We identified several chromosomal regions yielding suggestive LOD scores, including the HLA region on chromosome 6. These intervals could harbor potential susceptibility loci for alopecia areata. In order to exclude those regions that represent spurious positive scores and to confirm and refine the true susceptibility loci, we are currently undertaking a fine-mapping study in a larger group of AA families.

We anticipate that these studies will lead to the identification of AA susceptibility genes, and provide a foundation for understanding the interactions of these gene(s) with each other and with other variables such as the immune system and environmental factors.

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Neurotrophins in Autoimmune Diseases: Possible Implications for Alopecia Areata

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Neurotrophins are a family of structurally and functionally related polypeptides that include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4 (for a review see Roux and Barker, 2002). They bind a 75kDa transmembrane neurotrophin receptor (p75NTR), and also each neurotrophin binds a distinct receptor of the Trk family. When p75NTR and Trk are coordinately bound by neurotrophins, survival signal is initiated through Trk. But in absence of the Trk, p75NTR is activated alone to induce a variety of cellular responses including apoptosis.

Increased evidence of data suggests that neurotrophins play an important role during the development of autoimmune disorders: NGF levels are significantly increased in the synovium of patients affected by rheumatoid arthritis, in the cerebrospinal fluid of patients with multiple sclerosis, in plasma of patients affected by lupus erythematosus, and in the skin of patients with systemic scleroderma (for a review see Aloe and Tuveri, 1997). The mechanisms of neurotrophin involvement in pathogenesis of autoimmune disorders, however, are largely unknown. Because neurotrophins are expressed in skin affected by alopecia areata (AA) and promote hair follicle regression in normal non-affected skin (Botchkarev *et al*, 2000; Botchkarev, 2003), we asked if neurotrophins may play a role in AA pathogenesis.

CD8 lymphocytes were isolated from involved skin and peripheral blood of AA-affected C3H/HeJ mice as well as from non-affected control mice. In contrast with peripheral blood CD8 cells that displayed low p75 levels, cells from AA involved skin expressed significantly higher p75 level ($p < 0.001$, FACScan analysis). Multi-color immunofluorescence microscopy showed that p75-positive CD8 cells were assembled specifically around the hair follicles as well as inside the follicular epithelium.

To identify the phenotype of CD8 cells expressing p75NTR in skin affected by AA, the expression of interferon-γ (IFN-γ) and granzyme B as markers of effector CD8 cells was studied by FACS analysis and immunofluorescence. p75NTR-positive CD8 cells also showed the expression of IFN-γ and granzyme B suggesting their effector phenotype. By RT-PCR, however, these cells were negative for Trk (TrkA, TrkB, TrkC) receptor expression, suggesting that neurotrophin administration could induce apoptosis of these inflammatory cells.

Consistent with this hypothesis, NGF- and BDNF-induced apoptosis in CD8 cells isolated from skin of mice affected by AA and cultured *in vitro*, as compared with diluent alone. Furthermore, *in vivo* administration of agarose beads soaked with NGF or BDNF resulted in significant reduction of CD8 cells ($p < 0.01$) in AA-affected skin. These data suggest that neurotrophin-stimulated apoptosis in CD8 cells may play a role as a part of the protective response mechanisms limiting the development of AA and that p75NTR agonists could be used as a novel therapeutic intervention to arrest the development of AA.

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The Functional Relevance of the Type 1 Cytokines IFN-γ and IL-2 in Alopecia Areata of C3H/HeJ Mice

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Alopecia areata (AA) was regarded as a type 1 (Th1, Tc1)-mediated autoimmune disease of the hair follicle, because type 1 cytokines interferon-γ (IFN-γ) and interleukin (IL)-2 are expressed in lesional AA skin. Recently we have shown that the type 2 (Th2, Tc2) cytokine IL-10 also is expressed in