfrei
STABW	Standardabweichung
TCR	*T Cell Receptor*, T-Zellrezeptor
tg	transgen
TGF	*Transforming Growth Factor*, transformierender Wachstumsfaktor
TNBS	*2,4,6-Trinitrobenzene sulfonic acid*; Trinitrobenzolsulfonsäure = Picrylsäure
TNF	Tumor Nekrose Faktor
w	*weight*, Gewicht
WBC	*White Blood Cells*, Leukozyten
Wt	Wildtyp

Lebenslauf

PERSÖNLICHE DATEN

Name	Anja Andrea Kühl
geboren am	12. Mai 1970
in	Berlin
Familienstand	verheiratet, zwei Kinder

AUSBILDUNG

Schule

1976 – 1982	Michael-Grzimek-Grundschule, Berlin
1982 – 1989	Walther-Rathenau-Gymnasium, Berlin

Beruf

1990 – 1992	Lette-Verein Berlin *Ausbildung zur Technischen Assistentin für biologische und chemische Laboratorien (BCTA)*

Studium

1989 – 1990	Technische Universität Berlin *Amt des Lehrers mit fachwissenschaftlicher Ausbildung in Deutsch und Geschichte*
1993 – 1997	Technische Fachhochschule Berlin *Diplom-Ingenieur*

- Studiengang Biotechnologie (Schwerpunkte: Biologische Verfahren der Abwasser-, Abfall- und Abluftbehandlung, Gentechnologie, Immobilisierte Biokatalysatoren, Immunchemie)
- Durchführung der Diplomarbeit “Kinetic Studies of Thermophilic Treatment of Bleached Kraft Pulp Mill Effluent“ an der University of Toronto, Kanada; Förderung durch den DAAD

BERUFSERFAHRUNG

1990 – 1993	Institut Dr. E. Kirchhoff, Berlin *Chemisch-biologische Assistentin* • Mikrobiologie
1993 – 1994	Institut Dr. E. Kirchhoff, Berlin *Studentische Hilfskraft*
1997	Technische Fachhochschule, Berlin *Studentische Hilfskraft*
1998	unlimited communications marketing gmbh berlin *Freie Mitarbeit*
1998 – 2000	Co-Pharma im Auftrag von MSD Sharp & Dohme GmbH *Pharmareferentin*
2000 – 2001	NovaBiotec Dr. Fechter GmbH, Berlin *Freie Mitarbeit* • Abwasserreinigung, Enzymtechnik
seit 05/2001	Charité – Universitätsmedizin Berlin, CBF *Wissenschaftliche Mitarbeiterin* • Gastroenterologie – immunologisches Labor

QUALIFIKATIONEN

Sprachen	Englisch sehr gut, Latein Schulkenntnisse
EDV-Kenntnisse	Excel, Word für Windows, Power Point, SPSS für Windows, SigmaPlot, CellQuest
Auszeichnungen	1997: 2. Posterpreis im Master Level der AWMA 1998: 1. Preis für die beste Diplomarbeit (Joachim-Tiburtius-Preis des Senats von Berlin)
Aktivitäten	1999-2001: Leitung der „Kiezgruppe Malplaquetstraße“ 2001-2004: Ehrenamtliche Richterin am Landgericht Berlin, 3. Große Strafkammer

Publikationsliste

Publikationen

1. Anja A. Kühl, Christoph Loddenkemper, Jürgen Westermann, Jörg C. Hoffmann, 2002-03. “Role of Gamma Delta T Cells in Inflammatory Bowel Disease“ in Pathobiology, 70:150-155.

2. Jörg C. Hoffmann, Nina N. Pawlowski, Anja A. Kühl, Wolfgang Höhne, Martin Zeitz. 2002-03. “Animal Models of Inflammatory Bowel Disease: An Overview“ in Pathobiology, 70:121-130.

3. J.C.Hoffmann, N.N. Pawlowski, A.A. Kühl. 2003. „New Research Aspects of Crohn´s Disease: Animal Models“ in Sate of the Art: Current Research Stratewgies in Crohn´s Disease, Digestive Surgery, 20: 339-382.

4. Nina N. Pawlowski, Hacer Kakirman, Anja A. Kühl, Oliver Liesenfeld, Katja Grollich, Christoph Loddenkemper, Martin Zeitz, Jörg C. Hoffmann, 2005. “αCD2 mAb treatment safely ameliorates transfer colitis“ in Laboratory Investigation, 85: 1013-1023.

5. Anja A. Kühl, Nina N. Pawlowski, Katja Grollich, Christoph Loddenkemper, Martin Zeitz, Jörg C. Hoffmann. Aggravation of intestinal Inflammation by Depletion/Deficiency of $\gamma\delta$ T Cells in different Types of IBD Animal Models; *zur Publikation eingereicht*.

6. Anja A. Kühl, Hacer Kakirman, Markus Janotta, Stefan Dreher, Philipp Cremer, Nina N. Pawlowski, Christoph Loddenkemper, Katja Grollich, Martin Zeitz, Stefan Farkas, Jörg C. Hoffmann. Role of Neutrophil Invasion in Rat Tri-/Dinitrobenzene Sulfonic Acid induced Colitis; *zur Publikation eingereicht*.

Posterbeiträge

1. Anja Andrea Suchochleb, Chandra S. Tripathi, Milan Popovic, Grant Allen. ”Kinetic Studies of Thermophilic Treatment of BKME”. AWMA 1997, Kanada.

2. Philipp Cremer, Anja A. Kühl, Hacer Kakirman, Stefan Farkas, Stefan Dreher, Sven Henschke, Joachim F. Schenk, Martin Zeitz, Jörg C. Hoffmann. “INDUCTION OF FULMINANT RAT TNBS COLITIS BY ANTI-L-SELECTIN MAB“. DDW 2002, San Francisco, U.S.A.

3. Nina N. Pawlowski, Anja A. Kühl, Hacer Kakirman, Sven Henschke, Sabine Ring, Martin Zeitz, Jörg C. Hoffmann. “CD2 DIRECTED IMMUNOTHERAPY OF TRANSFER COLITIS“. DDW 2002, San Francisco, U.S.A.

4. Anja Kühl, Christoph Loddenkemper, Martin Zeitz, Jörg C. Hoffmann. “FUNKTION VON $\gamma\delta$ T ZELLEN IN EINEM MAUSMODELL CHRONISCH ENTZÜNDLICHER DARMERKRANKUNGEN“. DGVS 2002, Nürnberg.

5. Anja A. Kuehl, Nina N. Pawlowski, Christoph Loddenkemper, Katja Grollich, Martin Zeitz, Joerg C. Hoffmann. “EFFECTS OF γδ T CELL DEPLETION ON COLITIS ANIMAL MODELS: INCREASED INFLAMMATION AND CYTOKINE DYSREGULATION“. DDW 2003, Orlando, U.S.A.

6. Anja A. Kühl, Nina N. Pawlowski, Katja Grollich, Christoph Loddenkemper, Martin Zeitz, Jörg C. Hoffmann. ”Role of γδ T Cells in DSS-induced Colitis”. Falk-Symposium 2003, Berlin.

7. Nina N. Pawlowski, Katja Grollich, Sven Henschke, Anton J. Kroesen, Anja A. Kühl, Martin Zeitz, Jörg C. Hoffmann.“ Relevance of CD28 for Colitis Development”. Falk-Symposium 2003, Berlin.

8. Anja A. Kühl, Nina N. Pawlowski, Katja Grollich, Christoph Loddenkemper, Martin Zeitz, Jörg C. Hoffmann. ”Beeinflussen γδ T-Zellen histologisch Entzündung und Überleben in CED-Tiermodellen?”. DGVS 2003, Nürnberg.

9. Nina N. Pawlowski, Oliver Liesenfeld, Anja A. Kühl, Katja Grollich, Martin Zeitz, Jörg C. Hoffmann. “CD2-gerichtete Immuntherapie etablierter Transferkolitis und Untersuchungen zur Infektabwehr“. DGVS 2003, Nürnberg.

10. Anja A. Kuehl, Nina N. Pawlowski, Christoph Loddenkemper, Katja Grollich, Thomas F. Tedder, Douglas A. Steeber, Martin Zeitz, Jörg C. Hoffmann. “Role of Neutrophils for the Initiation and Perpetuation of chemical induced Colitis“. DDW 2004, New Orleans, U.S.A.

11. Kühl AA, Singer BB, Pawlowski NN, Grollich K, Loddenkemper C, Zeitz M, Lucka L, Hoffmann JC. “Behandlung mit anti-CEACAM1 Antikörper verschlimmert chemisch induzierte Colitis in Ratten“. DGVS, 2005, Köln.

12. Nina N. Pawlowski, Katja Grollich, Daniela Struck, Anja Kühl, Martin Zeitz, Oliver Liesenfeld, Jörg C. Hoffmann: “Role of CD2 in *Toxoplasma gondii* infection”. DGfI 2005, Kiel.

Vorträge

1. “Kinetic Studies of Thermophilic Treatment of BKME“. 1997, TISCUIT Conference on the Environment in Kanada.

2. “Role of γδ T Cells in Inflammatory Bowel Disease“. 2001, Workshop „IBD animal models: From pathogenesis to therapy“ des Kompetenznetzes „Chronisch Entzündliche Darmerkrankungen“ in Berlin.

3. „Die Rolle von γδ T-Lymphozyten bei der Colitis der IL-2 ko Maus“. 2002, DACED in Mainz.

4. „Die Bedeutung von L-Selektin bei chemisch-induzierter Colitis“. 2003, DACED in Mainz.

Erklärung

„Ich, Anja Kühl, erkläre, dass ich die vorgelegte Dissertationsschrift mit dem Thema „Regulatorische γδ T-Zellen bei Colitis: Ein neuer Ansatzpunkt für die Therapie?“ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

Datum Unterschrift