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## Electron microscopy in the diagnosis of inherited connective tissue diseases

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Martan syndrome is a dominantly inherited disorder characterized by Cardiovascular, ocular and skeletal abnormalities. The major cardiovascular complications of ascending aorta dilatation and dissection often lead to premature death in the absence of treatment and justify the requirement of relevant diagnostic criteria in the early years of life. The pathogenetic role of fibrillin has been confirmed by the identification of mutations in the fibrillin gene FBN1 in patients with classical Martan syndrome. Immunohistochemical and immunohistochemical analysis converged to demonstrate defective synthesis, secretion and extracellular matrix formation of fibrillin by cultured dermal fibroblasts. The skin biopsy thus appeared

as a noninvasive Clinical requirement allowing immunochemical, immunohistochemical and genetic assessments of fibrillin deficiency in early Marfan syndrome diagnosis.

Fibrillin is a large 350kDa matrix protein associated with one of the major subgroups of microfibrils morphologically characterized by 10-13 nm diameter, a hollow cross-section and a beaded appearance with some periodicity. Considered as integral components of elastic elements, these microfibrils are constituents of three types of fibers, namely oxytalan, elaunein and elastic. Oxytalan fibers consist mostly of microfibrils arranged in an orderly manner, although they contain some elastin. Elaunein fibers are present beneath the oxytalan fibers and contain both microfibrils and amorphous elastin. In all the probands the arborescent distribution of the elastic and elaunein fibers was lost and the oxytalan fibrils were scarce, with variable patterns of microfibril alteration.

These patterns of microfibril alteration extended to the elaunein and elastic fibers in which the peripheral microfibrillar apparatus appeared either condensed with vanishing of the microtubular structure or scarce with preservation of ultrastructure. In any case, the close interconnection between the elastic fibers and the collagen fiber bundles supported by microfibrils appeared ruptured or slender, thus emphasizing the discontinuity between the tensile elastic and architectural collagenic frameworks of the dermis in the Marfan patients. The dermal microvasculature was variably affected in relation to the decreased density of microfibrils anchoring the elastic network to the perivascular basement membrane, and displayed gradual constrictive features.

While fibrillin immunodetection in cultured skin fibroblasts allows pathologists to appreciate the level of fibrillin expression deficiency, ultrastructural tissular immunolabeling renders account of the pleomorphism of the pathological implications in the dermal connective matrix and the microvasculature.

## Electron microscopy of melanin-synthesizing tumors

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With the availability of relatively new antibodies such as HMB-45, HMB-50 or MART-1 (Melan-A), the identification of melanocytic phenotype in an undifferentiated neoplasm has become much easier. These markers, however, are often negative in many (and sometimes in all) of the cells in a given tumor. In addition, there are situations in which the identification of melanin-synthesizing cells is not enough to reach a correct diagnosis. Electron microscopy may play a contributory role in many of these cases. In this part of the course, the application of electron microscopy in four specific settings will be reviewed, namely: i) poorly differentiated tumors, either primary or metastatic, in which malignant melanoma enters the differential diagnosis; ii) soft tissue tumors with melanocytic differentiation; iii) pigmented tumors of the central nervous system (mostly arising in the meninges); and iv) complex neoplasms with aberrant