STRUCTURAL CHANGES IN THE CONNECTIVE TISSUE MATRIX COMPONENTS IN THE DERMIS OF PATIENTS WITH INHERITED CONNECTIVE TISSUE DISORDERS

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The normal dermis is a thick, mechanically strong layer of the skin composed primarily of connective tissue. It includes bundles of collagen molecules of several types, a network of elastic fibers that spans the dermis from the dermal-epidermal junction to the subcutaneous tissue, filamentous glycoproteins and large, complex proteoglycans. Molecules in each of these classes occupy their own niche architecturally, but they interact with one another biochemically, structurally and mechanically to provide unique properties to the dermis according to region. Matrix organization defines papillary, intermediate and reticular regions, however, the factors responsible for this regional variation undoubtedly also reflect influences on the matrix by other cells and tissues within the skin (e.g., nerves, vessels, the epidermis and epidermal appendages), the external environment (e.g., ultraviolet light, topically applied compounds) and intrinsic properties of the individual (e.g., age, general health). The interactions among cells and matrix, matrix molecules with soluble mediators (e.g., cytokines, growth factors) and matrix molecules with one another are complex, thus interpreting structural alterations in skin from patients with inherited connective tissue diseases is difficult; more is involved than the reflection of the specific molecule defect and an alteration that is observed may be secondary rather than direct.

In spite of this limitation, skin biopsies from patients with connective tissue disorders have been useful for a variety of purposes: in preliminary screening to determine directions for further studies (e.g., dilation of the rough endoplasmic reticulum in dermal fibroblasts suggests a storage disorder; thinned dermis and small fiber bundles suggests a reduction in collagen synthesis; both observations point to testable hypotheses); as a means of confirming a tentative diagnosis (e.g., composite collagen fibrils are characteristic of the dermis of patients with dominant forms of EDS; an absence or reduction of elastin from elastic fibers is characteristic of cutis laxa); and, to explore the effect of a specific mutation on the structure of the involved matrix component, other connective tissue molecules and the architecture of the dermis as a whole. Understanding the structural alterations in dermal matrix in adult skin has also been valuable in developing hypotheses about matrix interactions which can be tested in a developmental model.

Skin biopsy samples are evaluated histologically to investigate dermal
architecture and obvious changes in the structure or quantity of the major matrix macromolecules (collagen, elastin and proteoglycans) and to target specific components to be examined by electron microscopy. The ultrastructural work focuses on examination of individual collagen fibrils, elastic fibers, relationships between the two components and cellular morphology. Immunolabeling is performed to reveal the specific nature of certain molecules within cells and in the extracellular matrix.

These studies have led us to propose several generalizations which appear to correlate with the structure of dermal connective tissue from normal individuals and patients affected with inherited connective tissue diseases: 1) Collagen fibrils show a limited number of changes in morphology, regardless of whether these changes are induced by disease or by other factors or conditions. Fibrils can be unusually large or small in diameter, display mixed diameters within a bundle, appear unravelled, or assume the composite or "hieroglyphic" fibril structure; 2) Identical structural abnormalities in collagen fibrils can occur in the skin of patients with diseases of collagen as well as other matrix molecules (e.g., composite collagen fibrils are found in types I, II, III, VI & X EDS, osteogenesis imperfecta type, the Buschke Ollendorff syndrome and cutis laxa) and can occur under circumstances of different molecular defects; 3) Structural alterations in connective tissue fibers are rarely specific for a given disease (dermatosparaxis is an exception), nonetheless there are certain patterns of structural change in the matrix that are characteristic for a disorder (e.g., composite fibrils and a dense dermis are characteristic of the skin of patients with several forms of EDS); 4) Elastic fibers show a greater range in structural abnormalities than collagen fibrils. This may be because elastic fibers are assembled from two (microfibrillar and elastin) components and because both synthetic and degradative events can lead to abnormal, disease-related changes in these fibers; 5) A molecular defect in one connective tissue molecule may affect the structural properties of other matrix components (e.g., elastin synthesis is enhanced in the Buschke-Ollendorff syndrome where both collagen and elastic fibers show severe structural alterations and abnormal matrix organization); and 6) The morphology of fibroblastic cells may provide clues to a defect in a matrix component. These generalizations suggest that mutations of one molecule can elicit a broad spectrum of change in the connective tissue and architecture of the dermis and demonstrate that understanding the molecular basis of the disease does not necessarily explain the phenotypic changes in the skin. The level of complexity of matrix interactions overrides specific modulation of the tissue organization by any one molecule.

Reference
All primary references are reviewed in the following: