Intermediate Filaments: from the Elementary Dimer Structure to the Complete Filament Architecture

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Together with microtubules and microfilaments, the ~11 nm wide intermediate filaments (IFs) constitute the interconnected, dynamic cytoplasmatic network critically involved in cell division, motility and plasticity. While the structures of microtubules and microfilaments are known at atomic detail, IF architecture is presently much less understood. The elementary 'building block' of all IFs is a rod-shaped alpha-helical coiled-coil dimer flanked at either side the 'head' and 'tail' domains.

By introducing a 'divide-and-conquer' approach, we have determined the X-ray crystallographic structures of a series of human vimentin fragments. As the result, an atomic model of the full IF dimer could be proposed. In addition, we are working on the atomic structure of the nuclear IF protein lamin, including crystallographic studies of individual lamin fragments and complexes thereof. We show that the specific head-to-tail association of lamin dimers during filament assembly is likely to be driven by electrostatic attraction. Futhermore, we are investigating the structural effect of mutations in IF proteins that have been associated with human disease such as myopathies, skin and neuronal diseases. Towards this goal, we combine X-ray crystallography with other methods such as electron and atomic force microscopies and solution small-angle X-ray scattering.

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