Occasional abstract

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Inherited abnormalities of collagen

A recent editorial[1] in the *New England Journal of Medicine* draws attention to the advances in collagen chemistry which have led to a much better understanding of inherited collagen abnormalities such as the Ehlers-Danlos syndrome (EDS) and osteogenesis imperfecta (OI). There are now seven subgroups of EDS and five of OI, every one of which is itself variable. The situation closely resembles the inherited haemoglobinopathies with the added interest that collagen is much larger, has five genetic types with eight different chains, and is much more widely distributed in tissues as diverse as bone, skin, blood vessel, lung, tendon, and glomerulus. Thus the disease potential is enormous.

Just as haemoglobin chain deletions cause α and β-thalassaemias, so collagen chain deletions produce specific inherited diseases. EDS IV with type III collagen deficiency varying from zero to several percent[2 3] causes death from lethal arterial rupture in those most severely affected. Deletion of the α2 chain of type I collagen[4] causes moderately severe thin boned OI congenita. An α1 (I) chain deletion would probably be lethal as would type II and type IV collagen deletions.

Post-ribosomal modifications of collagens include lysine hydroxylation, ε amino crosslinks, and excision of procollagen extension peptides from secreted collagens.

Inherited defects of each step produce specific diseases which are also proving heterogeneous. EDS V has been described with[5] and without[6] lysyl oxidase deficiency. Byers *et al*[7] have recently clearly identified lysyl oxidase deficiency in an X linked form of cutis laxa, resulting in faulty crosslink formation. EDS VI, in which scoliosis, retinal detachment, and arterial rupture complicate otherwise typical EDS, has hydroxylysine deficient[8] and normal forms (McKusick, 1980, personal communication). Procollagen peptidase deficiency in animals causes a lethal disease (dermatosparaxis)[9] in which collagen fibril formation is interfered with by the persisting extensions. The puzzling benignity of the human variant[10] EDS VII has recently been explained (Steinemann, 1979, personal communication) by an amino-acid substitution at the cleavage site which allows the N terminal extension to persist.

Diseases analogous to sickle cell and haemoglobin C disease (from amino-acid substitution within the collagen molecule) are so far unidentified. Possibly single substitutions in the much larger molecule produce such insignificant changes as not to produce clinical disease or to be undetectable by electrophoresis. Amino-acid substitutions within the procollagen extension peptides do produce disease, however. EDS VII, as mentioned already, is caused by a mutation resulting in inefficient cleavage, and a recently described OI tarda variant[11] has a probable substitution which allows over-glycosylation and subsequent insolubility of procollagens. We may also expect that chain termination mutations analgous to haemoglobin Constant Spring will be detected among these diseases.

When modern molecular biological techniques allow the identification of specific collagen genes for α1(I), α2, and α1(III), then the way is clear with cloning and restriction enzyme techniques to allow the confident intrauterine diagnosis of subjects affected by these mutations, just as is already possible in some thalassaemias.

Already (theoretically) EDS IV and the α2 chain OI mutant could be diagnosed by fetoscopic skin biopsy if the need and opportunity arises. The vast majority of these diseases, however, are not identifiable in this way.

These collagen abnormalities are also relevant to the more common diseases. Osteoporosis and cerebral aneurysms are obvious examples in which genetic defects similar to those mentioned above could be to blame.

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