The Cardiovascular Manifestations of Genetic Disorders of Collagen Metabolism

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ABSTRACT

Current research in the biochemistry and molecular genetics of collagen metabolism has produced a sophisticated level of understanding of the mechanisms involved in the pathogenesis of a number of inherited diseases of connective tissue. Nowhere is this better exemplified than in the cardiovascular disorders associated with certain genetic disorders of collagen metabolism. For instance, the life-threatening vascular complications of Ehlers-Danlos syndrome IV, the Sack-Barabas type, appears to be related to a number of defects in the production of Type III procollagen. The large size of the collagen genes and the complexity of the biochemistry of collagen have not made research a simple task. Nevertheless, the location of certain genes is now known with a reasonable degree of accuracy and a few have been cloned in their entirety. The future investigation of these genetic mutations holds great excitement for those engaged in research in this fascinating field.

Introduction

Recent advances in protein chemistry and molecular genetics have increased our understanding of a number of genetic diseases of collagen metabolism. Ten types of collagen have been biochemically identified and their tissue distribution is shown in table I. Those which form fibrils are principally types I, II, and III. Of these, type I is the most abundant and is found in connective tissue, usually in association with type III, while type II is found mainly in hyaline cartilage. The most common type of non-fibrillar collagen, type IV, is found in basement membranes. Type V, another non-fibrillar collagen, is associated with blood vessels and smooth muscle.

Genetic Diseases of Collagen Metabolism

The relationship between genetic diseases of collagen and specific collagen metabolism...
**TABLE I**

Collagen Types and Tissue Distribution*

<table>
<thead>
<tr>
<th>Collagen Type</th>
<th>Tissue Distribution</th>
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<tbody>
<tr>
<td>I</td>
<td>Skin, bone, tendon; ubiquitous except in cartilage</td>
</tr>
<tr>
<td>II</td>
<td>Cartilage, vitreous, nucleus pulposus</td>
</tr>
<tr>
<td>III</td>
<td>Blood vessels, intestine, fetal skin</td>
</tr>
<tr>
<td>IV</td>
<td>Basement membrane</td>
</tr>
<tr>
<td>V</td>
<td>Ubiquitous, except in cartilage</td>
</tr>
<tr>
<td>VI</td>
<td>Aortic intima, skin, kidney, muscle</td>
</tr>
<tr>
<td>VII</td>
<td>Amnion, anchoring fibrils</td>
</tr>
<tr>
<td>VIII</td>
<td>Endothelial cells, Descemet's membrane</td>
</tr>
<tr>
<td>IX</td>
<td>Cartilage</td>
</tr>
<tr>
<td>X</td>
<td>Cartilage</td>
</tr>
</tbody>
</table>


Abnormalities is probably best understood for collagen types I and III. These are formed from procollagen molecules which have a triple helix flanked at one end by an N-propeptide and at the other end by a C-propeptide* (figure 1). Pro-collagens are secreted from fibroblasts, the terminal propeptides are cleaved by different proteases, and the collagen monomers become cross-linked by lysyl oxidase. The process is complex and, therefore, subject to a number of defects. This complexity is reflected in the size of the collagen genes which are extremely large, 18 to 38 kb in length, in contrast to the hemoglobin genes which are about 2 kb long.

Many of these disorders (table II) are associated with life-threatening problems of vascular integrity. This association is primarily caused by production of miscreant collagen and its incorporation into the walls of major blood vessels.

**Cardiovascular Manifestations**

One of the genetic conditions which is commonly associated with severe vascular problems was first described by a French pediatrician in 1896 and bears

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**Figure 1.** Pro alpha chain monomers are synthesized from mRNAs and undergo a series of post-translational steps before being secreted into the extracellular space as procollagen. Cleavage of the propeptides takes place and cross-linking provides the collagen fibrils with their rigidity.
his name. The phenotype in Marfan Syndrome (MS) is characterized by long, thin extremities, joint laxity, dislocation of the lens and dilatation, and rupture of the aorta. Clinical surveys suggest that 70 percent of these patients may have abnormal cardiovascular findings. Almost all patients have pathological echocardiograms demonstrating aortic dilatation, mitral valve prolapse, or both. Even in childhood, the echocardiogram demonstrates some dilatation of the aortic root.

The potentially lethal complications of MS are aortic regurgitation and dissection. Dissection usually begins in the descending aorta and may spread through the arch and entire descending aorta or may progress in a retrograde fashion, involve the coronary arteries, or rupture into the pericardial sac or mediastinum.

Aortic rupture or dissection has been reported in at least 20 women during pregnancy. It seems to be related to the presence of significant aortic dilatation, and the risk may be less in women with relatively normal echocardiograms.

Studies suggest that there may be defects in collagen cross-linking, but a deficiency of the important cross-linking enzyme, lysyl hydroxylase, has not been demonstrated. Hollister and colleagues have identified a group of patients who demonstrate an insert of about 20 amino acids into the alpha 2 procollagen molecule which may account for the defective cross-linking.

**Homocystinuria**

The Marfanoid habitus is sometimes seen in patients who have quite a different spectrum of vascular disease in association with a specific biochemical abnormality, homocystinuria. Affected patients frequently have tall stature with arachnodactyly and lens dislocation but, unlike Marfan syndrome, some have mental retardation and venous and arterial thromboses. Homocystinuria may be associated with a number of metabolic defects, one of the more common being a deficiency of the enzyme cystathionine synthase which causes an accumulation of homocystine and methionine in affected individuals. Treatment is determined by the exact site of the metabolic defect; unfortunately, some patients are severely affected and die in childhood.

The major life-threatening complication of homocystinuria is vascular thrombosis which may include acute arterial thrombosis in a limb, pulmonary embolism, cerebrovascular accidents, and mesenteric or renal artery thrombosis. Angiography is said to prompt thrombosis in these individuals. The arteries show characteristic histopathologic changes. The media is thin, the smooth muscle fibers are separated by increased quantities of ground substance, while the internal elastic lamina may be fragmented. The intima is severely affected by proliferation of fibrous and elastic tissue, a process that encroaches on the lumen, which may be occluded by organized thrombi. The arterial wall may be thin and the vessel diameter increased, but aneurysms are uncommon. Circumferential intimal bands are seen which may simulate a
coarctation. Occasionally, the coronary arteries are involved, and the endocardium is thickened so that it mimics endocardial fibroelastosis.

The pathogenesis remains unclear and three mechanisms have been postulated: (a) direct interference with collagen stability, (b) secondary disturbance of connective tissue organization, and (c) a direct effect on vascular endothelium and platelets.

Homocystinuria promotes arteriosclerosis, and primary treatment of the metabolic defect seems to reduce the frequency of the thromboembolic events. The beneficial effects of antiplatelet drugs such as aspirin are still in doubt.

**Ehlers-Danlos Syndrome**

Another group of patients who have significant vascular problems are those with joint laxity, skin hyperextensibility, and abnormal tissue fragility. They form part of a spectrum of diseases known as Ehlers-Danlos syndrome (EDS), which has now been expanded into at least ten different types. Each of the types has specific clinical characteristics, and some have well defined biochemical abnormalities.

Ehlers-Danlos Syndrome IV is a rare form which is associated with a number of abnormalities of type III procollagen. Decreased and absent secretion of type III collagen and the presence of a structurally abnormal type III collagen have all been described. Most families show an autosomal dominant inheritance pattern, and vertical transmission of the defect in type III collagen has been demonstrated. The presence of new mutations has been described, and an autosomal recessive form has also been suggested. It appears that a wide range of defective collagen genes may give rise to this relatively restricted phenotype.

Arteriography has resulted in further arterial hemorrhage at the puncture site, and the usual techniques for managing arterial rupture are fraught with problems because of the friability of the vessel wall. The results of surgery are sometimes tragic, with the eventual sacrifice of limbs of organs in attempt to achieve hemostasis. No definitive therapy is available. Patients are advised to avoid trauma wherever possible, and some patients survive for many years without serious hemorrhage.
The association of increasingly severe neurological dysfunction, unusual hair, failure to thrive, and a collagen disorder is seen in the kinky hair syndrome first described by Menkes. This is an X-linked recessive condition which is characteristically associated with downhill course and death before three years of age. The patients have an apparent block in intestinal transport, low serum copper levels, low levels of copper in the CNS but high levels in the kidney and other tissues. Connective tissue is involved in intestinal transport, low serum copper levels, low levels of copper in the CNS but high levels in the kidney and other tissues. Connective tissue is probably affected by defective cross-linking of collagen fibers secondary to a deficiency of lysyl oxidase, a cuproprotein enzyme. There is tortuosity of vessels with numerous small aneurysms. The internal elastic lamina is split, the intima is hyperplastic, and many vessels are tortuous and stenosed. The central nervous system shows extensive neuronal atrophy and glial proliferation. There is no satisfactory treatment.

Development in our understanding of the molecular genetics of defects in collagen metabolism is proceeding apace. For example, the gene for pro-alpha1(I) has already been located on chromosome 17 and that for pro-alpha2(I) on chromosome 7. Both genes have been cloned in their entirety, and restriction fragment linked polymorphisms have been described. The molecular basis for the heterogeneity seen in the Ehlers-Danlos syndromes is slowly being elucidated. Although the defects in types I through III are not understood, EDS IV has been associated both with decreased secretion of type III collagen and with a structurally abnormal type III collagen. The future exploration of these genetic defects, using the tools of the molecular geneticist and collagen biochemist as well as the skills of an experienced clinician, holds great excitement for those engaged in research work in this fascinating field.

References


17. HOLLISTER, D. W., BYERS, P. H., and HOL...


