STRUCTURAL STUDIES ON THE NUCLEAR LAMINS AND OTHER INTERMEDIATE FILAMENT PROTEINS

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ABSTRACT

A number of aspects of IF chain and molecular structure, as well as molecular aggregation, have been examined. These include the delineation of periodicities in the sequences of structural domains of IF proteins, the distribution of amino acid residues within the heptad substructure, the flexibility of the peptide backbone, the extent of homology among the IF proteins, the packing of chains in the dimeric molecule, and the axial packing of molecules in the IF. Particular focus has been placed on the newly sequenced type V IF proteins (the nuclear lamins and the *Helix pomotia* B protein) and on a type III IF protein (peripherin).

A parallel in-register arrangement of chains in the molecule is predicted for peripherin and the type V chains from a consideration of interchain ionic interactions. Also, periodicities in the linear distribution of charged residues in the rod domains of these proteins are shown to be comparable with periods in other IF chains. Ionic interactions between lamin molecules have been used to assess the likely modes of molecular aggregation in an *in vitro* assembly and a model is presented which also satisfies the constraints imposed by electron microscope data. In this model, antiparallel arrays of molecules are half-staggered and an extended conformation for the carboxy-terminal domains is predicted. Simple explanations are given for the transition between paracrystalline and lattice structures and for the disassembly of the lamin meshwork concommitant with hyperphosphorylation. The method of calculating intermolecular ionic interaction profiles is enhanced and a new, three-dimensional method is developed.

The inhomogeneous distribution of residues in the heptad substructure can be correlated to the coiled-coil structure and chain packing in the molecule. In particular, the ~75% occupancy rate of apolar residues in the internal a and d heptad positions is shown to be a general feature of α-fibrous proteins. Variability of residues in the outer b, c and f positions indicates that structural or functional specificity in the rod domain may be determined by these parts of the sequence. The predicted flexibilities of IF chains have been compared to the underlying structure for the chains.

Evidence from sequence homology studies suggests that several new subtypes are appropriate in the classification scheme. For the hard keratins the terms types Ia and IIa are proposed and for the soft keratins, types Ib and IIb; the need to separate the neurofilaments into the type IV class separate from the type III IF chains is confirmed; and division of the type V chains into cytoskeletal and karyoskeletal groups is indicated. A more detailed delineation is made of regions within the amino- and

carboxy-terminal domains than has been possible previously. Periodic features of the homology profiles for the rod domain are examined and found to be similar to those in the linear distribution of residues in the amino acid sequences. Comparison between amphibian and mammalian keratins, and also between hard and soft keratins reveals that type II chains are maintained at a higher level of fidelity than type I chains. Consensus rod domain sequences are derived for the various IF subtypes: absolutely conserved regions of primary structure identify types or subtypes.

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