Electron Microscopy in the Study of Myofibroblastic Lesions
Brian Eyden, PhD

Electron microscopy in the diagnosis and academic study of myofibroblastic lesions is discussed. Myofibroblasts from granulation tissue and tumor stroma are regarded as the nearest equivalent to a "normal" myofibroblast population with which to define myofibroblastic differentiation in tumoral and pseudotumoral lesions. Histological features include a plump-spindle-cell morphology, with an ill-defined cytoplasm paler and less fibrillar than in smooth-muscle cells, and matrix collagen. Myofibroblasts stain for α-smooth-muscle actin, fibronectin, and vimentin. Desmin is found in some lesional myofibroblasts. The main ultrastructural features are prominent rough endoplasmic reticulum, modestly developed myofilaments with focal densities ("stress fibers"), and fibronexus junctions. The latter are foci on the cell surface where intracellular myofilaments and extracellular fibronectin filaments converge. Myofibroblastic lesions vary in the extent to which they mirror this overall phenotype. Hypertrophic scar, Dupuytren's disease, nodular fasciitis, the fibromatoses, and inflammatory myofibroblastic tumors have the most developed myofibroblastic features. Keloid, postoperative spindle-cell nodule, and fibroma of tendon sheath are less well differentiated. Myofibroblastoma is among many lesions described as myofibroblastic which, however, appear to show a kind of smooth-muscle differentiation. Some spindle-cell malignancies express myofibroblastic features.

INDEX WORDS: Myofibroblast, pathology, electronmicroscopy, fibronexus, fibronectin-fibril

Compared with most cells of the connective tissues (the fibroblast, smooth-muscle cell, pericyte, and so on) for which tumoral equivalents have been known for some time, the myofibroblast has been identified only comparatively recently.1,2 Partly on this account, it is a less well understood cell. In spite of this, many lesions have been classified as myofibroblastic (Table 1). For some of these lesions (especially nodular fasciitis, the fibromatoses—including the nodular palmar variant, Dupuytren's disease—and inflammatory myofibroblastic tumor), there is widespread agreement on their myofibroblastic nature. For other lesions, some authors have found the claims for myofibroblastic differentiation unconvincing (for example, the myofibroblastomas3-5). Such controversies have arisen partly because of the difficulty in reaching an agreed definition for the myofibroblast. Because the myofibroblast was initially defined in ultrastructural terms,1,2 electron microscopy has been central to identifying the myofibroblast and diagnosing myofibroblastic tumors and lesions. More recently, the convenience of a definition based on light microscopy and immunohistochemistry has been argued.6,7 Within this context, this review deals with the main applications and controversies of electron microscopy in diagnosing myofibroblastic lesions.

THE DEFINITION OF THE MYOFIBROBLAST AS THE BASIS FOR IDENTIFYING MYOFIBROBLASTIC LESIONS

Diagnosing tumors partly consists of identifying features observed in a putative normal cellular counterpart: for example, S100 protein and melanosomes in malignant melanoma, and α-sarcomeric actin and sarcomeres in rhabdomyosarcoma. For myofibroblastic lesions, however, there is no normal cellular counterpart: with 1 or 2 exceptions,8,9 the myofibroblast is not found in untraumatised adult tissues (see refs 6,10,11). Myofibroblasts in granulation tissue and tumor stroma are argued here as the nearest equivalent to the normal cell counterpart with which to define and identify myofibroblastic lesions. Such myofibroblasts (referred to here as "reactive" myofibroblasts) are recognized by characteristic light and electron microscopy features. They are spindled cells with fusiform nuclei, set in a more or less collagenized matrix, with a rather ill-defined cytoplasm, which is paler and less fibrillar than the usually brightly eosinophilic cytoplasm typical of smooth-muscle cells12 (Fig 1). They stain for α-smooth-muscle actin, fibronectin, and vimentin. Lesional myofibroblasts also express some desmin staining, a finding that requires some comment. Tumors cannot be expected to mirror exactly their putative normal cell counterparts12; the genetic abnormalities that characterize...
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2. FF (Figs 4, 5)
3. FF (eg. Fig 4)
4. FF (Figs 6, 7a)
## Table 1. (Cont'd) Myofibroblastic Lesions: Immunohistochemical and Ultrastructural Features

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Abbreviations: A, actin; SMA, α-smooth-muscle actin; MSA, muscle specific actin (using HHF35); AMA, anti-muscle actin (equivalent to MSA); D, desmin; CK, cytokeratin; FN, fibronectin; IF, intermediate filaments seen by electron microscopy and not specified as to type; rER, rough endoplasmic reticulum; MF, smooth muscle myofilaments with focal densities; FF, fibronectin fibril; FNX, fibronexus; L, lamina ("basement membrane"); AP, attachment plaque; IB, inclusion body.

2. Not referred to as such or not referred to at all and variously described as basement membrane-like material, microtendon, filamentous extracellular material, basal lamina-like material or hemi-desmosome-like material.
3. Dupuytren's disease
4. Indicates smooth-muscle differentiation
5. Intranodal hemorrhagic spindle-cell tumor with amianthoid fibers
6. Smooth-muscle differentiation in a minority of cells
7. Referred to as myofibroblastoma
8. Fibroblastic lesion
the neoplastic process can explain loss of anticipated features, as well as the appearance of unexpected ones (such findings from the field of immunohistochemistry are often referred to as anomalous or aberrant). Desmin staining in myofibroblastic lesions is interesting because granulation tissue and tumor stroma myofibroblasts express very little of this intermediate filament\textsuperscript{13,14}. Desmin, therefore, should not be considered part of the primary definition of the myofibroblast, even though it is recognised in some lesions. It is compatible with myofibroblastic differentiation, but arguably it would be inappropriate to use it to support a myofibroblastic interpretation—just as, by analogy, the fair number of malignant melanomas which are positive for cytokeratin would not justify making cytokeratin a primary marker for melanoma on the same level of importance as S100 protein or HMB45 (see below for further discussion).

One of the difficulties in understanding the myofibroblast derives from the idea that it arises from a precursor cell that undergoes a series of differentiation steps, and that for some pathologists it has been difficult to define the precise location of the myofibroblast within this dynamic process. The widely accepted working hypothesis is of a quiescent fibroblast (Fig 2) which, on activation, synthesises abundant rough endoplasmic reticulum cisternae (rER) for matrix production, then switches on genes for smooth-muscle actin myofilaments for contractility.\textsuperscript{15} These 2 ultrastructural features especially (Fig 3) (but also, for example, gap junctions and collagen secretion granules\textsuperscript{16-19}) are widely understood and accepted as markers for the myofibroblast, but this cell also has a further distinctive feature, at the cell surface — the fibronexus, which is less well recognized (Fig 3).

The first detailed ultrastructural descriptions of the myofibroblast\textsuperscript{1,2} not only described rER and myofilaments but also a component on the cell surface desig-
ULTRASTRUCTURE OF MYOFIBROBLASTIC LESIONS

Fig 2. Diagrammatic representation of the fibroblast-myofibroblast transformation. Four stages are identifiable ultrastructurally. An activated fibroblast showing peripheral myofilaments but not fibronexus filaments ("myoid" fibroblast) is a theoretical precursor to the fully differentiated myofibroblast (stage 4). Both stages 3 and 4 would be compatible with the light microscope criterion for the myofibroblast of a spindled-cell positive for smooth-muscle actin. rER, rough endoplasmic reticulum; SLD, subplasmalemmal linear density; CSG, collagen secretion granule.

nated as basement membrane-like material. Further study showed that this differed from basal lamina ("basement membrane") and represented the external component of a cell-surface specialization called the fibronexus or fibronexus junction.2-20,24 At the fibronexus, intracellular myofilaments and extracellular fibronectin filaments (these forming the fibronectin fibril) converge to form a cell-to-matrix adhesive device. Fibronexus junctions have been promoted as an important myofibroblastic feature for two reasons: they formed part (albeit under a different terminology) of the original definition of the granulation tissue myofibroblast, and they are consistently and sometimes exuberantly expressed in tumor stroma myofibroblasts.2,23,25

These features — rER, peripheral myofilaments and fibronexus junctions — in an appropriate histology and immunophenotype, constitute one basis for defining the myofibroblast and identifying myofibroblastic differentiation in tumors and tumor-like lesions. The features conform to stage 4 in the fibroblast-myofibroblast transformation (Fig 2) and collectively amount to arguably the highest level of myofibroblastic differentiation possible ("fully differentiated" myofibroblasts). The extent to which these features are found in the wide variety of lesions described as myofibroblastic is documented in Table 1.

SPECTRUM OF DIFFERENTIATION IN MYOFIBROBLASTIC TUMORS AND TUMOR-LIKE LESIONS: UNDER-IDENTIFICATION OF THE FIBRONEXUS

A number of broad conclusions, as well as some areas of controversy, arise from the data in Table 1. Using the ultrastructural criteria of fibronexus junctions, prominent rER and modestly developed peripheral myofilaments as representing the highest level of myofibroblastic differentiation (in a consonant histological and immunophenotypic picture), a spectrum of myofibroblastic differentiation is evident. Those lesions containing the most highly differentiated myofibroblasts are hypertrophic scar, Dupuytren's disease (Fig 4) and other fibromatoses, nodular and proliferative fasciitis (Fig 5), and inflammatory myofibroblastic tumor. Those lesions with lesser but still distinct myofibroblastic differentiation include keloid, fibroma of tendon sheath and post-operative spindle-cell tumor (Fig 6). These less well-differentiated lesions depend to a certain extent for their identification on the ability to identify fibronectin fibrils on their own, since the fibronexus-associated myofilament bundles may be absent or sparse. In this respect, it is important to be able to distinguish the fibronectin fibril of the myofibroblast from the lamina of smooth-muscle differentiation. Compared with lamina, the fibronectin fibril tends to be more densely staining, straighter in profile, with a finely filamentous substructure, often a co-linear relationship with nearby intracellular myofilaments, and is often seen diverging away from the cell surface (Figs 3B and 5; and refs 24 and 25).

It is worth emphasising that the fibronexus and the fibronectin fibril are under-interpreted structures in that several papers exist (Table 1) where these structures are illustrated but either not mentioned or are misinterpreted as lamina or basement-membrane-like material of indeterminate significance. Examples include nodular and proliferative fasciitis,29,30 myositis ossificans,32 as well as some fibromatoses,34 and inflammatory myo-
Fig 3. Myofibroblasts from tumor stroma (keratinizing squamous cell carcinoma, skin of neck in an 85 year old man). (A) Abundant rER, peripheral myofilaments, and cell surface fibronectin fibrils. Note abundant intercellular collagen. x5,000. (Reprinted with permission.24) (B) Detail of fibronectin fibril and myofilaments at a fibronexus. Note that the fibronectin fibril has high staining density, co-linearity with myofilaments and filamentous substructure. x12,000. (Reprinted with permission.25) Electron micrographs. Abbreviations and labelling (Figs 3-8): *, rough endoplasmic reticulum; arrow, myofilaments; arrowhead, fibronectin fibril; L, lamina; Go, Golgi apparatus; N, nucleus; co, collagen.
fibroblastic tumors. In short, the incidence of the fibronexus or fibronectin-fibril is higher than is recognised, and true myofibroblastic differentiation is therefore arguably more widespread than perceived.

Often, these myofibroblastic lesions are described as consisting of myofibroblastic and fibroblastic cells to reflect observations that not all cells have the ultrastructural features of myofibroblasts. However, some lesions, such as elastofibroma, appear to be essentially fibroblastic, in which abundant intermediate filaments have been misinterpreted as actin (ie, muscle) filaments.

**Fig 4.** Dupuytren's disease. (A) Spindled cells with rER, a Golgi apparatus, myofilaments and fibronectin fibrils, amid abundant collagen. x5,900. (B) Fibronectin fibril and myofilaments at a fibronexus. x30,000. (C) Golgi apparatus with collagen secretion granules (small arrows). x30,000. (Specimen courtesy Professor Hartwig Kosmehl and Dr Alex Berndt, Jena, Germany).

**SMOOTH-MUSCLE DIFFERENTIATION IN SO CALLED MYOFIBROBLASTIC LESIONS**

Just as some so called myofibroblastic lesions are more properly to be regarded as fibroblastic, there are compelling reasons on the grounds of ultrastructure and/or strong desmin staining to consider certain other lesions as expressing a kind of smooth-muscle (non-myofibroblastic) differentiation. While many of the ultrastructurally examined fibromatoses, as already indicated, exhibit fibronexus junctions and so are fully myofibroblastic, a few others have the lamina indica-
Fig 5. Lesional myofibroblast in a nodular fascitis (suprapubic mass in a 66-year-old woman) showing myofilaments and a straight fibronectin fibril projecting into extracellular space. x8,000. (Reprinted with permission. 24)

Desmin has been used as a marker for myofibroblast lesions 13 but it should be remembered that this intermediate filament is not well expressed in reactive ("normal") myofibroblasts, although it is prominent in a number of myofibroblastic lesions such as the fibromatoses. It has to be considered whether in these situations one should consider desmin staining as a further marker for myofibroblastic differentiation, or whether it should be more appropriate to think of it as indicating an element of smooth-muscle differentiation, especially since some fibromatoses show smooth-muscle ultrastructure. 35

In identifying smooth-muscle differentiation fine structurally, attachment plaques with overlying lamina (sometimes with intervening plasmalemmal caveolae) constitute an important smooth-muscle feature distinct from the fibronexus of the myofibroblast. 25 These smooth-muscle surface features have been seen in a number of myofibroblastomas (Fig 7). 3, 4, 5, 6, 7, 5 These smooth-muscle surface features have been seen in a number of myofibroblastomas (Fig 7). 3, 4, 5, 6, 7 By contrast, there is only one study where there is a suspicion of a fibronectin fibril. 58 Many of the tumors referred to as myofibroblastomas may, therefore, be exhibiting a kind of (nonmyofibroblastic) smooth-muscle differentiation. This argument, especially given the strong desmin staining in some cases, applies also to the angiomyofibroblastomas. Here, the cytoplasm contains little of the rER expected of the myofibroblast, no myofilaments, the fibronexus has never been identified, and one study has even shown smooth-muscle lamina. 61

THE LIGHT MICROSCOPY DEFINITION OF THE MYOFIBROBLAST

Other so called myofibroblastic lesions that are arguably showing a form of smooth-muscle differentiation include paratesticular plexiform tumor, 69 leiomyomatosis peritonealis disseminata 70 (which appears to be expressing a synthetic or matrigenic smooth-muscle phenotype to judge by the prominent rER), and massive ovarian edema. 71 In certain other lesions—dermatofibroma, 64 Dermatofibrosarcoma protuberans, 55, 66 atypical fibroxanthoma, 65 dermatomyofibroma, 67 pseudoangiomatous stromal hyperplasia 72 — the evidence for myofibroblastic differentiation is based either on the less strict ultrastructural combination of rER with myofilaments (without fibronexus — stage 3 in Fig 2), or the light microscopy definition encompassing spindle-cell morphology and immunostaining for α-smooth-muscle actin and/or desmin.

This light microscopy definition merits attention because of the acknowledged decline in the use of electron microscopy. 5, 7 It remains an argument held by some authorities, however, that the light microscopy definition is more imprecise and open to greater interpretational uncertainty in the sense that a variety of spindled cells can express α-smooth-muscle actin — smooth-muscle cells, myofibroblasts, pericytes, myoepithelial cells, epithelium undergoing mesenchymal transformation. 25 To illustrate this point further, electron microscopy can distinguish, for example, a myofibroblast from a matrigenic smooth-muscle cell, ie, one
which has transdifferentiated from the contractile to the synthetic phenotype, and which, in spite of containing abundant rER and relatively few peripheral myofilaments like a myofibroblast, differs from it by its smooth-muscle cell surface. The ultrastructural definition is useful, therefore, in situations of diagnostic uncertainty associated with spindle-cell tumors positive for smooth-muscle actin and or desmin. An additional area of utility is for intra-abdominal spindle-cell lesions positive for c-kit, which might be true gastro-intestinal stromal tumors or myofibroblastic.

**Fig 6.** Postoperative spindle-cell nodule (vulva, 33 year old). (A) Lesional myofibroblasts containing variable numbers of rER cisternae, and very modestly developed myofilaments. One cell process has a fibronectin fibril. Ma, macrophage. x7,100. (B) Detail of fibronectin fibril from A. x32,000. (C) Nearby endothelium to show different ultrastructural appearance of lamina. x32,000.

**MYOFIBROBLASTIC MALIGNANCIES**

The early studies on tumor stroma and granulation tissue emphasised the reactive nature of the myofibroblast. Increasingly in recent years, however, spindle-cell malignancies with myofibroblastic differentiation have been documented. Figures 1 and 8 illustrate an unambiguous myofibroblastic sarcoma (myofibrosarcoma) where the patient died of metastatic disease. Importantly, the bulk of the tumor consisted of myofibroblasts bearing many fibronectin fibrils, ex-
cluding the argument that the myofibroblastic differentiation in such tumors was due to reactive cells. Any poorly differentiated spindle-cell sarcoma could benefit from ultrastructural input on the basis that some may show evidence of myofibroblastic differentiation. The complex and controversial entity, malignant fibrous histiocytoma, also contains variable numbers of myofibroblasts as neoplastic elements. ACKNOWLEDGEMENTS

My sincere thanks go to Professor Hartwig Kosmehl (Erfurt, Germany) and Dr Alexander Berndt (Jena, Germany) for supplying a resin block of Dupuytren’s disease; Professors F Hernández, JV Johannesssen, JM Nesland and B Baccetti, for permission to reprint figures; Dr John Coyne (Manchester, UK) for providing clinical details of the case of postoperative spindle cell nodule: Varsha Mistry for word-processing assistance; and Paul Chantry for drawing Figure 2.

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