Alopecia and Vitiligo in Autoimmune Polyendocrine Syndrome Type I

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Autoimmune polyendocrine syndrome type I (APS I) is a recessively inherited disease caused by mutations in a recently identified gene, AIRE, on human chromosome 21. Two of the classical triad of mucocutaneous candidiasis, hypo-parathyroidism and adrenocortical insufficiency are required for the clinical diagnosis. Other severe manifestations such as autoimmune chronic active hepatitis and insulin-dependent diabetes mellitus (IDDM) may also affect the patients. Furthermore, ectodermal manifestations such as vitiligo, alopecia, and nail and enamel dystrophy are frequently seen. Alopecia and vitiligo are common manifestations in APS I patients and have been reported in 30% and 15% of the patients, respectively. Severe forms of these diseases are common among APS I patients. The aim of the investigations was to study dermal structures targeted by the immune system in patients with alopecia areata and vitiligo.

Initially, we analyzed the presence of autoantibodies against structures in hair follicles in sera from 39 APS I patients by use of immunofluorescence staining of a human scalp biopsy. Five of these sera displayed immunoreactivity against the differentiating precortical matrix keratinocytes of the growing hair follicle. All of these 5 patients had alopecia totalis, representing 63% of the 8 patients with this severe form ($p<0.0001$). One serum of 9 from patients with alopecia totalis unrelated to APS I also showed this reactivity. Immunoreactivity against hair follicle melanocyte nuclei was also detected in some of the sera from the APS I patients by use of this method (Fig.).

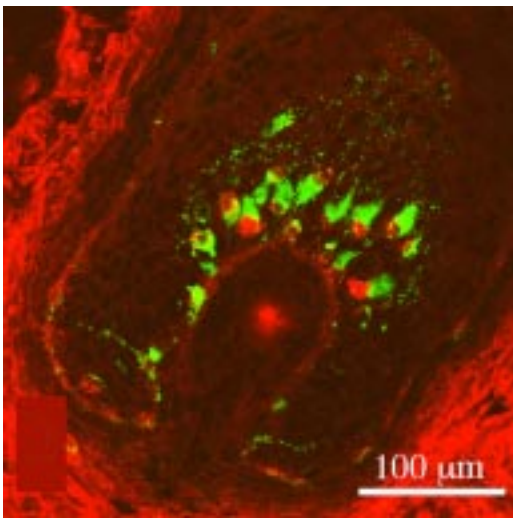
In order to be able to further identify the proteins (autoantigens) targeted by the immune system in APS I patients, we constructed a cDNA library containing "gene copies" of all proteins normally expressed in the skin. Then these proteins can be produced in the laboratory and subsequently be used for immunoscreening of a large number of patient sera. Altogether we used 94 APS I sera in this screening assay and found major reactivity against three autoantigens. One was tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of dopamine, epinephrine and norepinephrine. The other two were the transcription factors SOX9 and SOX10.

Immunoreactivity against TH was detected in 44% of the sera and there was a correlation between this immunoreactivity and alopecia areata in this patient group ($p<0.02$).

Immunoreactivity against SOX9 and SOX10 was seen in 20% of the sera and was strongly correlated with vitiligo among the patients ($p<0.0001$). Immunoreactivity against SOX10 was also shown to be related to the staining of melanocyte nuclei mentioned above and we were able to show that both SOX9 and SOX10 are expressed in these cells in hair

follicles and epidermis. Immunoreactivity against SOX10 was also found in 3% of patients with vitiligo unrelated to APS I which may indicate a role for these autoantigens in idiopathic vitiligo. SOX10 has been shown to be involved in melanin synthesis induction, but the function of SOX9 in melanocytes is still unknown.

We were not able in this study to identify the autoantigen related to the immunoreactivity seen against the differentiating hair follicle keratinocytes. This autoantigen, related to alopecia totalis thus remains to be identified.



Immunofluorescence staining of an anagen hair follicle with serum from a patient with APS I showing immunoreactivity against nuclei (red) of melanocytes (green) within the hair bulb. Reprinted by permission of Blackwell Science, Inc.

Identification of the antigenic structures in hair follicles and epidermis related to alopecia totalis and vitiligo is of great importance for further understanding of the autoimmune mechanisms related to these symptoms. We also believe that the SOX9 and SOX10 autoantigens may provide a new tool in the development of new immunotherapeutic approaches for the treatment of melanoma.

List of original publications

I. Hedstrand H, Perheentupa J, Ekwall O, Gustafsson J, Michaëlsson G, Husebye E, Rorsman F, Kämpe O. Antibodies against hair follicles are associated with alopecia totalis in autoimmune polyendocrine syndrome type I. J Invest Dermatol 1999; 113: 1054–1058.

II. Hedstrand H, Ekwall O, Haavik J, Landgren E, Betterle C, Perheentupa J, Husebye E, Rorsman F, Kämpe O. Identification of tyrosine hydroxylase as an autoantigen in autoimmune polyendocrine syndrome type I. Biochem Biophys Res Com 2000; 267: 456–461.

III. Hedstrand H, Haavik J, Landgren E, Olsson T, Mårtensson A, Rorsman F, Kämpe O. High-titre autoantibodies against tyrosine hydroxylase in a patient with Parkinson's disease. Submitted.

IV. Hedstrand H, Ekwall O, Olsson M, Landgren E, Kemp H, Weetman A, Perheentupa J, Husebye E, Gustafsson J, Betterle C, Kämpe O, Rorsman F. The transcription factors SOX9 and SOX10 are melanocyte autoantigens related to vitiligo in autoimmune polyendocrine syndrome type I. Submitted.