CHAPTER 4

Matrix Composition

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4 MATRIX COMPOSITION AND ARCHITECTURE

4.1 Chemical compostion vs. architecture of extracellular matrices

(see *Rubin and Farber, 1988*).

At the scale of the unit cell process (*ca*. 10 μm) the protagonist cell is associated with a small control volume of extracellular matrix (ECM). A particular connective tissue (eg., tendon, dermis, cartilage) can be modeled as a large (scale *ca*.1 cm) aggregate of ECM of relatively homogeneous composition and specific architecture. This is an approximation which is useful in setting up a first-order model of the structure. The ratio of the various macromolecular components of the ECM is largely tissue-specific. It might appear that the ECMs of an organism constitute a hopelessly complicated array of structures. However, two rules can be used to simplify their first-order description:

a. A relatively small number of distinct macromolecular components account for all ECMs of an organism. A few distinct proteins, a few distinct glycosaminoglycans (GAGs) and water (60-65%) constitute all ECMs. Two of these proteins, collagen and elastin, are typically present in the form of fibers made up of aggregates of macromolecules. These fibers have diameters in the size range 1-100 μm (depending on tissue type and tissue site). Thus, the control volume dV of a unit cell process, order of magnitude 10 μm^3, can be said to comprise just one cell and a mass of an associated fibrous protein (or two) which has roughly the dimension of one fiber width. Cell and matrix component are usually connected by two cell-adhesion adhesion macromolecules (typically an integrin receptor and a cell-adhesion macromolecule such as fibronectin). A matrix component is usually connected to another matrix component with a proteoglycan (a protein chain to which are attached GAG chains). For many tissues the precise nature of most of these connecting macromolecules is unknown at present.

b. The average orientation of the axes of these fibers is one of the characteristics of the architecture of a tissue. Occasionally, the most distinctive difference between two tissues is not the chemical composition but the architecture. An example of such a distinction is that between dermis and dermal scar. Even though the chemical composition of the two tissues is very similar, in dermis the average collagen fiber orientation is approximately random in three dimensions whereas in scar it is strongly planar. In the cornea the collagen fibers are arranged as in a cross-ply laminated composite material, with fiber orientation strictly uniaxial within a given plane but rotated by 90^o relative to the neighboring plane. In the aorta the collagen fibers are arranged helically about the axis of the vessel. In relaxed tendons and ligaments the collagen fibers are wavy although the axes of these fibers are oriented. However, in a slightly stretched tendon or ligament the fibers are not wavy and the average fiber orientation is highly axial. The orientation of elastin fibers is experimentally less accessible and less concrete information is accordingly available. In the ligament of the neck the elastin fibers are randomly oriented .

4.2 Systematics of configurational order in macromolecules

(*see Yannas, 1972*)_.

A macromolecular component may be present in a control volume dV either as a single macromolecule or as an aggregate of identical macromolecules. The structure of a macromolecular component can be described by rules based on periodic repetition of a geometric parameter or of a chemical feature. In many cases a specific periodic repetition is observed at each of several scales of magnitude. In such cases it is possible to identify different "levels of order", eg., primary, secondary, tertiary and so forth. The biologic specificity of these macromolecular components is expressed during the highly cooperative interactions which characterize cell-matrix bonding phenomena or other specific interactions (eg., enzyme-substrate interactions). Clearly, biologic specificity depends on the intactness of the complete structure up to the level of order where the interaction occurs.

Macromolecular structure can be modified (denatured) by temperature (eg., helix-coil transition), pH (eg., loss of collagen fiber periodicity) or enzymatic action (eg., degradation of GAGs by chondroitinases). Denatured macromolecules usually do not participate in cooperative interactions with cells.

a. Primary structure of a macromolecule: the sequence of mers for the entire chain. In a protein, it is the complete sequence of the different (at least 18) amino acids which constitute the polypeptide chain or chains. In most GAGs it can be approximated by the structure of the disaccharide repeat unit. The latter consists of a hexosamine (either glucosamine or galactosamine) and one of the following: glucuronic acid, iduronic acid or galactose. A proteoglycan is a protein chain ("protein core") to which are attached several GAG chains, usually of unique composition. Primary structure is usually identified by biochemical analysis (peptide sequence studies).

b. Secondary structure is the local chain configuration (over 2-3 mers). In collagen, it is a steep left-handed helix. In elastin, there seems to be no regularly repeating unit. If crystals are available, secondary structure can be studied by wide-angle x-ray diffraction.

c. Tertiary structure is the configuration of the entire macromolecule. In elastin it is a random coil whereas in collagen it is a triple helix. Proteoglycans probably have tertiary structures which trace the topography of the fibrous macromolecules that are connected by the proteoglycan molecule. If crystals can be obtained, the tertiary structure can be studied by x-ray diffraction; in solution, it can be studied by nuclear magnetic resonance.

d. Quaternary structure is the packing pattern of several molecules. The packing pattern can be highly orderly (crystalline) or it can be amorphous. In collagen, it is a crystallite, the well-known banded collagen fiber visible in the electron microscope (periodicity: 64 nm). Certain macromolecular components are probably present as single molecules in vivo and, therefore, lack quaternary structure (eg., proteoglycans, cell-adhesion macromolecules, integrins, regulators). Sometimes, these macromolecules can be crystallized in vitro; although very useful for structural studies of the lower levels of order, such an artificial quaternary structure is of unknown biologic significance. Quaternary structure is visible in the electron mictoscope. If periodic, quaternary structure can also be studied by wide-angle x-ray diffraction.

e. Architecture is the porous scaffold comprised of several protein fibers, each fiber with its distinctive quaternary structure. One of the distinctive features of architecture is average fiber orientation. Another feature is the average pore diameter. Architecture is visible in the light microscope.

4.3 Collagens

(*see Nimni, 1983*).

a. Description of levels of structural order. Tissue specificity.

b. Discrete melting phenomena.

Helix-coil transition (loss of tertiary structure).

Acid-swelling (loss of quaternary structure).

c. Biological specificity vs. level of structural order.

Degradation by collagenase during tissue remodeling.

Platelet aggregation requires the quaternary structure.

Mechanical reinforcement of developing and adult tissues. "Composites".

Physiological function involves collagen fibers in extension. X-ray data show deformation of the quaternary structure rather than of the triple helix during load-bearing functions within physiological limits.

Bone formation involves deposition og hydroxylapatite crystals in "holes" within the collagen quaternary structure.

4.4 Elastin

(*see Aaron and Gosline, 1981; Yannas, 1981*).

a. Randomly coiled structure. The Bernoulli distribution and the random walk.

b. Interaction with water. Gibbs free energy and hydrophobic bonding.

c. Elastin as an ideal rubber. Elastic ligament. Vascular wall.

4.5 Proteoglycans and glycosaminoglycans

(*see Silbert, 1987*).

a. Primary structure.

b. Electrostatic interactions. Debye length.

c. Effect of electrostatic interactions on stiffness. Articular cartilage.

4.6 Adhesion Proteins

(*see Hynes, 1990*).

a. Fibronectins.

b. Laminins.