INTERNATIONAL ACADEMY OF PATHOLOGY MONOGRAPH

CONNECTIVE TISSUE DISEASES

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Connective Tissue Diseases

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Foreword

This series of Monographs in Pathology was initiated by the International Academy of Pathology in 1959 and is based on Long Courses presented at the annual meetings. Unfortunately, the earlier Long Courses, which were started in 1953, were not published. "Connective Tissue Diseases" is the 24th monograph in this series. The various chapters are based on presentations for the Long Course entitled "Connective Tissue and Diseases of Connective Tissue" given on March 2, 1982, at the time of the 71st Annual Meeting.

This monograph allows for a more extensive treatment of each subject. Due to time constraints, the last chapter, entitled "Cytochemistry of Complex Carbohydrates by Light and Electron Microscopy: Available Methods and Their Application" was not planned for presentation at the time of the Long Course, but it was planned for publication and forms an important aspect of this book.

It is worth noting that in 1965 Dr. Bernard Wagner directed the Long Course on "The Pathologic Physiology and Anatomy of Connective Tissue" and edited the corresponding monograph entitled "The Connective Tissue" that was published in 1967. On reviewing this earlier monograph, which at that time was very up to date, one cannot help being impressed with the revolution in the understanding of these diseases, the significant developments in the principles on which these understandings are based, and the newer methods available for these studies.

The Academy wishes to express its appreciation to Dr. Bernard Wagner, Dr. Raul Fleischmajer, to the other distinguished contributors to this monograph, and to the publisher, Williams & Wilkins, for their valuable support and cooperation.

NATHAN KAUFMAN, M.D.
Series Editor

Preface

Since the publication of the last IAP monograph on "Connective Tissue" in 1967, an enormous amount of important research has been accomplished. The molecular synthesis of collagen has been largely elucidated. However, the process of collagen assembly is still under investigation. There appear to be a multiplicity of pathways in which collagen is transported to the cell surface, discharged, processed biochemically, and then deposited to an existing structure without altering the architecture. Sensitive immunocytochemical methods have demonstrated that a variety of collagens exist and that the typing of collagen in disease states may be important.

During the last decade, significant advances have been made in understanding the nature of the extracellular matrix or ground substance. Fibronectin, a unique glycoprotein, appears to function as an adhesive protein and also has the ability to be cross-linked with collagen. The intracellular localization of fibronectin molecules and their specific fragments to bind to various macromolecules as well as to mediate cell attachment has been studied.

Another glycoprotein, laminin, has been found solely in basement membranes and has been shown to bind epithelial and endothelial, but not other cells, to type IV collagen. Recent studies have shown that the heparan sulfate proteoglycan, also known as BMI proteoglycan, forms an ionic shield over the basement membrane which blocks the passage of negatively charged macromolecules. Type IV collagen, laminin, and the heparan sulfate proteocoglycan are constant components of basement membrane. The possibility of relating diseases to specific components of basement membranes is now possible.

Scleroderma, systemic sclerosis, is a connective tissue disease associated with remarkable fibrosis of various organ systems. Modern research into this well-known disease is beginning to open new vistas in understanding the regulation of the connective tissue steady state. Although amyloid has been known since 1854, its chemical identity has eluded scientists until the last decade. Amyloid proteins appear to have been observed in almost every mammalian species studied as a function of aging. The emerging picture of amyloid as a connective tissue disease is most exciting.

Systemic lupus erythematosus was one of the key diseases which lead Klemperer to develop the concept of collagen disease. Today, it is regarded as a classic disorder of the immune system. SLE deserves to be included as a connective tissue disease because of the extracellular fibrinoid deposits in connective tissue sites. The expanded studies of SLE have served to focus on the interaction of immune reactants with connective tissue structures. This has led to the exciting notion of an "attack complex" as a pathogenetic mechanism.

Rheumatoid arthritis is a systemic disease full of paradoxes. It is clearly a disease of the connective tissues with significant multiorgan involvement. Attempts to isolate etiologic infectious agents have been unsuccessful. In this disease, the pluripotentiality of the mesenchyme is observed. A variety of biological probes continues to be used to elucidate this unique connective tissue disorder.

For most practicing pathologists, skin biopsies are the most frequent tissues studied in an attempt to establish a diagnosis of connective tissue disease. A striking panorama of pathology can be observed using a variety of methods. Connective tissue diseases are not limited to humans. During the past decade, a diverse group of spontaneous connective tissue disorders in animals has been discovered. Recognition of these models has provided pathologists with experimental systems capable of extrapolation to human tissue observations.

It is safe to predict that the next 10 years will bring expanded knowledge to the field of connective tissue diseases. Laboratories throughout the world are busy exploring the pathobiology of these disorders. From these laboratories, we can expect to develop more precise diagnostic tools for the benefit of patients and the development of new specific therapeutic agents.

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Contents

Chapter 1

Connective Tissue Disease—Historical Perspective

BERNARD M. WAGNER

In 1953, it was my good fortune to join the Department of Pathology, Mount Sinai Hospital, New York, N.Y., as a senior resident. Dr. Paul Klemperer was director of the department and the hospital's chief pathologist. His concept of the "collagen diseases" some 10 years earlier had set the medical world buzzing. I had worked with Dr. William E. Ehrich, Chief of Pathology, Philadelphia General Hospital, in studying the cellular response to antigenic stimulation. Our studies in rabbits clearly confirmed the role of the plasma cell in producing specific immune globulins. Ehrich had been a student with Aschoff in Berlin. This experience gave Ehrich a penetrating view of inflammation and a commitment to experimental pathology. Klemperer had worked with Sternberg in Austria, and it was only natural that Ehrich and Klemperer would be friends. As an experimentalist, Ehrich had reservations about the concept of "collagen diseases." Klemperer's hypothesis was primarily based on detailed studies on human tissues obtained at autopsy. Ehrich had stimulated my interest in the pathogenesis of rheumatic heart disease and suggested that I continue this work with Klemperer.

Klemperer's laboratory was a ferment of intellectual activity. A superb medical historian and scholar, Klemperer was also a master of autopsy pathology. His residents were infused with an enthusiasm and dedication to clinical pathological correlations. As serious students of human disease, we were expected to be scholarly and objective.

It is interesting to note, as part of the historical record, that Klemperer's original paper defining the concept of collagen disease was rejected by the editor of a well-known pathology journal as being "too vague, unsupported by facts and highly conjectural." Of course, the paper was accepted by another journal and stands as a milestone in the advance of medicine. At first, clinicians rallied to the concept rapidly while pathologists remained more reserved. Klemperer's laboratory had a steady stream of clinical investigators, many of whom became some of our most distinguished biochemists, immunologists, and rheumatologists. How did Klemperer arrive at his novel, innovative concept? As the father of connective tissue disease, what facts, theories, and observations lead him to conceive of the primacy of connective tissue in disease states? Klemperer was a

medical historian and scholar. He could relate current science to its historical roots. His detailed studies of postmortem tissues from patients with systemic lupus erythematosus (SLE) and generalized scleroderma played a major role in the evolution of "collagen disease."

THE CONCEPT OF FIBRINOID AND THE COLLAGEN DISEASES

The pathologist Neumann in 1880 noted that picrocarmine stained degenerated collagen in a manner resembling that of fibrin. These changes were observed in inflamed serous membranes, the wall of a ruptured aortic aneurysm, and verrucous endocarditis. He suggested the term "fibrinoid degeneration" of connective tissue for these alterations and regarded the resulting hyaline mass as the "fibrinoid substance." Because of the location of fibrinoid and its relationship to the cellular components of the connective tissue, Neumann concluded that fibrinoid represented the change of collagen fibers into final protein end-products which were similar to fibrin. Apparently, this phenomenon could be initiated by a variety of heterogeneous inflammatory conditions. Neumann clearly defined fibrinoid as a degeneration of collagen fibers characterized by the development of bands or clumps of hyaline masses which resemble fibrin in their staining properties.

Attempts to understand allergic reactions in human and experimental disease were made by Klinge. He was the first to realize that fibrinoid degeneration was not caused by changes in collagen fibers but that it was due to the deposition of fibrin-like material in the ground substance. Because Klinge could produce fibrinoid changes in anaphylactic-type hypersensitivity in animals, he concluded that fibrinoid in human tissues was also hypersensitivity related. Thus, began a sweeping generalization that the anatomic finding of fibrinoid was proof of an allergic pathogenesis of the particular disease studied. Klemperer did not completely accept this attractive hypothesis. He stated that "Hypersensitivity is too complex and obscure a biologic state to serve as a final explanation for an equally ill-defined morphologic phenomenon."

Klemperer was impressed by the fibrinoid changes of the connective tissues in systemic lupus erythematosus and generalized scleroderma. Influenced by the concept of Neumann, Klemperer advocated that the basic pathomorphologic feature of these diseases was an abnormality of the collagen fiber due to a defect in the steady state of the collagen protein. The obvious increase in collagen fibers in generalized scleroderma seemed to strengthen this notion. The term "collagen disease" was chosen to describe a group of diseases which were characterized morphologically by systemic alterations of the connective tissue, especially of the collagen fibers.

COLLAGEN DISEASE

Collagen disease is a conceptual term and does not imply pathogenetic definition. As a concept, it calls attention to the significance of the connective tissue as the site of pathologic changes and serves to stimulate research as to the reasons for these changes. Rheumatic fever, systemic lupus erythematosus, generalized scleroderma, rheumatoid arthritis, dermatomyositis, periarteritis no-

dosa, and serum sickness were grouped as the diseases embraced by the term collagen disease.

One of the major objections against the generic term "collagen disease" was the fact that the morphologic criteria were indefinite and generalized. A reason for the vagueness was the implied belief that fibrinoid alteration of the connective tissue was a clear-cut, always identical expression of tissue injury. According to Klemperer, the striking fact that fibrinoid occurs in such diverse morbid and experimental situations should force one to think that the apparent similarity of histopathologic changes might be evasive and might not denote identity. The overwhelming evidence to date indicates that a variety of fibrinoids exists and is not confined exclusively to a connective tissue origin. It has been shown that the fibrinoid of malignant hypertension is probably derived from smooth muscle necrosis.

The term collagen disease was evolved from careful observations on generalized scleroderma and SLE as they related to the older work of Neumann. As a conceptual symbol, the term remains acceptable. Because the original common denominator of all the disease in this group was the presence of fibrinoid, the term, "systemic fibrinoid diseases" was proposed. This term suffers from failure to indicate pathogenesis or etiology. A variety of terms can be advocated, depending on which single entity common to the group is singled out for sole consideration.

As time passed and research data accumulated, it seemed appropriate to expand the limiting descriptive terms to include all diseases characterized by systemic involvement of the connective tissues. Thus, the simple generic term "systemic connective tissue disease" evolved.

PRESENT AND FUTURE

Research today continues to be directed towards understanding the complex cellular biology of the connective tissue. Pathogenetic mechanisms must be elucidated in order to develop appropriate therapeutic strategies. Pathologists will continue to play an important role in this important undertaking. It is the responsibility of pathologists to make detailed observations of human tissue responses correlating them with clinical events. In this manner, the enigmas of the connective tissues in human disease may be resolved.

Chapter 2

The Structure of Collagen

EDWARD J. MILLER

INTRODUCTION

Information concerning the structure and function of collagen has grown rapidly within the past two decades. This circumstance has been due largely to the acquisition of data indicating the existence of multiple forms and types of collagen.[13] The polypeptide chains composing the different types of collagen molecules are clearly derived from information contained within a unique set of closely related structural genes. The different molecular species of collagen show a certain degree of specificity with respect to tissue distribution. Nevertheless, all types of collagen molecules are destined to form supramolecular structures in extracellular spaces. These aggregates function largely as the major supporting elements of the various connective tissues. This presentation deals with the major structural features of the different forms and types of collagen. This information provides a framework for our current understanding of certain connective tissue diseases at the molecular level.

FORMS OF COLLAGEN

Table 2.1 lists the known forms of collagen and provides a succinct definition for each form. Preprocollagen and procollagen chains arise as a result of the assembly of amino acids in peptide linkage in an order specified by a particular collagen mRNA. From the physiological point of view, the preprocollagen chain is largely a conceptual entity. It probably never exists as such since its NH_2-terminal leader sequence is removed from the nascent chain once the latter has penetrated the membrane of the endoplasmic reticulum. The procollagen chain thus represents the final product attained on assembly of all amino acids in the chain. This process is normally accompanied by a number of posttranslational modifications such as hydroxylation and glycosylation reactions. The procollagen chain therefore contains the primary structural features required for all subsequent events involved in the production and metabolism of collagen.

The procollagen molecule is formed on the alignment and folding of three procollagen chains. These events occur within the endoplasmic reticulum. At this point, then, the secondary and tertiary structures of the procollagen and collagen molecule are established. The conversion of procollagen to collagen occurs extracellularly. This process generates the monomer collagen molecule and involves proteolytic cleavage and removal of precursor-specific segments from

both ends of the procollagen molecule. For the most part, these segments represent globular domains. Their loss, then, results in the removal of virtually all sequences exhibiting elements of tertiary structure.

Under physiological conditions, collagen molecules generated in the conversion of procollagen to collagen generally precipitate to form supramolecular structures. The latter may be regarded as examples of quaternary structure. For type I, II, and III collagen molecules, the formation of quaternary structure involves the lateral alignment and discrete displacement of individual molecules, a process which generates the fibrous elements which are readily recognized in the electron microscope as classic collagen fibers or fibrils. Type IV collagen molecules, however, apparently form more open structures in which a three-dimensional network is generated through end-to-end contacts on the part of individual molecules.[18] Intuitively, the latter type of aggregate is much more appropriate for type IV molecules, which serve to provide the supporting scaffold in basement membranes where a certain degree of flexibility and permeability are crucial to function.

TYPES OF COLLAGEN

As of this writing, nine unique and genetically distinct collagen chains have been identified and characterized at least with respect to overall compositional features.[13] These chains are listed in Table 2.2 (column 2) as constituents of individual triple-helical molecular species. As indicated in the table, the chains participate in the formation of at least nine molecular species which are commonly recognized as belonging to five different "types" of collagen. The designation of collagen type with respect to individual chains or molecular species primarily reflects similarity in chemical properties and implies a unique functional role.[2, 3, 11, 13]

TABLE 2.1. FORMS OF COLLAGEN

1. Preprocollagen chain—Initial biosynthetic product formed on translation of a collagen mRNA.
2. Procollagen chain—Final biosynthetic product formed on translation of a collagen mRNA.
3. Procollagen—Precursor molecule formed on association of three procollagen chains.
4. Collagen—Molecule formed through processing of procollagen.
5. Collagen fiber (fibril)—Functional element formed through precipitation and precise lateral alignment of collagen molecules (type I, II, and III collagens).
6. Collagen aggregate—Functional network formed on association (end-to-end) of collagen molecules (type IV collagen).

TABLE 2.2. CHEMISTRY AND BIOLOGY OF THE COLLAGENS

Collagen	Chemistry	Biology
Type I	$[\alpha 1(I)]_2\alpha 2(I)$ $[\alpha 1(I)]_3$	Large, well-structured fibers
Type II	$[\alpha 1(II)]_3$	Fibrils of hyaline cartilages
Type III	$[\alpha 1(III)]_3$	Reticular networks (distensible connective tissues)
Type IV	$[\alpha 1(IV)]_3$ $[\alpha 2(IV)]_3$	Structural aggregates of basement membranes
Type V	$[\alpha 1(V)]_2\alpha 2(V)$ $[\alpha 1(V)\alpha 2(V)\alpha 3(V)]$ $[\alpha 1(V)]_3$	Pericellular membranes

In this regard, type I collagen represents two molecular species, *i.e.*, a heteropolymeric molecule composed of two α1(I) chains and one α2(I) chain as well as a homopolymeric molecule composed of three α1(I) chains. The predominant molecular species of the type I system is the heteropolymer, which comprises greater than 95% of the collagen attributed to the type I system in all tissues thus far examined. This collagen is widely distributed throughout the organism to sites where it forms the relatively large well-structured fibers easily recognized in appropriately stained electron micrographs.

Type II collagen is comprised predominantly of a single homopolymeric molecular species. It is found largely in hyaline cartilages, where it generally forms fibrils of somewhat smaller diameter than those produced by type I collagen. Fibrils derived from type II molecules are also prevalent in sites such as the nucleus pulposus and vitreous humor. Nevertheless, type II collagen exhibits a much more restricted anatomical distribution than type I collagen. Indeed, the location in which type II is prevalent strongly suggests that this collagen has evolved specifically for function in tissues largely demanding resistance to compressive forces.

Type III collagen likewise is comprised of a single homopolymeric molecular species. For the most part, structural elements formed by type III collagen molecules are widely distributed and take the form of small fibrils organized into reticular networks which are more prevalent in distensible connective tissues. This collagen, then, exhibits supramolecular structures which are compatible with maintaining support for the tissues while at the same time allowing a certain degree of distensibility and compliance as a function of external forces.

Current data indicate that type IV collagen exists in the form of two molecular species, both of which represent homopolymers. Type IV collagen is apparently confined in distribution to major basement membrane structures. The more open network formed on precipitation of type IV collagen molecules is admirably suited to serve as the supporting scaffold in sheets of basement membrane as noted above.

Type V collagen represents the most recently described collagen system. It appears to be comprised of at least three chains which form as many as three molecular species. This collagen is widely distributed, although it often comprises only a small fraction of the total collagen in a given connective tissue. Current evidence indicates that this collagen is localized in membranous sheaths adjacent to or surrounding a variety of connective tissue cells.[10] It thus may be regarded as a component of a specialized basement membrane system uniquely adapted to function in pericellular environments.

The extant data indicates that still other collagen chains exist, and complete characterization of these chains, along with an evaluation of the biological functions of molecules in which the chains occur, can be anticipated as future developments. Information concerning the structural genes for collagen synthesis has been inferred largely from investigations on the protein present in connective tissues. However, recent studies on a series of overlapping clones derived from two libraries of chick genomic DNA have indicated that the gene for the pro-α2(I) chain spans approximately 37 kb and contains up to 50 intervening sequences of widely divergent sizes.[14] Insofar as the genes for collagen synthesis