Aberrant Intercellular Adhesion Molecule-1 (ICAM-1) Expression by Hair-Follicle Epithelial Cells and Endothelial Leukocyte Adhesion Molecule-1 (ELAM-1) by Vascular Cells Are Important Adhesion-Molecule Alterations in Alopecia Areata

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The most obvious clinical manifestation of alopecia areata is significant hair loss. The precise metabolic alteration responsible for the failure of the follicular unit to produce a terminally differentiated hair shaft in alopecia areata patients is not currently known. It is widely believed that disruption of follicle metabolism is related to the presence of mononuclear leukocytes in and around the peri-bulbar zone. The numbers of both monocyte/macrophages and T lymphocytes in the peri-bulbar region of the affected hair-bearing skin in alopecia areata patients are dramatically increased over normal, non-inflamed cycling hair follicles [1]. Presumably cytokines released by the infiltrating inflammatory cells localized in close proximity to the follicular epithelium, can contribute to the overall pathophysiology of hair loss in alopecia areata by altering keratinocyte-keratinocyte and/or keratinocyte–stromal cell interactions. The purpose of this report is to summarize our results, which address the molecular basis for the increased mononuclear cell trafficking seen in alopecia areata. In other words, we sought to determine which new cell-surface molecules were being expressed by the dermal microvasculature supplying the hair follicle, as well as the follicular epithelial cells themselves. These adhesion molecules would mediate leukocyte migration from the circulation, and entry into the inner portion of the hair follicle.

The primary types of molecules that we have focused our attention on in alopecia areata are cellular adhesion molecules. There are essentially five broad families of adhesion molecules/receptors that can mediate cell-cell and cell-matrix interactions [2], which include 1) intergins; 2) immunoglobulin-like adhesion molecules; 3) cadherins; 4) lectin, epidermal growth factor, and complement homology domains of cell-adhesion molecules (LEC-CAM); and 5) homing receptors. Because of space constraints, we will restrict our current discussion to consideration of the intergrins and endothelial-cell adhesion molecules expressed aberrantly in scalp biopsies of patients with alopecia areata. The first step in an immune-based inflammatory cascade within the skin is the binding of circulatory monocytes and T cells to vascular endothelial cells. The three best characterized endothelial-cell adhesion molecules mediating binding with leukocytes are intercellular adhesion molecule-1 (ICAM-1), endothelial-leukocyte adhesion molecule-1 (ELAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [2]. Because the majority of circulatory leukocytes express ligands for the endothelial-cell adhesion molecules, the induction of white blood cell emigration primarily relates to activation of endothelial cells with expression of ICAM-1, VCAM-1, and ELAM-1. The primary stimulus for endothelial-cell expression of these adhesion molecules in vitro [2] are cytokines such as tumor necrosis factor-alpha (TNF-α) or interleukin-1 (IL-1), which are probably produced both by neighboring macrophages and the epithelial cells (i.e., keratinocytes) themselves [3]. In normal skin, the endothelial cells only weakly express ICAM-1, and display no immunoreactivity for either ELAM-1 or VCAM-1 [4]. However, in alopecia areata the perifollicular dermal vessels strongly express ELAM-1, VCAM-1, and ICAM-1.* We are particularly interested in ELAM-1 expression because in a recent study of 35 cases of acute and chronic inflammation in non-cutaneous organs (i.e., lung, gastrointestinal tract, thyroid gland, etc), there was only slight and focal endothelial-cell ELAM-1 expression. In contrast to the almost complete absence of ELAM-1 outside the skin, in 36 biopsies of cutaneous inflammatory processes such as psoriasis, allergic contact dermatitis, mycosis fungoides, and leprosy, there was strong and diffuse ELAM-1 expression. This suggests that ELAM-1 may be functioning as a skin-specific vascular addressin responsible for organ-specific homing. Thus, in alopecia areata, the endothelial cells express several different adhesion molecules (ELAM-1, VCAM-1, ICAM-1) that can mediate the adherence of leukocytes and subsequent trafficking into the dermis. The next question we asked is, how do mononuclear leukocytes move from the perivascular spaces into the follicular epithelium of the hair follicle?

In normal skin, the epidermal keratinocytes and the follicular epithelia are devoid of ICAM-1 [1]. ICAM-1 expression by keratinocytes is important because adherence between mononuclear leukocytes and cultured keratinocytes is mediated by lymphocyte function–associated antigen-1 (LFA-1)–expressing leukocytes binding to ICAM-1–positive keratinocytes (reviewed in [5]).

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ICAM-1 expression by keratinocytes can be induced by TNF-α and interferon-gamma (IFN-γ). In alopecia areata, the follicular epithelium is strongly ICAM-1 positive, and there is excellent spatial co-localization between LFA-1–positive mononuclear leukocytes and ICAM-1–expressing follicular epithelial cells [1]. This aberrant expression of ICAM-1 by the follicle cells permits the entry of monocyte/macrophages and T cells directly into the follicular epithelial compartment of the hair follicle. We believe it is this unusual and intimate cellular association between leukocytes and follicle cells mediated by LFA-1/ICAM-1, respectively, that is responsible for the alteration of hair metabolism in alopecia areata.

The principal support for this pathophysiologic proposal is derived from our previously published clinical pharmacologic results using cyclosporin A [1]. Six patients with alopecia areata of the scalp were given oral cyclosporin A (5 mg/kg) for 12 weeks. Sequential punch biopsies were immunohistochemically stained for ICAM-1 and other immunologic parameters, with correlation to the clinical response. After 2–4 weeks of treatment all patients experienced hair regrowth, and there was a good correlation between new hair growth and dimunition in the ICAM-1 expression by involved follicular epithelium. Because cyclosporin A is known to inhibit several important mononuclear cell–derived cytokines such as IFN-γ and TNF-α, we suggested that the pathologic interplay between infiltrating leukocytes and the hair follicle was interrupted by cyclosporin A in the alopecia areata patients. By the end of the study, patients with complete hair regrowth had no residual follicular epithelial-cell ICAM-1 expression, and only rare peri-bulbar leukocytes remained. This scenario of cellular and molecular immunologic events, and changes induced by cyclosporin A (involving both keratinocyte ICAM-1 and clinical response) as described for alopecia areata, were also observed in a group of psoriatic patients [6]. Our current molecular dissection of the cytokine network in psoriasis is in a more advanced state compared to alopecia areata [7]. However, both alopecia areata and psoriasis share some immunopathologic features such as a prominent dermal T cell, monocyte/macrophage infiltration, lesional keratinocyte ICAM-1 expression, extensive endothelial-cell adhesion molecule expression (ELAM-1, VCAM-1, ICAM-1), and responsiveness to cyclosporin A. Moreover, other investigators have suggested that psoriatic epidermal lesions and hair follicle growth share a similar "switch-on" mechanism [8]. Thus, the psoriatic cytokine network involving dermal dendrocyte/macrophage production of TNF-α, and overlying keratinocyte expression of IL-8, ICAM-1 with increased production of TGF-α [7], may be more relevant to alopecia areata than appreciated at first glance.

In conclusion, we have reviewed some of the salient immunopathologic features of alopecia areata with emphasis on the aberrant endothelial-cell expression of leukocyte adhesion molecules (particularly ELAM-1), and the follicular epithelial expression of ICAM-1. We have indicated the usefulness of the cyclosporin A results (with clinical-pathologic correlation) in contributing to our understanding of the pathophysiology of alopecia areata, and recommend a more complete dissection of the cytokine network as already accomplished for psoriatic lesions. Thus, although there have been significant advances in detailing more precisely the specific molecular and cellular immunologic alterations in the skin of alopecia areata patients, there still exists a considerable void in an understanding of functional relationships between keratinocyte-keratinocyte, keratinocyte-matrix, and keratinocyte-immunocyte interaction, which will serve as a formidable challenge to investigative skin biologists beyond 1990. We believe that the key to elucidating these complex cellular associations will be derived from an analysis of the ability of the aforementioned molecules (i.e., ELAM-1, VCAM-1, ICAM-1, TNF-α, IL-8, IFN-γ) to mediate such intercellular communications.

Note Added in Proof: Another group has independently proposed that ELAM-1 may be functioning as a skin-specific vascular addressin [9].

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