THE MUSCULOSKELETAL SYSTEM

Embryology, Biochemistry, and Physiology

RICHARD L. CRUESS, M.D.

CHURCHILL LIVINGSTONE

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Churchill Livingstone
New York, Edinburgh, London and Melbourne 1982

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Distributed in the United Kingdom by Churchill Livingstone, Robert Stevenson House, 1–3 Baxter's Place, Leith Walk, Edinburgh EH1 3AF and associated companies, branches and representatives throughout the world.

First published 1982
Printed in U.S.A.

ISBN 0-443-08108-5
9 8 7 6 5 4 3 2 1

Library of Congress Cataloging in Publication Data
Main entry under title:

The Musculoskeletal system.

Bibliography: p.
Includes index.
1. Musculoskeletal system. I. Cruess, Richard L. [DNLM: 1. Musculoskeletal system. WE 100 M9854]
QP301.M755 612.'74 82-4476
ISBN 0-443-08108-5 AACR2

Manufactured in the United States of America

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Preface

The period since World War II has seen extraordinary changes in our understanding of human disease and in its management. This has been true in almost every clinical field, and nowhere has progress been more rapid than in those disciplines related to the musculoskeletal system. We have come to understand the structure and organization of the musculoskeletal system, its normal homeostatic mechanisms, and its response to both normal and abnormal external stimuli. Anatomical structures that were previously thought to be relatively inert are now known to be constantly changing, and very small increments in the rates of turnover are known to have serious consequences. With a greater understanding has come an enhanced ability to manipulate normal responses and to influence the outcome of human disease. All of these advances have been based upon a better understanding of the basic structure, embryology, biochemistry, and physiology of the musculoskeletal system.

It is the objective of this book to organize this vast body of knowledge in a way that should be understandable to someone either in training for a clinical discipline or practicing a specialty. It is hoped that the material will be concise and clear, and up-to-date and representative bibliographies have been provided in order that those who wish to expand their knowledge further can do so with ease. An attempt has been made to avoid duplication of material among the various chapters; wherever information is presented twice, it is because it was essential for the meaning of the chapter. The ultimate objective of the book is, of course, to improve the scientific foundation of the practice of medicine and in that way to influence the care of the sick.

R.L.C.

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Chapter

1

The Mesenchymal Cell—Its Origin, Structure, and Function

Huntington Sheldon, M.D.
Valerie Jaeger, Ph.D., M.D.

INTRODUCTION

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- **The interior of the cell**
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    - Intermediate filaments
    - Myosin filaments
    - Actin filaments
  - Cytoplasmic microtubules
  - Endoplasmic reticulum
  - Golgi complex
  - Mitochondria

MESENCHYMAL CELLS

- **Fibroblasts and fibrocytes**
- **Cartilage cells**
- **Osteoblasts, osteocytes, and osteoclasts**
- **Adipose cells**
- **Muscle**
  - Skeletal muscle
  - Smooth muscle

SUMMARY

ACKNOWLEDGMENT

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INTRODUCTION

Mesenchyme is as much a concept as it is a tangible reality. Older texts define mesenchyme as the loose connective tissue that lies between the ectoderm and the endoderm in the embryo. It is equated with the layer of mesoderm. Ectoderm contributes the covering epithelium of the organism and the nervous system, endoderm differentiates into the gastrointestinal and respiratory systems and portions of the genitourinary tracts, and the mesodermal layer is responsible for muscle, cartilage, bone, and the hematopoietic and lymphoid systems. This chapter focuses on the origin and the features of the differentiated mesenchymal cell, which can be identified as a chondrocyte, osteocyte, fibrocyte, adipose cell, or muscle cell. Before the mesenchymal cell reaches this stage of differentiation, however, it may be impossible to identify.

In the embryo perhaps the earliest appearance of mesenchyme is the point at which blood cells and blood vessels can be seen. This may be at the six somite stage in the chick, where islands of angioblasts give indication of specialization of mesenchymal cells. Subsequent specializations of all mesenchyme may well arise from derivatives of blood vessel cells. Because of the absence of particular morphological features which could identify the potential smooth muscle, adipose cell, or bone cell it is not possible at this time to deny the unitary or stem cell theory, which attributes the origin of all these tissues to a paravascular cell as anticipated more than 100 years ago (Fig. 1-1).

HISTORICAL REVIEW

The 19th century was a period of enthusiastic investigation into the origins and characteristics of tissues in general and connective tissue in particular. The concept that bone, cartilage, fat, and loose connective tissue owe their origins to a primitive mesenchymal cell could develop only after two essential principles had been accepted by the scientific community: first, that there is a continuity in the emergence of tissues, whether embryologically or in growth and repair, and, second, that in mesenchyme it is the cells that are responsible for the origin of other cells and for the production of the extracellular matrix.

The first principle was well accepted by investigators of the early 19th century, having been set out by William Harvey as early as 1651:[38]

> *Since in Animal Generation (and indeed in all other subjects upon which information is desired) inquiry must be begun from the causes, especially the material and efficient ones, it appears advisable to me to look back from the perfect animal, and to inquire by what process it has arisen and grown to maturity, to retrace our steps, as it were, from the goal to the starting place; so that when at last we can retreat no further, we shall feel assured that we have attained to the principles; at the same time we shall perceive from what primary matter and from what efficient principle, and in what way from these the plastic force proceeds; as also what processes nature brings into play in the work. For primary and more remote matter, by abstraction and negation (being stripped of its garments as it were) becomes more conspicuous; and whatever is first formed or exists primarily in generation, is the material cause of everything that succeeds.*

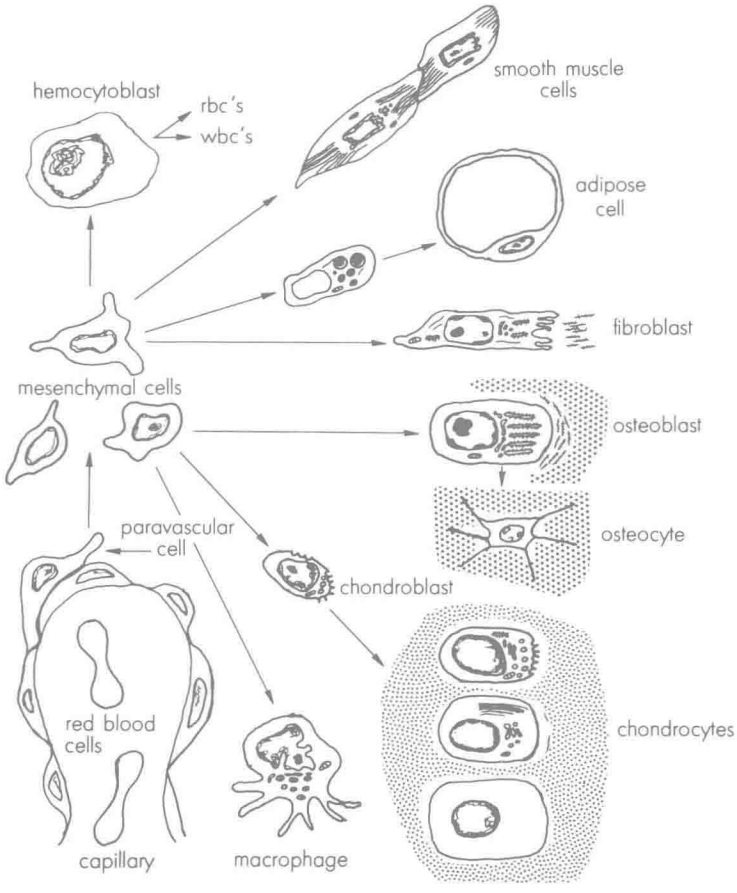

Figure 1-1
Origin and relationship of mesenchymal cells. The primitive mesenchymal cell shown at left center of the field may differentiate into a hemocytoblast or into smooth muscle cells, adipose cells, fibrocytes, osteocytes or blasts, chondrocytes, and/or macrophages. The presumed predecessors of these cells are paravascular cells as shown in the bottom left of the field.

With regard to the second principle, there was much contention as to the primacy of fibers versus cells in the genesis of the connective tissues and over whether or not cells could arise de novo from some sort of condensation of the ground substance. The work of Thomas Schwann emphasized the importance of cells over fibers:

> *There is one universal principle of development for the elementary parts of organisms, however different, and . . . this principle is the formation of cells.*[93]

He still believed, however, that these cells arose from a structureless substance, fluid or gelatinous, which had the chemical qualities and "vitality" required to produce cells.

Virchow strongly disagreed with this notion and put forward the Law of Continuous Development:

> *No development of any kind begins de novo and consequently we reject the theory of equivocal (spontaneous) generation just as much in the history of the development of individual parts as we do in that of entire organisms.*[122]

Much of the research used in formulating this theory involved mesenchymal tissues. Virchow showed that even predominantly fibrous tissue was populated in adult life by active cells. He considered the connective tissue as the common stock (Keimstock) for the development of all new body formations whether physio-

logic, inflammatory, or neoplastic. Although a substantial portion of this theory was later shown to be false (e.g., Thiersch and Waldeyer proved the epithelial origin of cancer cells), his advocation of the stepwise differentiation of the cells of the connective tissue provided the impetus for subsequent investigations of the developmental potential of the primitive mesenchymal cell.[50]

The cells first visible in the processes of repair and differentiation (the connective tissue "corpuscles") were described as round and slightly granular with a dark edged nucleus. At later stages the cells elongated and threw out processes.[4,76] Although we have this description of how the histologists of Virchow's day saw the primitive mesenchymal cell, there is little indication as to where they thought this cell was coming from. They did, however, acknowledge the importance of blood vessels to connective tissue and vice versa.

The first mention of the presence in capillaries of cells other than endothelial cells appears in two short notes of Charles Rouget.[87,88] In studying the capillaries in the hyaloid membrane of frog's eye and in amphibian larvae, he found that even the smallest vessel possessed a second, albeit discontinuous, layer of cells outside the endothelium. The cells had long, oval nuclei arranged in the direction of the long axis of the vessels and branching cytoplasmic processes which extended along and around the capillary. He observed the contractions of these cells and concluded that they were related to the smooth muscle cells of larger vessels. He also thought they had an origin distinct from both that of the endothelium and that of the adjacent connective tissue, and he thought that they derived from wandering cells. His work was largely ignored, and no mention was made of it in histology texts of the day[91] until 1902, when Sigmund Mayer[64] rediscovered the long stellate cells on the outside of capillaries. These, Mayer believed, were true smooth muscle cells continuous with those of arteries and veins. A subsequent, more detailed study showed that transitional forms between these pericapillary cells and normal spindle shaped smooth muscle cells could be demonstrated along arterioles. The form of the paracapillary cells varied with the state of contraction of the capillary.[121] Proposed functions for these cells ranged from contraction of the capillaries[53] to control of the diffusion of substances through the capillary wall.[128] The cells were variously known as pericytes, paravascular cells, or Rouget cells (after their original discoverer).

It was known that connective tissue, fasciae, tendons, adipose tissue, cartilage, bone, smooth muscle fibers, and blood corpuscles all derived from mesenchyme (Figs. 1-2 and 1-3). This term had been proposed by Otto Hertwig in 1883 for those cells that embryologically are found between the two epithelial germ layers. The term comes from the Greek μέσος (mesos), meaning middle, and ἔγχυμα (enkhyma), an infusion.[12,91] In the early 1900s many investigators made the connection between the embryologic mesenchymal cell and the Rouget cell. Clark and Clark watched the growth of vessels in live tadpole tails for 8 days and followed and drew individual cells.[15] They found that some of the mesenchymal cells became definite Rouget cells. Although no particular group of mesenchymal cells was predestined for such a fate, once a cell had flattened out as an adventitial cell, its relation seemed permanent. The formation of Rouget cells occurred only on vessels that were growing or increasing in diameter, again emphasizing the close relation between mesenchyme and blood vessels (Fig. 1-3).

Maximow[63] and his students recognized that not only was the Rouget cell a primitive mesenchymal cell but also that under appropriate stimulation it could develop into other cell types.[55,62]

> *Among the fixed cells of the common connective tissue, as well as in the reticulum of the blood-forming organs, there are fixed undifferentiated cells which keep their embryonic mesenchymal potencies . . . .*

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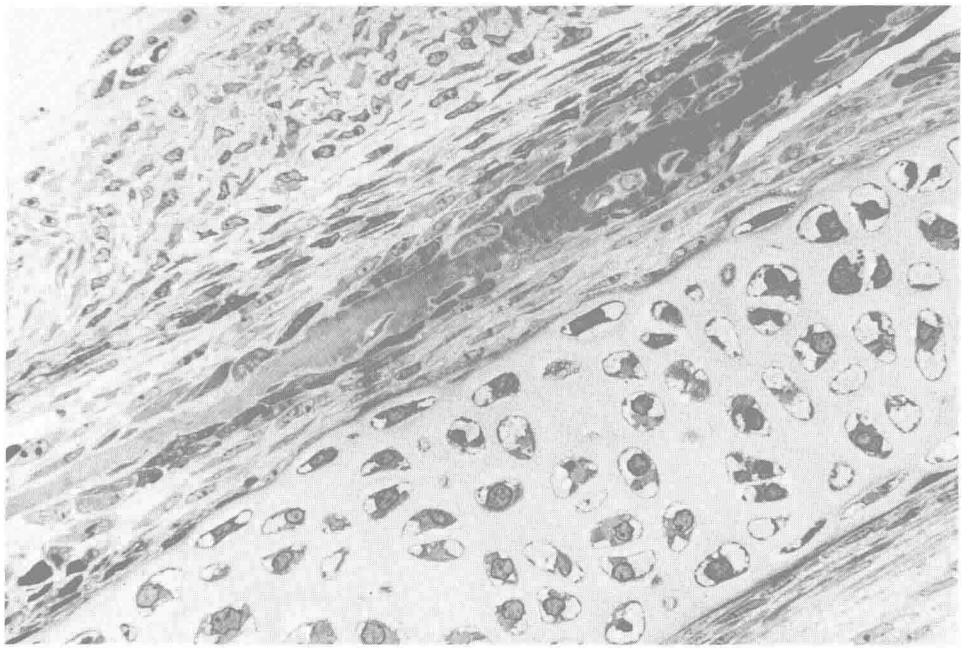

Figure 1-2
Toluidine blue stained, epon embedded section from the calvarial cortical bone of newborn mouse. In the upper left, there is undifferentiated mesenchyme; in the extreme upper left corner, there is a vascular channel with an erythrocyte. In the middle, running from left to right, is bone showing osteoblasts and mineralized matrix. Then there is an area of differentiating mesenchyme, including the perichondrium. The wide band is cartilage, which shows kidney bean shaped cells with central nuclei separated from one another by large amounts of matrix. On the lower right is the pericondrium and more mesenchyme. ×450

> *In the common connective tissue and in the omentum they are arranged especially along the smaller blood vessels in the form of so-called "pericytes." Under physiological conditions they remain quiescent for an indefinite time. In case of inflammation or other stimulus they awake, recede from the vessels and differentiate into hemocytes, histiocytes or fibrocytes.*[63]

The two most common results of the differentiation of Rouget cells were the phagocytic and dye-storing histiocytes and common fibroblasts. In local inflammation—for example, following the injection of carbon particles—they were seen to move away from the vessels and become transformed. The pericytes were described as being very similar to typical fibroblasts but smaller and paler,[63] a description not very different from that found in modern texts.

In 1927, Maximow[63] described the following functions of loose connective tissue: support and mechanical protection, facilitation of movement of adjacent surfaces through lubrication, nutrition of tissues, and participation in reactions related to the immune system, such as phagocytosis and antibody production. Current views of the structure and function of connective tissue do not differ, although substantial progress in identification and description of its component

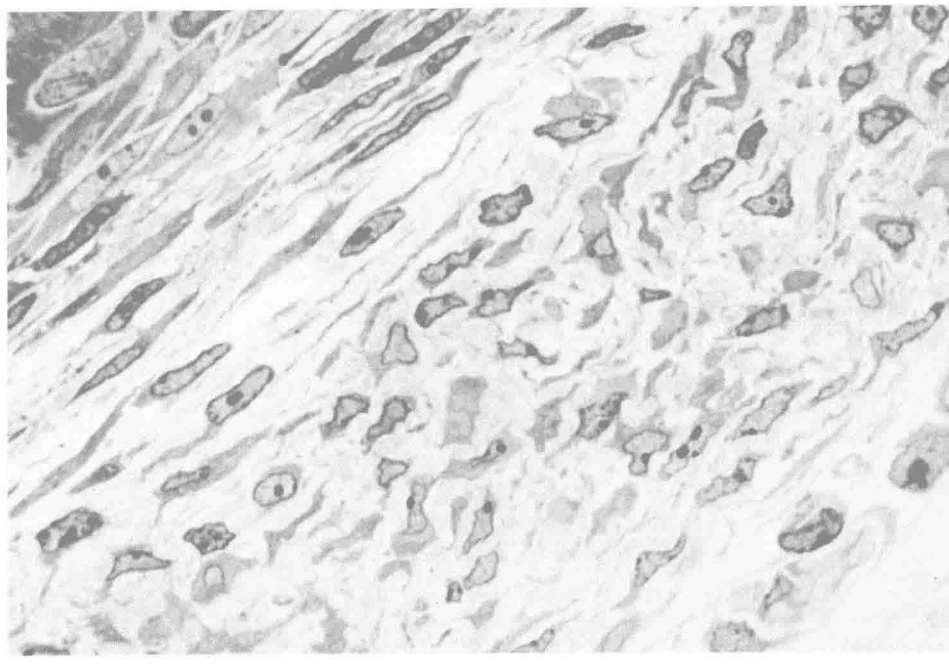

Figure 1-3
Undifferentiated mesenchymal cells from mouse calvarium shown in Figure 1-2 at higher power. ×1100

parts has been made since the introduction of electron microscopy, immunochemistry, and biochemical analysis.

Connective tissue occurs throughout the body. Its form varies according to need, but wherever it is found it has three major components—*cells, fibers,* and *ground substance.* This arrangement is phylogenetically very old and is basically the same whether one considers the cellulose of plants, the collagen of animals, or the chitin of arthropoda. Supporting tissues require high tensile strength, some degree of flexibility, and little extensibility. These demands are met by using asymmetric molecules such as collagen which are unbranched and capable of crystalline aggregation. Where a degree of elasticity is desired—e.g., in the elasticae interna and externa of arteries—a branched molecule such as vertebrate elastin is found. The form taken by connective tissue in a particular anatomic location is influenced just as much by physical and chemical stresses as by any inherited determinants:[61]

> Responsiveness to environmental influences appears to be an essential property of supporting tissues. It is an important element in the phylogenesis of structures, in embryonic development mechanisms and in mechanisms of physiological adjustment during maturation, aging and pathological conditions.

For example, collagen fibers in tendon are quite different from those in loose connective tissue, and it is an interesting question why this is so: Is it because of small differences in amino acid composition, or does some extracellular

component of the connective tissue, such as proteoglycan, have a key role in determining fibril structure?[81]

THE CELL

The modern era of cytology could be defined as starting with transmission electron microscopy of cells and tissues. Methods for fixation, embedding, sectioning, and staining became routine in the middle 1950s, and an avalanche of information about the fine structure of cells followed during the next two decades. At first, descriptive reports filled the literature, but soon there were correlated biochemical and morphological studies that revealed new insights into the relationship between structure and function. Autoradiography, enzyme histochemistry, cell fractionation studies, and immune cytochemistry have continued to provide data on the meaning of the elegant microphotographs which began to appear during the golden age of modern microscopy.

It is useful to recapitulate some of the elementary features of the fine structure of cells in order to provide a background for descriptions of the particular types of connective tissue cells discussed in the succeeding sections.

Cell Surface

The distinction between intracellular and extracellular space has undergone constant revision as our understanding of membranes has developed. The plasma or cell surface membrane has been the subject of active investigation for nearly 60 years and was one of the first portions of a cell's anatomy to be probed by modern methods. We recognize its structural and chemical diversity as well as its highly dynamic role in secretion, absorption, motility, and cell recognition.[7] During the early stages of fine structure studies the cell membrane could be seen to be irregular and to show a variety of conformations that ranged from the brush border modifications of the intestinal absorptive and renal tubular cells, to the peculiar thickenings of transitional epithelium,[40] to the specialized regions of cell contacts.[23] The regularly arranged and two dimensional lipoprotein layers of the Schwann cell, which compose myelin, formed the basis for many studies to confirm the chemical and physical nature of the plasma or cell surface membrane.[25]

The idea that the external surface was the repository of extracellular enzyme or enzyme adherent to the cell surface membrane, which facilitates absorption, was clearly anticipated in early histochemical studies with the electron microscope.[11,109] The dynamic properties of cell membrane turnover in relation to pinocytosis and phagocytosis were supported by studies that related the morphological appearance of phagocytes to oxygen consumption.

Specialized regions of cell surface membrane, such as coated vesicles (those specialized invaginations with a particularly thickened cytoplasmic wall),[47,86] desmosomes (specialized areas of cell contact characterized by cytoplasmic filaments ending on their inner aspect),[23] and tight and complex junctions (other areas

which allow intercellular communication),[35,83] have all become well recognized as features of different cell types and often have allowed distinctions to be made between different types of tumors.

A contemporary view of the plasma membrane portrays it as a dynamic structure that is constantly internalized and reformed, a structure that has many specifically different regions (antigens are not uniformly present over the whole surface), one that is composed of a thin film of bimolecular lipid leaflets in which proteins of different sizes for different purposes are placed much as decorations and candles on a birthday cake.[111] This model has been called the lipid mosaic model. Some proteins extend through the bimolecular lipid leaflet, protruding at both surfaces; others may be limited to an appearance of one interface (external or internal). It is these proteins that confirm specific features on cells and that are responsible for some of the particular qualities of one or another cell type.

Studies with electrophysiologic methods and intracellular dye particles of different sizes have demonstrated that many epithelia are closely coupled and that the gap junctions permit cell-to-cell exchange of small molecules and signals.[58] A variety of names have been suggested for these specialized areas of the cell surface membrane, such as communicating junction, but the synonyms of nexus, close junction, macula occludens, and gap junction all have been used interchangeably.[110]

The carbohydrate components of the exterior of cells have become the focus of much interest recently, and an immense literature on glycoprotein complexes has developed rapidly. This interest was anticipated in the early 1950s when basement membranes and poorly defined extracellular material could be visualized with the electron microscope. These areas were recognized as identical to the material that stained with periodic acid–Schiff stain. Lectins, plant derived substances which agglutinate erythrocytes and induce a variety of cellular changes, have been used increasingly as tools to probe the surface structure of mammalian cells.[69]

The old concept that there exists a distinct line of demarcation between the cell surface and the extracellular matrix is now being questioned, and much of the evidence comes from studies of connective tissue.[9] Research suggests that the interaction of the extracellular matrix with the connective tissue cell is important in directing cell migration, maintenance of cell shape, organization of the complex matrix, cell adherence to surfaces, and tissue differentiation. A key step in the development of this idea was the discovery and identification of fibronectin, also known as LETS (large external transformation sensitive protein, cell surface protein, galactoprotein).[126] It has been known for a long time that collagens aided cell growth, differentiation, and survival in tissue culture and that fibroblasts required a protein from serum before they would attach to collagen. The active protein from serum was identified as a glycoprotein, fibronectin. A very similar, although perhaps not identical, fibronectin is found on the surface of fibroblasts and in granular intracytoplasmic structures.[36,125]

Fibronectin is a large glycoprotein of 220,000 MW (molecular weight) with two disulfide linked subunits containing different binding sites for collagen, heparin, and cell surfaces.[49] It occurs on the surface of many different types of cells, particularly mesenchymal cells. Its distribution on the cell surface parallels that of collagen. It is required for maintenance of cell shape and for normal contact inhibition, as evidenced by the fact that it is decreased in transformed cells

and that treatment of cells with antifibronectin leads to the cells assuming a round shape.[124] This is reversed by addition of fibronectin.

Fibronectin is synthesized intracellularly under the influence of the genome, and its appearance is subject to alteration both in the genome (transformed cells) and by local factors (absent in differentiated cartilage cells in situ but present in dissociated cartilage cells).[19]

The Interior of the Cell

CYTOPLASMIC FILAMENTS

Immediately beneath the cell surface membrane in many parts of connective tissue cells—in particular epithelial cells—cytoplasmic filaments are present. These filaments appear to terminate on the cell surface membrane, and their importance in the maintenance of cell shape has often been discussed.[56,80]

Such filaments have recently been shown to be related to fibronectin; a protein bridge between cytoplasmic filaments identified as actin and the extracellular fibronectin has been reported.[22] Agents that disrupt cytoplasmic filaments (cytochalasin and plasmin) release fibronectin into the extracellular space; conversely, the addition of fibronectin to cultured cells is associated with the appearance of actin filaments. Tilney has shown that actin can exist in a nonfilamentous form.[117,118]

But the subject of cytoplasmic filaments is much larger. Three main types have been described: large filaments, which have been identified as myosin; small filaments, which have been identified as actin; and intermediate filaments, which we shall now discuss.

INTERMEDIATE FILAMENTS. This term describes a chemically heterogeneous set of filaments with the common properties of forming a discrete fibrous system in cells and having diameters of 100 Å when viewed under the electron microscope. Using freeze-dried cytoskeletons rotary replicated with platinum and viewed under the transmission electron microscope (TEM), one sees that intermediate filaments seem to form three dimensional webs of individual filaments rather than sheets or trabeculae. The extent of cross-linking between the filaments is unknown, but no fusion with microtubules or with the membranes of cell organelles could be demonstrated. The whole scaffoldlike structure appeared to be embedded in a granular cytoplasmic matrix.[39]

Five different classes of intermediate filaments have been described: keratin (tono) filaments,[42] desmin filaments,[41] vimentin filaments,[26] neurofilaments,[97] and glial filaments.[17] Of these desmin and especially vimentin filaments are important in a discussion of the skeletal system and of the mesenchymal cell. Keratin filaments are absent from cells of mesenchymal origin and reflect the state of differentiation of epidermal cells. Neurofilaments and glial filaments are found in the cells for which they are named and are immunologically distinct from each other and from vimentin and desmin (Fig.1-4).

Desmin filaments are named from the Greek δεσμός (desmos), meaning link. Their role in providing structural support for the contractile elements in muscle cells is the first well documented cytoskeletal function for intermediate

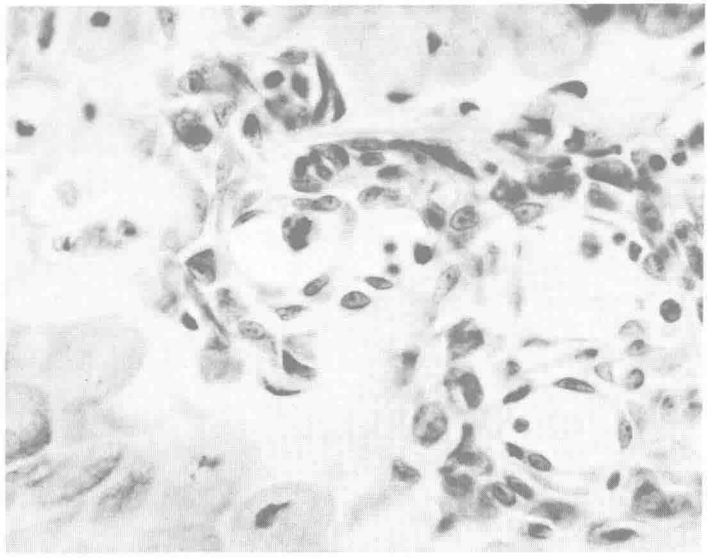

Figure 1-4
Light micrograph of vascular buds growing into epiphyseal cartilage of a rat femur. In the upper portions of the field are chondrocytes. The vascular channel contains cells. Abundant perivascular cells are shown. × 500

filaments. They are found in smooth, skeletal, and cardiac muscle at all stages of development, but they are most obvious in adult smooth muscle. Here they link sarcoplasmic electron dense bodies, believed to be analogous to striated muscle Z lines, with electron dense plaques bound to the cell membrane.[16] In skeletal muscle desmin filaments link Z discs laterally to each other, to the plasma membrane, and to other cytoplasmic membrane organelles. They may also play a role in the development of the T tubule–sarcoplasmic reticulum system, since they have affinity for both Z disc and membrane.

Vimentin filaments are found in both mesenchymal and nonmesenchymal cells. In cultured fibroblasts these wavy filaments are found in increased concentrations around the nucleus. They are seen to end on both the nuclear membrane and the adhesion plaques of cytoskeletons seen after detergent extraction of the cells. Their consistent association with the cell nucleus may indicate a role in maintaining it in a definite place or supporting it mechanically. Some association with normal fibroblast cell adhesion and spreading onto a substrate is suggested by the fact that these intermediate filaments transiently form perinuclear caps during these cell activities. Formation of these filament caps can be reproduced by treating cells with colcemid. Under these conditions the cells are found to contain equimolar amounts of two polypeptides: vimentin, MW 52,000–55,000, and desmin, equivalent to that of smooth muscle, MW 50,000–54,000. Therefore two chemically different intermediate filaments can coexist in the small cell, although it is possible that the vimentin and desmin are copolymerized into one filament.[113,115] Other functions proposed for the vimentin filaments are the intracellular transport of organelles and as an aid to cell locomotion.[33]

MYOSIN FILAMENTS. The largest filaments seen in mesenchymal cells are those of myosin. They are about 150 Å in diameter, and they were first described in skeletal muscle in detail by Bennett[6] and by Huxley.[43] These filaments have been identified more recently by immunologic methods in the cleavage fur-

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