SANATAN DHARM COLLEGE MUZAFFARNAGAR
(Affiliated to Maa Shakumbhari University, Saharanpur)

CELL BIOLOGY

THE CYTOSKELETON

Topic: Intermediate Filaments (IFs)

For

Subject Zoology

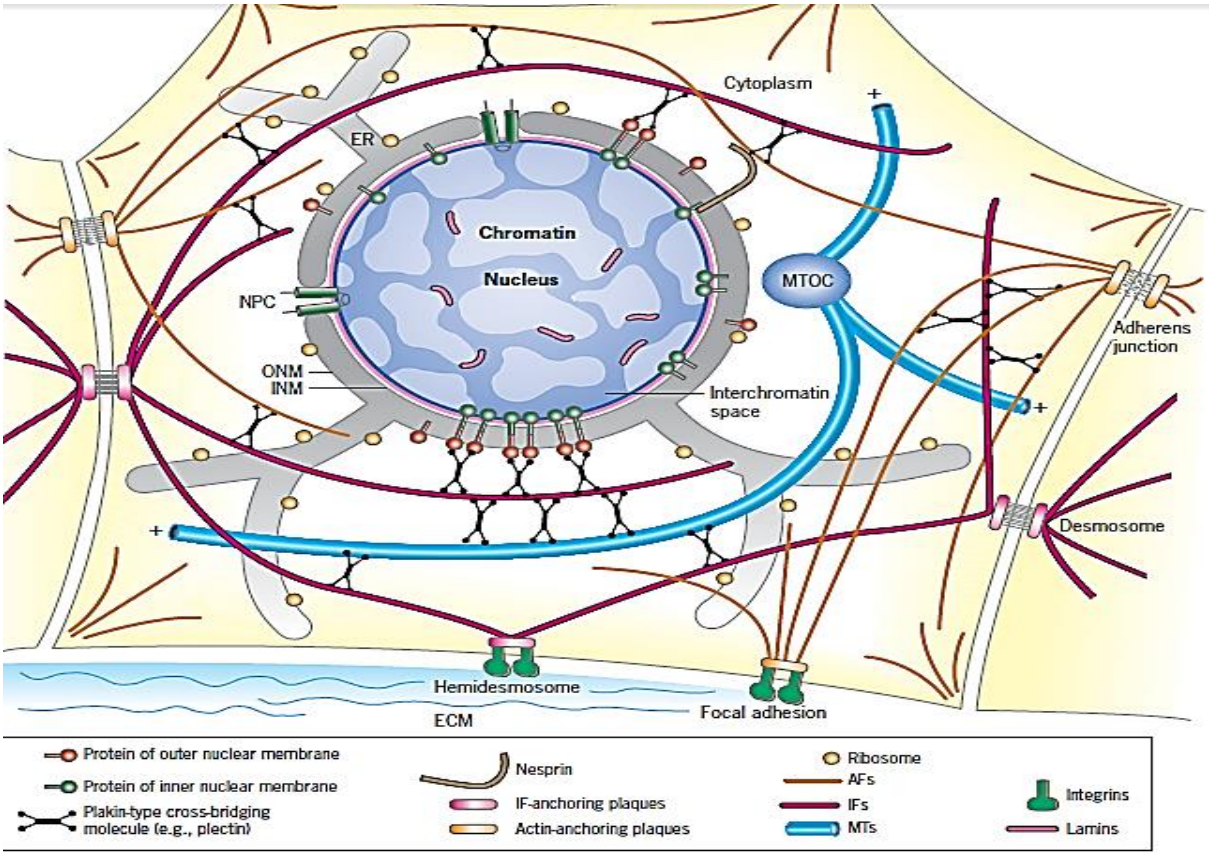
&

M.Sc. I Sem

DR. ARUN RATN, Ph.D.
[CSIR-JRF/SRF, CSIR-NET/LS
GATE, CEEB-BIT (DBT-JNU)]
(ASSISTANT PROFESSOR)
(arunratnbt14@gmail.com)
DEPARTMENT OF ZOOLOGY,
SANATAN DHARM (P.G.) COLLEGE,
MUZAFFARNAGAR-251001,
UTTAR PRADESH (INDIA).

Intermediate filaments

- **Intermediate filaments** are a diverse group of helically wound fibrous elements, **10 nm** in diameter.
- Intermediate filaments are composed of **linear polypeptide monomers** of various types.
- In animal cells, for example, the **nuclear lamins** are composed of **a specific polypeptide monomer**, while the **keratins**, a type of intermediate filament found in the cytoplasm, are composed of a different polypeptide monomer.
- Following figure depicts the interconnections between IFs and the cell's microtubules and actin filaments, which transforms these otherwise separate elements into an integrated cytoskeleton. Because of these various physical connections, the IF network is able to serve as a scaffold for organizing and maintaining cellular architecture and for absorbing mechanical stresses applied by the extracellular environment.



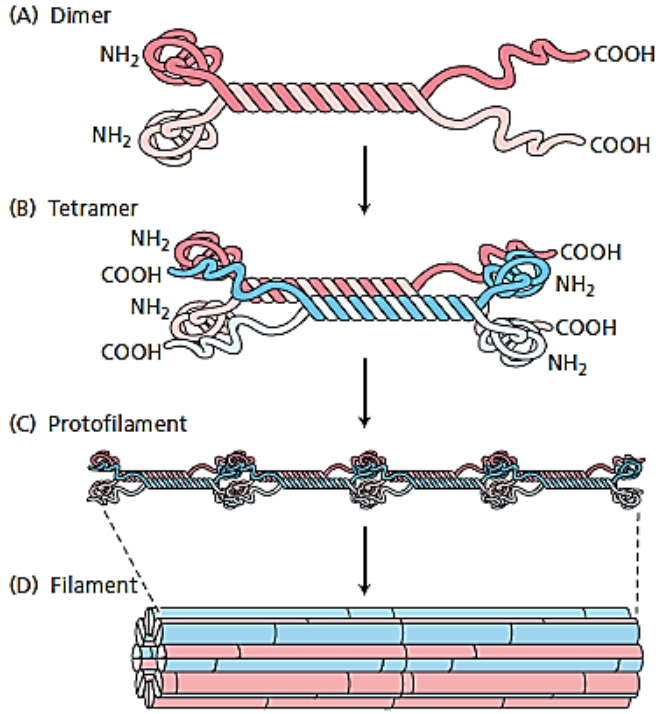
The current model for the assembly of intermediate filaments from protein monomers (in following figure).

(A) Coiled-coil dimer in parallel orientation (i.e., with amino and carboxyl termini at the same ends).

(B) A tetramer of two dimers. Note that the dimers are arranged in an antiparallel fashion, and that one is slightly offset from the other.

(C) Two tetramers.

(D) Tetramers packed together to form the 10 nm intermediate filament.



Type I	Keratin	protect epithelial
Type II	Keratin	found in hair, nails, and scales
Type III	Vimentin	strengthen cells and secure organelles
Type IV	Neurofilaments	strenthen axon and regulate nerve impulse speed, change axon diameter
Type V	Laminin	nuclear lamina
Type VI	Nestin	Nerve cells, regulate diameter

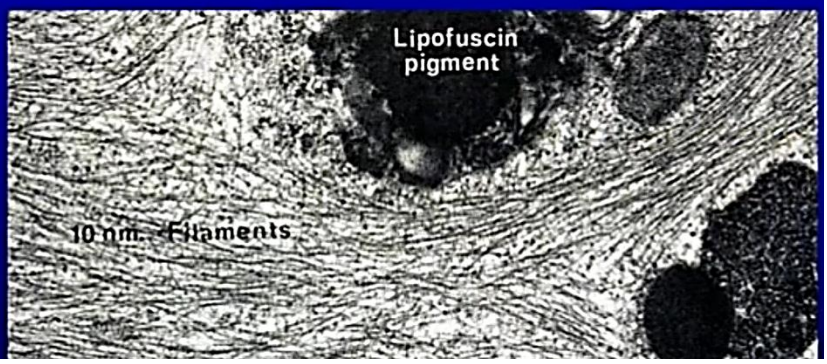
TABLE 9.2 Properties and Distribution of the Major Mammalian Intermediate Filament Proteins

IF protein	Sequence type	Primary tissue distribution
Keratin (acidic) (28 different polypeptides)	I	Epithelia
Keratin (basic) (26 different polypeptides)	II	Epithelia
Vimentin	III	Mesenchymal cells
Desmin	III	Muscle
Glial fibrillary acidic protein (GFAP)	III	Astrocytes
Peripherin	III	Peripheral neurons
Neurofilament proteins		Neurons of central and peripheral nerves
NF-L	IV	
NF-M	IV	
NF-H	IV	
Nestin	IV	Neuroepithelia
Lamin proteins		All cell types
Lamin A	V	(Nuclear envelopes)
Lamin B	V	
Lamin C	V	

Intermediate filaments

Five classes (not conserved)

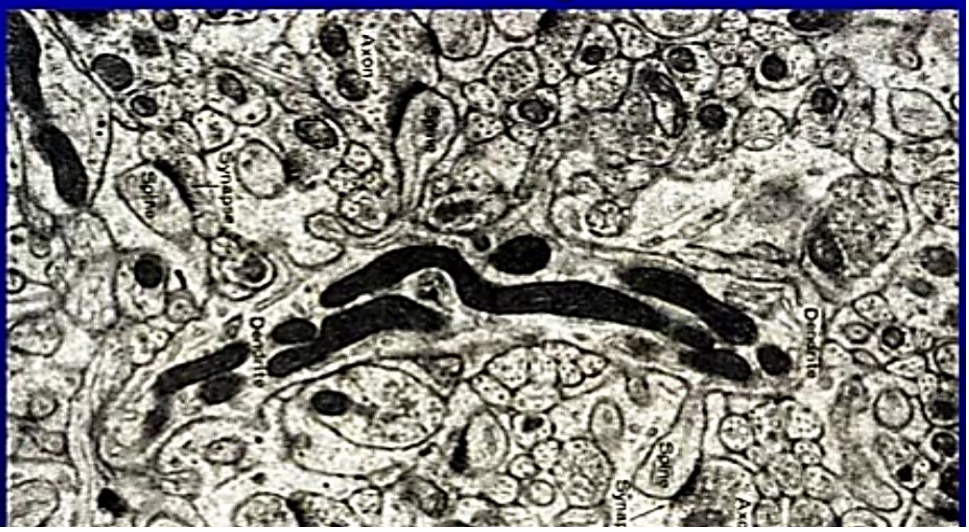
1. Keratin – insoluble substance, epithelium
2. Desmin – cytoskeleton in muscle
3. Vimentin – nuclear envelope for mechanical support and stability of its location in cell, mesenchymal cell



Intermediate filaments

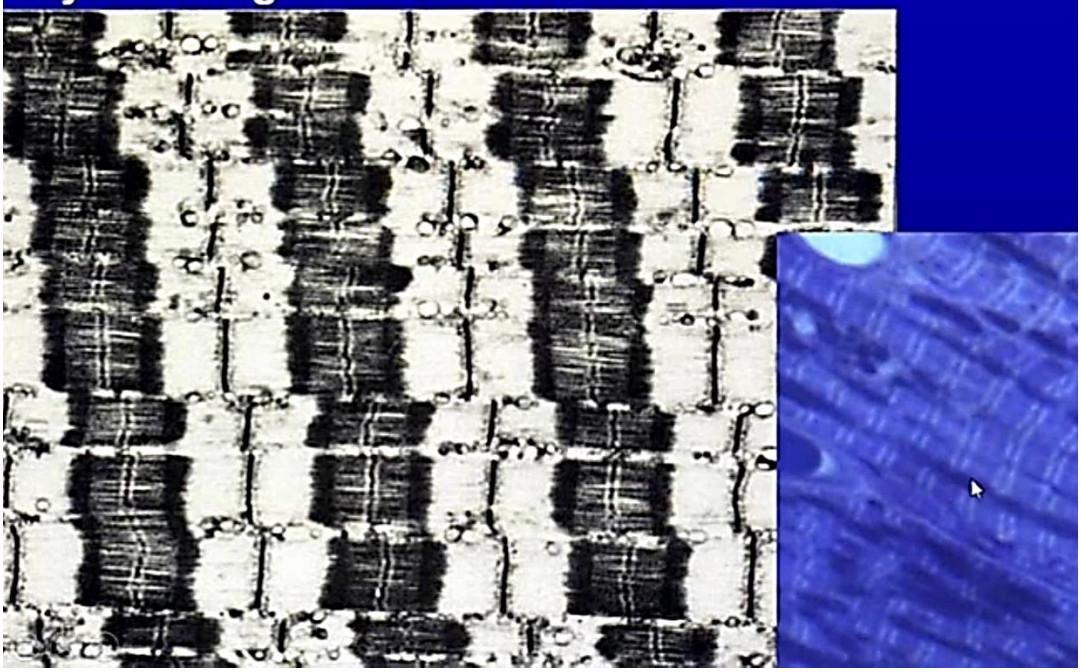
Five classes con't

4. Neurofilaments
   - Dendrites and axons of nerve cells
   - Internal support - gelated state of cytoplasm
5. Glial filaments - astrocytes



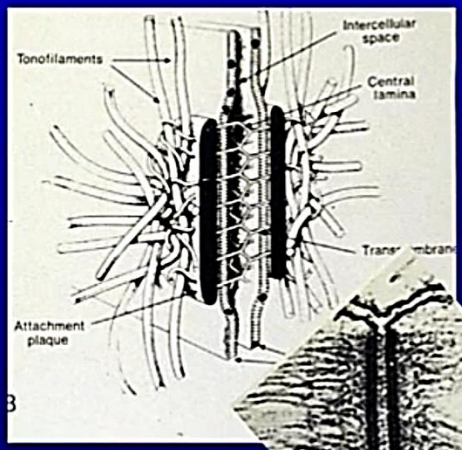
Intermediate filaments - function

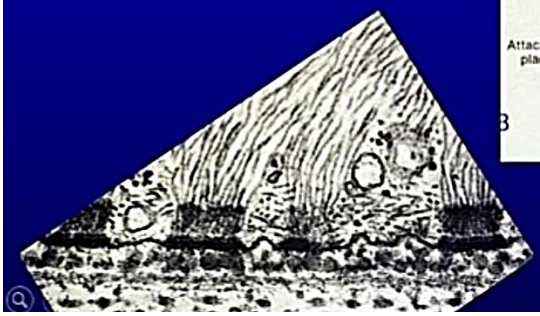
Myofibril organization - muscle

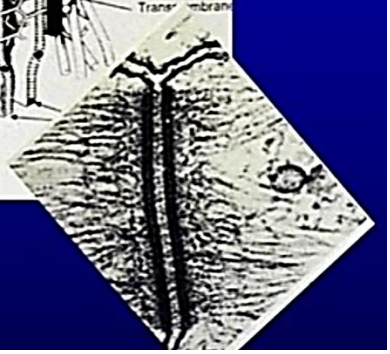


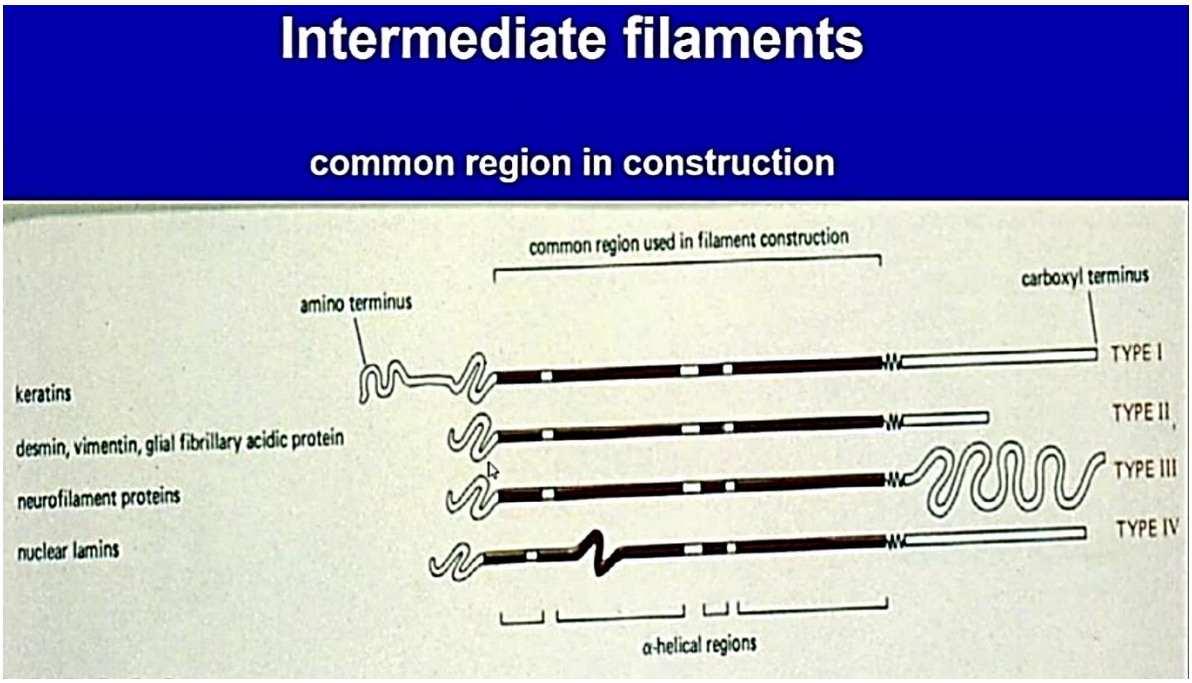
Intermediate filaments - function

Structural support of epithelial desmosomes and hemidesmosomes









Intermediate Filaments Occur in the Cytosol and Nucleus of Plant Cells

- Relatively little is known about **plant intermediate filaments**. Intermediate filament–like structures have been identified in the cytoplasm of plant cells (Yang et al., 1995), but these may not be based on keratin, as in animal cells, since as yet **no plant keratin genes** have been found.
- **Nuclear lamins**, intermediate filaments of another type that form a dense network on the **inner surface of the nuclear membrane**, have also been identified in plant cells (Frederick et al., 1992), and genes encoding lamin-like proteins are present in the ***Arabidopsis* genome**. Presumably, plant lamins perform functions similar to those in animal cells as a structural component of the nuclear envelope.
- **Intermediate filaments** tend to be **less sensitive to chemical agents** than other types of cytoskeletal elements and more difficult to solubilize. In fact, treatment of a cell with ionic detergents extracts just about everything except the cell's intermediate filaments. Because of their insolubility, IFs were initially thought to be permanent, unchanging structures, so it came as a surprise to find that they behave dynamically in vivo. When labeled keratin subunits are injected into cultured skin cells, they are rapidly incorporated into existing IFs.
- Unlike the other two major cytoskeletal elements, assembly and disassembly of IFs are controlled primarily by **phosphorylation and dephosphorylation of the subunits**. For

example, phosphorylation of vimentin filaments by protein kinase A leads to their disassembly.

- **Keratin filaments** constitute the primary structural proteins of epithelial cells (including epidermal cells, liver hepatocytes, and pancreatic acinar cells).
- **Keratin-containing IFs** radiate through the cytoplasm, tethered to the nuclear envelope in the center of the cell and anchored at the outer edge of the cell by connections to the **cytoplasmic plaques of desmosomes and hemidesmosomes**.
- The cytoplasm of neurons contains loosely packed bundles of intermediate filaments whose long axes are oriented parallel to that of the axon (see Figure 9.7b). These **IFs, or neurofilaments (NFs)**, as they are called, are composed of **three distinct proteins**: NF-L, NF-H, and NF-M, all of the **type IV group** of Table 9.2.
- Unlike the polypeptides of other IFs, **NF-H** and **NF-M** have **side arms** that project outward from the neurofilament. These side arms are thought to maintain the proper spacing between the parallel neurofilaments of the axon (see Figure 9.7b).
- In the early stages of differentiation when the axon is growing toward a target cell, it contains very few neurofilaments but large numbers of supporting microtubules. Once the nerve cell has become fully extended, it becomes filled with neurofilaments that provide support as the axon increases dramatically in diameter.

Defective intermediate filaments (IFs) causes following disorders:

- **Aggregation of NFs** is seen in several human neurodegenerative disorders, including **ALS** and **Parkinson's disease**. These NF aggregates may block **axonal transport**, leading to the death of neurons.
- Efforts to probe IF function have relied largely on genetically engineered mice that fail to produce a particular IF polypeptide (a gene knockout) or produce an altered IF polypeptide. These studies have revealed the importance of intermediate filaments in particular cell types. For example, mice carrying deletions in the gene encoding **K14**, a **type I keratin** polypeptide normally synthesized by cells of the basal epidermal layer, have serious health problems. These mice are so sensitive to mechanical pressure that even mild trauma, such as that occurring during passage through the birth canal or during nursing by the newborn, can cause severe blistering of the skin or tongue. This phenotype bears strong resemblance

to **a rare skin blistering disease in humans**, called **epidermolysis bullosa simplex** (**EBS**).

- Similar types of **blistering diseases** can be caused by defects in proteins of the **hemidesmosome**, which holds the basal layer of the epidermis to the basement membrane. EBS can also be caused by mutations in the gene encoding the IF crosslinking protein **plectin**, but such patients also suffer from late onset **muscular dystrophy**, showing the importance of IF networks in muscle as well as skin.
- Subsequent analysis of EBS patients has shown that they carry mutations in the gene that encodes the **homologous K14 polypeptide** (or the K5 polypeptide, which forms dimers with K14). These studies confirm the **role of IFs in imparting mechanical strength to cells** situated in epithelial layers.
- Similarly, **knockout mice** that fail to produce the **desmin polypeptide** exhibit serious cardiac and skeletal muscle abnormalities. **Desmin** plays a key structural role in maintaining the **alignment of the myofibrils of a muscle cell**, and the absence of these IFs makes the cells **extremely fragile**.
- An inherited human disease, named **desmin-related myopathy**, is caused by mutations in the gene that encodes desmin. Persons with this disorder suffer from **skeletal muscle weakness, cardiac arrhythmias, and eventual congestive heart failure**.
- Not all IF polypeptides have such essential functions. For example, mice that lack the **vimentin gene**, which is expressed in **fibroblasts, macrophages, and white blood cells**, show relatively minor abnormalities, even though the affected cells lack cytoplasmic IFs.
- It is evident from these studies that **IFs have tissue-specific functions**, which are more important in some cells than in others.