Published in final edited form as:
Curr Opin Cell Biol. 2007 October ; 19(5): 578–583. doi:10.1016/j.ceb.2007.09.005.

Extracellular matrix:

from atomic resolution to ultrastructure

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Abstract

The extracellular matrix (ECM) is a highly organized multimolecular structure, essential for life in higher organisms. Although substantial high-resolution structural information is available for relatively small fragments of ECM components, the inherent difficulty in preparing and analyzing samples of large, fibrous polymers impedes structural efforts. Here, we review recent advances in understanding the structure of three important ECM components: collagen, fibrillin and fibronectin. Emphasis is placed on the key role of intermolecular interactions in assembling larger, μm scale, structures.

Introduction

The extracellular matrix (ECM) is a complex network of glycoproteins and proteoglycans that originated with the advent of multicellular organisms [1]. Cells generate well-ordered ECM-complexes to surround and support themselves. The ECM then plays an essential role in the survival, migration and proliferation of these adjoining cells. Continuous ECM remodeling, catalyzed by various degradation enzymes, is common, and the arrangement and concentration of different macromolecules gives rise to a wide diversity of ECM forms in the various tissue types (skin, bone, cornea of the eye, etc.) [2]. The structure of the constituent polymers is rather well known at the domain or fragment level but is less well known at the levels of intact molecule or higher. The monomeric subunits are large, multi-domain and often inherently flexible, thus presenting problems to atomic resolution techniques such as single crystal diffraction or NMR. The polymers formed retain substantial heterogeneity and are cross-linked and difficult to extract from the matrix in undamaged form. Although progress is relatively slow, new approaches and tools are beginning to have an impact.

In this brief review, we have chosen to illustrate this field by discussing recent structural studies and current understanding of three archetypal ECM proteins: collagen (the most abundant protein in mammals), fibrillin and fibronectin. The first is a biopolymer of characteristic amino acid sequence, while the last two are modular proteins, constructed from repeating, autonomously folding domains with a high degree of structural similarity [3]. A major remaining structural problem is to define the various inter and intramolecular interactions made by molecules, especially in the context of structure at the μm level. We

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This review comes from a themed issue on Cell to cell contact and extracellular matrix Edited by Lawrence Shapiro and Barry Honig

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appreciate that this selection, with only three proteins, neglects many other important ECM molecules and provides only a part of the picture, however, space is limited. A particular area of neglect is polysaccharides, such as hyaluronan [4] which, with its receptors [5], plays a pivotal role in ECM hydration and elasticity.

Collagen

Collagen has a characteristic three residue repeat, Gly-Xaa-Yaa, in its primary structure, which results in a stable triple-helical conformation with the glycine residues at the core of the helix [6-8]. Proline and 4-hydroxyproline residues, usually found in positions Xaa and Yaa, function to stabilize the three individual polyproline II-like helices. After post-translational modification, secreted collagen helices self-assemble to cross-linked microfibrils and eventually μm-long fibrils. This spontaneous process creates large-scale molecular structures with properties of obvious interest to bioengineers [9]. Biology exploits the exceptional mechanical properties of collagen but it also uses it as a scaffold to attach a number of binding proteins to specific sites [10•].

The most abundant collagens are types I, II, and III, found in a range of tissues including tendon and skin; these form characteristic fibrils with identifiable repeat bands separated by 67 nm. These periodic patterns are still not very well understood but were early suggested to be related to the arrangement of triple-helices in fibrils and the inherent periodicity in the collagen primary structure, yielding five so-called D-periods [11-13]. The ability to generate recombinant collagens with defined composition is beginning to have an impact in structural studies; for example, there is evidence, from mutagenesis [14•] and thermostability experiments [15•], of unique domain-like characteristics in collagen type II and a recent study showed that some of these D-periods are in fact dispensable for banded fibril formation [16•].

New structural observations are also helping to achieve a better idea of how collagen fibrils are assembled. Using contact-mode atomic force microscopy Bozec *et al.* [17••] proposed a model for collagen where individual triple-helices, or, possibly, microfibrils, twist around each other along the long axis of the fibril. This concept is comparable to a nanoscale rope composed of multiple twisted fibers, in agreement with past suggestions and observations (Figure 1a). Similar conclusions were reached in perhaps the most detailed study of fibrils so far [18••] with Orgel *et al.* investigating the structure of crystallite elements of collagen type I fibrils *in situ* using X-ray fiber diffraction techniques; a low resolution electron density map was obtained that allowed main chain tracking and some amino acid identification. Individual microfibrils were shown to adopt a right handed supertwist and to interdigitate with neighboring microfibrils. The overall packing is similar to the proposed quasihexagonally packed liquid-crystal collagen model (Figure 1b and c) [19] with intermolecular interactions involving the collagen N- and C-telopeptides critical in maintaining this arrangement, a result supported by computation [20,21].

Fibrillin

Fibrillin-1 is a large (350 kDa) multidomain glycoprotein that forms the major structural component of 10-12 nm elastic microfibrils in the ECM [22,23]. With elastin, it provides the necessary elasticity and resilience of a variety of tissues. A large number of matrix components that interact with fibrillin-1 have been identified, including integrins [24•], heparin [25•], latent transforming growth factor β-binding proteins and fibulin-2 [26]. These, together with homotypic fibrillin interactions, are likely to regulate microfibril assembly [27•]. Fibrillin-1 contains 47 epidermal growth factor-like (EGF) domains interspersed with seven transforming growth factor β-binding protein-like domains; 43 of the EGF domains are expected to bind calcium. Structural studies of fibrillin at the domain level are relatively advanced; a ‘dissection’ approach has been used to study recombinantly expressed domains a few at a time (e.g. [24•]). Ca^{2+}-binding to EGF domains is believed to affect the large-scale fibrillin structure, a hypothesis extensively tested at the level of EGF domains [28] and fragments [29] using wildtype protein and mutations that are known to cause the Marfan syndrome.

Guanidine-extracted fibrillin microfibrils have a ‘beads on a string’ appearance, with approximate 57 nm periodicity when viewed by rotary shadowing electron microscopy (EM) [30] (Figure 2a). These periodic features of approximately 2.5 MDa mass are conserved between different tissue types [31] and, thus, can be mainly attributed to fibrillin molecules. The important issue of how microbrils are constructed from fibrillin molecules is not yet resolved. Several possible models have been proposed to explain the observed periodic pattern, including different orientations (parallel or antiparallel), globular (‘pleated’), non-globular, staggered or non-staggered arrangements of fibrillin molecules [30].

A number of recent studies have addressed microfibril structure by different means. EM image analysis was used on samples extracted by collagenases [32••], giving data that supported a parallel, ‘pleated’ model, with fibrillin molecules occupying a single microfibril repeat. A similar model was assumed in a different study [33••] where recombinantly expressed fibrillin fragments were analyzed by small-angle X-ray scattering and EM single particle reconstruction. In contrast, a recent study of EM images of microfibrillar extracts analyzed by proteolytic degradation and antibody epitope mapping yielded data in support of a non-pleated, staggered model [34••], with individual fibrillin molecules extending over multiple repeats (Figure 2b). Although these published models still differ significantly, it is encouraging that they seem to be more convergent than previous ones. Some of the observed uncertainties and differences, for example the different extensibility of the extracted microfibril [34••], almost certainly arise from use of different extraction procedures.

Fibronectin

Fibronectin (FN) is a large dimeric plasma glycoprotein found only in vertebrates. FN is composed of three different domain types, FNI, FNII and FNIII, high-resolution structures of which have been available for some time [35]. A tightly controlled process transforms plasma FN to a fibrillar form within the ECM. Little is known about the fibrillogenesis process, or the structure of the fibrillar matrix formed. It is, however, believed that FN

interdomain interactions [36-41,42•] and tension exerted through cell-surface receptors [43] are essential. Some of the association sites detected are cryptic [37,39], as interactions can only form after molecular rearrangement, possibly induced by FN stretching. Fibrillar FN has many binding partners including integrin cell-surface receptors, heparin, collagen, fibrin and fibulin [43]. It also has remarkable mechanical properties, including the ability to be stretched as much as fourfold by living cells [44].

Two different mechanisms have been proposed to explain this observed elasticity [45]. The first, postulates that multiple FNIII domains are reversibly unfolded under tension, hence the extension corresponds to stretching of the polypeptide chain [42•,46]. In contrast, the second mechanism assumes that FN extension is because of dissociation of weak inter-domain interactions, many of which involve the first two FNIII domains. In this case, FN extension involves FN transformation from a compact to an extended state. Although the domain-unfolding mechanism has been shown to be important in superfibronectin, a non-physiological FN aggregate [47•], two recent studies present data that favour the second mechanism.

Abu-Lail *et al.* [48••] showed that FNIII and green fluorescent protein (GFP) domains have very similar mechanical unfolding strengths by single molecule force spectroscopy, and earlier studies showed that FN fibrils with embedded GFP domains maintain fluorescence under stretching in cell cultures [49••]. The fact that cell-tension does not unfold GFP domains or, by implication, FNIII domains, supports the domain-rearrangement mechanism. A separate study showed that disruption of a complex formed by the first two FNIII domains unveils a novel cryptic association site in the interdomain linker [50••]. This disrupted, 'open' state ($^{1\text{-}2}$FNIII^{open}) displays dramatically increased affinity to nM levels for the FN N-terminal domains (FN 30 kDa). Thus, a model was proposed where *in vivo* $^{1\text{-}2}$FNIII^{open} is reproduced by cell-generated tension, leading to formation of a tight complex between two FN N-termini and the creation of a FN protofibril (Figure 3). This proposed mechanism could, in principle, be a general way of producing tension-induced signals.

Conclusion

In all three ECM molecules visited, association interactions are the key to understand higher order structures. Intermolecular interactions define the packing order of collagen [18••], inter-domain interactions have a major role in models of fibrillin [27•] (whether 'pleated' or staggered) and interdomain association sites lead directly to FN fibrillogenesis models [50••]. Detailed structural descriptions of module interactions are, comparatively, fewer than structures of individual modules [3]. However, increasing attention to extraction procedures, new structural tools and an ability to express a variety of defined recombinant molecules can lead to a much better understanding of how the network of large, cross-linked molecules are laid down in the insoluble ECM by a series of precise association events.

Acknowledgement

Financial support was provided by the Wellcome Trust.

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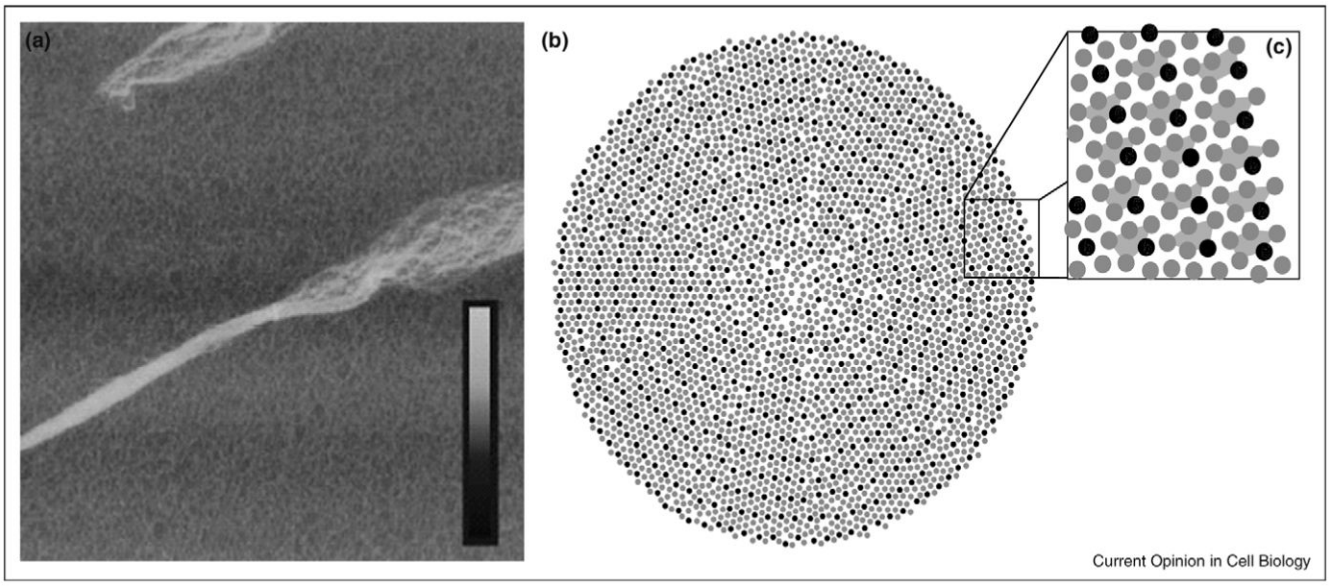

Figure 1.

Supramolecular organization of collagen fibrils. **(a)** The superhelical twist of individual fibrillar elements can be seen in this atomic force microscopy image of a mechanically disrupted collagen fibril (ref. [51], reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Copyright Wiley-Liss, 2006). The box size is 5 μm × 5 μm and the inset height scale corresponds to 0-30 nm. **(b-c)** Cross-section model of molecular packing in collagen fibrils (adapted with permission from ref. [19]. Copyright Elsevier, 2002). Thousands of individual collagen triple-helices interact to form a single fibril with both ordered and disordered packing features. Collagen microfibrils are formed by five collagen molecules in a staggered arrangement, shown connected by trapezoids in **(c)**.

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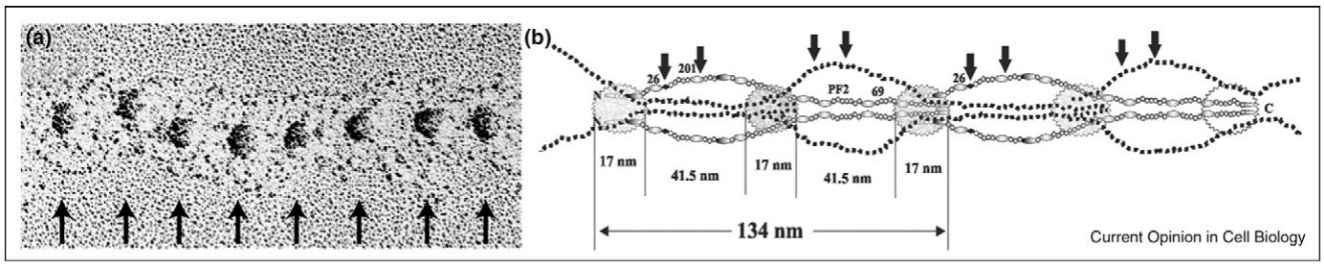

Figure 2.

Proposed model of fibrillin microfibrils (adapted with permission from reference [34••], Copyright The American Society for Biochemistry and Molecular Biology, 2007). **(a)** Rotary shadowed micrographs of guanidine-extracted microfibrils show characteristic repeats of approximately 57 nm (indicated by arrows). **(b)** A possible model of microfibril structure involves staggered, parallel molecules of fibrillin-1 with the N-terminal halves on the outside of the microfibril and C-terminal halves in the core. Individual fibrillin molecules extend over multiple sequential microfibril repeats. Antibody epitopes (mAb 26, mAb 201, and mAb 69) are labeled, and major collagenase cleavage sites are marked with arrows.

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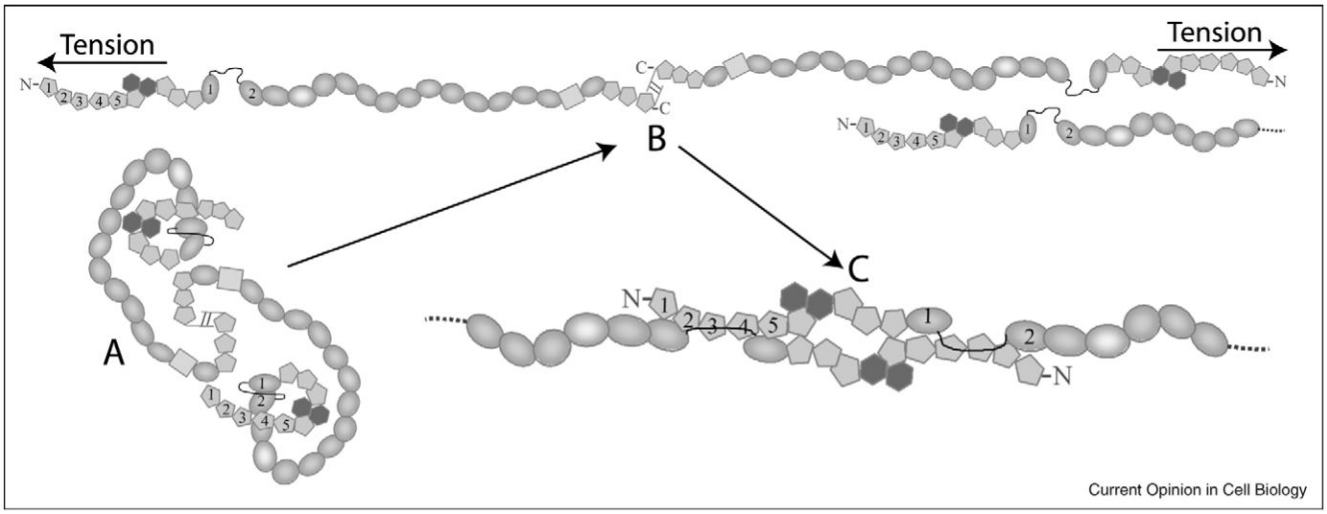

Figure 3.

Proposed model of fibronectin fibrillogenesis [50••]. **(A)** FN exists in a globular, soluble state in plasma. The interdomain interactions defining this state are disrupted by cell-generated tension **(B)**. **(C)** The N-termini of two extended FN molecules form a tight complex through the FN 30 kDa-$^{1\text{-}2}$FNIII^{open} interaction, thereby creating FN protofibrils.