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We salute Roche Dermatologics, Division of Hoffman – La Roche Inc. for their contribution to the Endowment Fund and for their continued support of clinical and investigative dermatology.

D.A.N., Denver, CO

In This Issue . . .

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Is Kaposi's Sarcoma Induced by Retrovirus Infection?

One very fascinating aspect of human biology is that certain pathologic processes present in different patient populations with different onset, pace, outcome and even separate pathomechanisms. Kaposi's sarcoma (KS) is a histologically distinctive malignancy that is found in several distinct clinical patterns: classical indolent KS in elderly Jewish men; the more aggressive endemic African KS, organ-transplant–associated KS, and aggressive epidemic KS in HIV-1–infected patients.

Immunosuppression is an important component of some of these presentations, and it has long been proposed that retrovirus infection may also have a direct role in inducing malignant transformation in KS. In this issue a multinational group headed by Georg Stingl report a detailed histopathologic and immunopathologic investigation of endemic KS in the Southern Peloponnesus. This work provides new insights on this endemic focus of KS and a better perspective on the cell of origin of KS. Finally, it leads us to infer that such lesions are associated with an unidentified retrovirus.

Epidemiologically this Mediterranean focus of KS is similar in incidence to endemic African KS, although the proportion of affected females is greater than in endemic or classic KS. Clinically, the lesions in different stages on the hands and feet are similar to classical and endemic KS, whereas the widespread and "streaky" lesions, and especially the involvement of face, genital, mucosal, and gastrointestinal tract, are more similar to KS seen in patients with AIDS. Immunohistochemical and electronmicroscopic studies confirm that the cells lining the cleft-like lumina and forming the tumor bundles in the KS tumors are most likely of lymphatic endothelial cell origin. Most importantly, the authors identified in five of 12 patients studied tubular-reticular structures and cylindrical confronting cisternae within the KS cells and extracellular structures that strongly suggest the presence of a retrovirus. Serologic tests for antibodies to HIV-1, HIV-2, and HTLV-1 were consistently negative. Although rigorous searching for known retroviral protein or amplification of retroviral genes has not yet been done, Dr. Stingl believes that these results force us to "entertain the possibility that this represents a new retrovirus involved in the pathogenesis of Kaposi's sarcoma." The findings open many interesting possibilities of how different retroviruses in combination with host immunologic and genetic factors might determine the very different clinical features of the variants of KS.

Transforming Growth Factor Alpha and Malignant Transformation

There is great interest in the complex multistage process of carcinogenesis, and in the role of growth factors as mediators of malignant transformation. Many oncogenes code for growth factors or receptor proteins for growth factors, and it has been proposed that autocrine effects of growth factors may be an important mechanism of malignant transformation.

Eric Finzi of the Johns Hopkins University and his colleagues in the Laboratory of Cellular and Molecular Biology in the National Cancer Institute studied the autocrine effects of transforming growth factor α (TGF-α) on fibroblasts and keratinocyte cell lines. They constructed a retroviral vector for TGF-α cDNA, and were able to produce cell lines that expressed TGF-α RNA and synthesized and secreted TGF-α. However, none of the multiple fibroblast cell lines showed morphologic characteristics of malignant transformation. They also used a keratinocyte line which was EGF dependent. Because TGF-α and EGF activate the same receptor, it was reasoned that this would be an appropriate model for autocrine transformation by TGF-α. Retroviral expression of TGF-α in these cells was mitogenic, but failed to relieve the dependence of these cells on exogenous EGF.

Dr. Finzi notes that some growth factors, such as platelet-derived growth factor (PDGF), have autocrine transforming activity in some tissues, and that increased expression of the EGF receptor is seen in some squamous cell carcinomas. In addition, another labora-

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tory has shown that autocrine production of TGF-α is sufficient to transform a fibroblast cell line.

"How the growth factor is processed in a particular tissue may be crucial in determining transforming activity," explained Dr. Finzi. He surmised that levels of receptor, partitioning of growth factor, degradation of the growth factor, and interference of ligand/receptor binding may all influence the ability of exogenous growth factors to effect malignant transformation. The process of malignant transformation promises to be complex, with no single trigger or simple common pathway.

What is Porokeratosis?

The porokeratoses have distinctive clinical and pathologic findings, but unknown etiologies. It has been proposed that the porokeratoses represent a clonal growth of epidermal cells. It should be possible to test this hypothesis using modern techniques of cellular and molecular biology.

In this issue Alice Ma and her collaborators at the University of Chicago have identified some unusual characteristics of porokeratosis that raise further questions of the nature of this distinctive clinical pattern. Five patients with porokeratosis were studied using modern techniques to identify matrix protein patterns in lesional skin, and to study the growth of epidermal cells and the pattern of keratin production from these patients. Interestingly, type IV collagen was identified in the patients' stratum corneum by immunohistochemistry, and positive intraepidermal staining of laminin and type IV collagen implied the transepidermal passage of basement membrane components in porokeratosis lesions. Epidermal cells plated from lesions showed unusual characteristics of growth in culture and also demonstrated a keratin not normally seen in normal glabrous skin.

Dr. Ma feels that the findings support the hypothesis that porokeratosis represents an unusual proliferation of ductal epithelial cells with associated abnormal patterns of basement membrane components. Although the unusual characteristics of the cultured epithelial cells "may represent clonal proliferation," she noted "further work using modern molecular techniques is necessary to determine true clonality of the proliferating cells." This is another example of how modern investigative techniques can be effectively applied to clinical problems of disordered epidermal growth and differentiation.

Proteolysis in the Stratum Corneum

Cohesion of the cells in the stratum corneum is crucial to maintenance of the epidermal barrier, and conversely the desquamation of these cells is an important biologic process that we are just beginning to understand. Torbjörn Egelrud and Anita Lundström from the University of Umeå have previously shown that cell dissociation from plantar skin is associated with degradation of the desmosomal protein desmoglein I. Their work supports the contention that endogenous proteolytic activity degrades DGI and perhaps other adherence structures. In this issue they extend these findings to non-plantar skin, demonstrating that detergent-induced dissociation of cells from the stratum corneum, but not from spinous or basal layers of the epidermis, is prevented by the protease inhibitor aprotinin. The authors conclude from this model system that protein structures are crucial for maintenance of stratum corneum integrity and that the action of local endogenous proteases mediates the cell dissociation that occurs during desquamation.

An active proteolytic environment in the stratum corneum may also influence other important biologic functions besides desquamation. Epidermal keratinocytes produce many important cytokines that can be secreted or displayed in the cell membrane. Some, such as IL-1β, require proteolytic degradation for activation. It is intriguing to wonder whether such cytokines are activated by proteolysis in the stratum corneum, and what might be the activity and specificity of this proteolytic environment in diseases such as psoriasis.