IIT Guwahati Lecture 36

Course BT 631

Protein Structure, Function and Crystallography

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The structure and function of fibrous Proteins

- Fibrous proteins were named because they were found to make many of the ‘fibres’ found in the body.
- Fibrous proteins have a common role in conferring strength and rigidity to these structures as well as physically holding them together.
- These proteins are widely distributed in cells as well as in making up connective tissues such as tendons or ligaments.
- A common feature of most fibrous proteins is their long, drawn-out or filamentous structure.
- Essentially, these proteins tend to occur as ‘rod-like’ structures extended in three dimensions and lacking the compactness of globular proteins.
- As a result fibrous proteins tend to possess architectures based around regular secondary structure with little or no folding, resulting from the long range interactions. In other words they lack the true tertiary structure.

Amino acid composition and organization of fibrous proteins

In fibrous proteins three structural designs are known,

(i). Structure composed of ‘coiled-coils’ of α helices are represented by α keratins,

(ii). Structures made up of extended antiparallel β sheets are exemplified by silk fibroin a collection of proteins made by spiders or silkworms

(iii). Structures based on triple helical arrangement are shown by collagen family of proteins.

Keratins

Keratins are the major class of proteins found in hair, feathers, scales, nails or hooves of animals.

In general, the keratin class of proteins are mechanically strong and resistant to most forms of stress.

At least two major groups of keratins are identified,

i) α keratins are typically found in mammals, while
ii) β keratins are found in birds and reptiles as part of feathers and scales containing a higher proportion of β sheet.

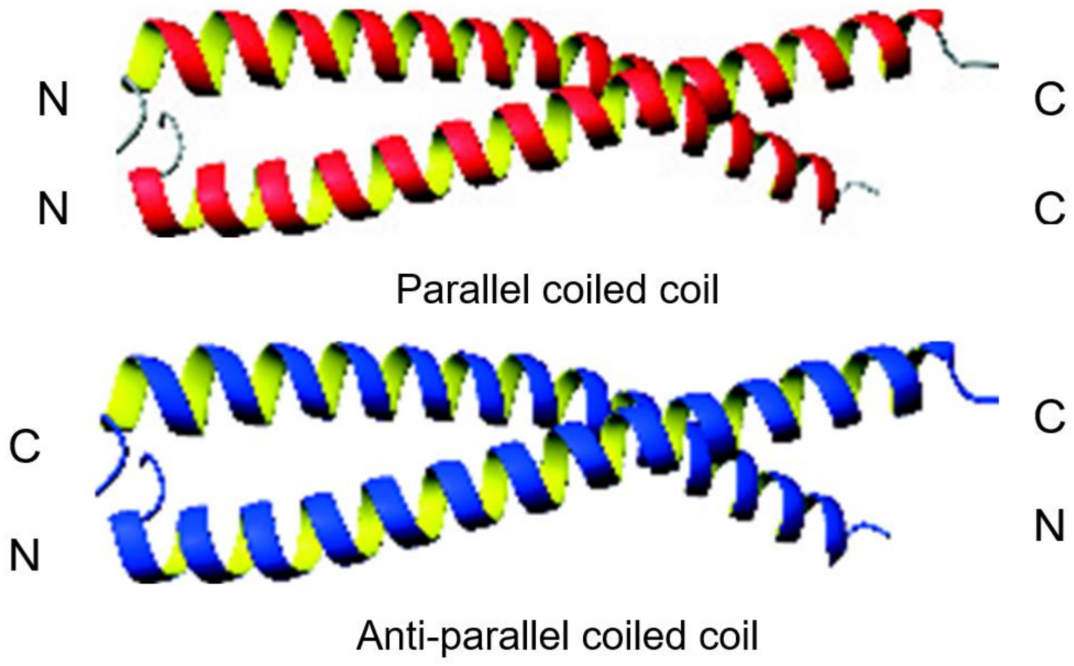
The β keratins are analogous to the silk fibroins produced by spiders and silkworms.

Keratins

In mammals around 30 variants of keratin are known. In each keratin the ‘core’ structure is similar and is based around α helix.

The most common arrangement for keratin is a coiled-coil of 2 α-helices, although 3-helical stranded arrangements are also known for extracellular keratins, while 4-stranded coiled coils are found in insects.

In 1953 Francis Crick postulated that the stability of α helices would be enhanced if pairs of helices interacted not as straight rods but in a simple coiled-coil arrangement (Figure). This coiled coil arrangement is also called a super helix.



α- Helices pairs forming a super helix

Keratins

- The hydrophobic residues form a seam that twists about each helix.
- By interacting with neighbouring hydrophobic surfaces helices are forced to coil around each other forming the super helix.
- Besides the high content of hydrophobic residues α keratins also have significant proportions of cysteine.
- The cys residues participate in -S-S- bridges that cross-link neighbouring coiled-coils to build up a filament or bundle and ultimately the network of protein constituting hair or nail.

Keratins

- **The keratins are group of filamentous proteins based on coiled coils making up the cytoskeletal system and are called as intermediate filaments (IF).**
- **IF are generally between 8 and 10 nm in diameter and are more common in cells that have to withstand stress or extreme conditions.**
- **At least 6 different IF have been identified with classes I and II represented by acidic and basic keratins.**
- **The terms ‘acidic’ and ‘basic’ to domains of keratin refer to their overall charge.**

Keratins

- **Acidic and basic monomers are found within the same cell and the coiled coil or dimer contains one of each type giving rise to a heterodimer.**

- **Each coiled-coil dimer aligns in a head to tail arrangement and in two staggered rows to form a protofilament.**

- **The protofilament dimerizes to form a protofibril and with four protofibrils uniting to make a microfibril.**

- **The assembly of coiled coils into microfibrils is shown in the Figure.**

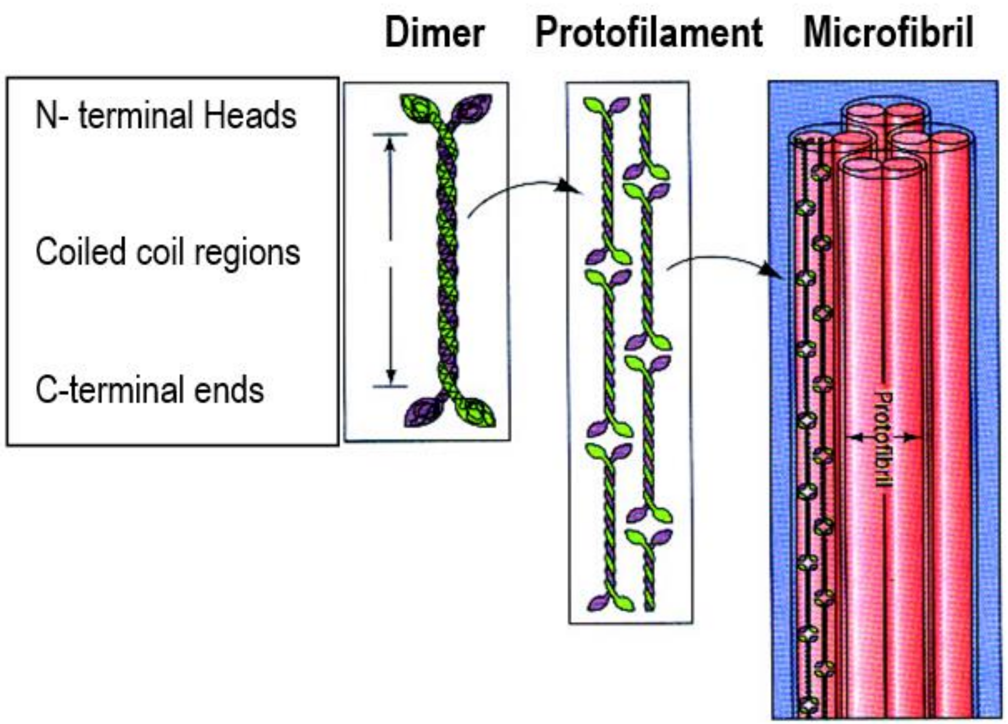


Fig. Higher order α keratin structure. Left: heterodimeric arrangement of two α-helices to form a coiled-coil with both acidic and basic domains. Middle: protofilaments formed by the association of two coiled coils in a head-tail order and in two staggered or offset rows. Right: dimerization of protofilaments to form a protofibril followed by four protofibrils uniting to form a macrofibril.

Keratins (Springiness of hair)

- Keratins are the most abundant proteins in epithelial cells.
- The springiness of hair is a result of the extensive number of coiled-coils and their tendency in common with a conventional spring to regain conformation after initial stretching.
- For the hair, the use of dithiothreitol, mercaptoethanol or thioglycolate allows the reduction of disulphide bridges and the relaxing of hair from a curled state to a straightened form.
- Removal of the reducing agent and the oxidation of the thiol groups allows the formation of new disulphide bridges and in this way, the hair may be reformed in a new 'curled' or 'permed' conformation.
- The reduction of disulphide bridges in hair allows a keratin fibre to stretch to over twice their original length.

Keratins

- Mutations in the genes coding for keratin lead to impaired protein function. In view of the almost ubiquitous distribution of keratin these genetic defects can have severe consequences on individuals.
- Defects prove particularly deleterious to the integrity of skin and several inherited disorders are known where cell adhesion, motility and proliferation are severely disturbed.
- Since many human cancers arise in epithelial tissues where keratins are prevalent, such defects may predispose individuals leading to more rapid tumour development.