NATURE AND CELLULAR ORIGIN OF CONNECTIVE TISSUE MATRIX.

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The chemistry and organization of glycosaminoglycans (GAG) have been well covered in the previous lectures at this symposium. The collagenous component of connective tissue matrix comprises a family of genetically distinct molecules of which there are at least four types. Type I collagen contains two alpha chains of the α1(I) type and one α 2 chain, type II is composed of [α1(II)$_3$], type III of [α1(III)$_3$], and type IV of [α1(IV)$_3$]. At least two additional collagens of the basement membrane type have been characterized in part and perhaps others will be identified in the future (see Miller, 1976).

The cells of the fibrocyte or mesenchymal cell family that produce copious amounts of collagen and GAG (fibroblasts, chondroblasts, osteoblasts) have a highly developed granular endoplasmic reticulum in which the newly synthesized procollagen accumulates and is hydroxylated before being transferred to the Golgi complex (Olsen et al., 1975) where it combines with GAG synthesized in the Golgi vacuoles (Revel, 1970) before being secreted from the cell, probably as a collagen-GAG packet (Revel and Hay, 1963; Trelstad et al., 1974). Chondroblasts seemingly produce only type II collagen and certain fibroblasts, such as those in the avian cornea, produce only type I collagen (see von der Mark, this symposium). Osteoblasts produce type I collagen and in certain mesenchymes, especially reticular connective tissue, both types I and III are produced, although not necessarily by the same cell (see von der Mark, this symposium).

Autoradiographic and biochemical evidence for secretion of collagen by epithelium (Hay and Revel, 1963; Dodson and Hay, 1971) and epithelial cell lines (Green and Goldberg, 1965) has been confirmed and extended, especially for the developing cornea, where it has been shown that corneal epithelium secretes types I and II collagens (Trelstad et al., 1974; Linsenmayer et al., 1977) and probably produce the type IV collagen (see von der Mark, this symposium) of its basement membrane. Interestingly, type III collagen has not been identified in a matrix known to be entirely epithelial in origin, i.e., the primary corneal stroma. Not only epithelial cells, including neuroepithelium (Cohen and Hay, 1972; Newsome et al., 1976), but also muscle cells (Ross, 1971) produce basement membranes (and probably other collagens as well).

The basement membrane class of collagens is especially interesting. They seem to be unique in retention of nonhelical telopeptides and organization into sheets or felt works rather than fibrils (Kefalides, 1975). Basement membranes are only associated with epithelium and muscle, never with connective tissue cells *per se* (e.g. fibroblasts). In certain locations, such as the lens and yolk sac, they are very thick, presumably for support (Kefalides, 1975). Basement membranes, at least in the embryo, contain GAG (Trelstad et al., 1974) and they probably influence transport of substances into and from embryonic

epithelium and muscle. Epithelial and muscle cells produce GAG (Manasek et al., 1973; Meier and Hay, 1974) and probably other glycoproteins as well.

GAG is also intimately related to forming and formed collagen fibrils of the type I-III class and may influence their polymerization (see Toole, 1976). It is interesting to note that type II collagen characterizes cartilage and the primary corneal stroma, both of which are very rich in chondroitin sulfate. However, the morphological appearance of the collagen fibrils is quite different in the two cases. Moreover, the type I collagen of the secondary corneal stroma is also associated with chondroitin sulfate. While type III collagen seems to characterize loose reticular connective tissues rather than compact tissues, type III collagen does occur in GAG-rich areas and can form 60 nm thick collagen fibrils. All the collagens that have been studied seem to be able to interact with the cell surface of both epithelial and mesenchymal cells to stabilize their differentiation in vitro (Meier and Hay, 1974; Kosher and Church, 1976). While much is now known about the nature and cellular origin of connective tissue proteins, we are really at a loss to explain in structural and functional terms, the multiplicity of genetically determined forms of certain of these proteins, especially collagen.

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