Principles of Intermediate Filament Assembly: Integrators of Cellular Space but also Sensors and Modulators of Ionic Strength and PH

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Intermediate filaments (IF) are major constituents both of the cytoskeleton and the nucleoskeleton in all metazoan cells. They are of prime importance for the functional organization of basic structural elements within cells, but also for the coordination of cell-cell and cell-matrix interactions, and therefore eventually for organogenesis. In man, IF proteins constitute a protein family that is coded for by 70 genes. Their expression proceeds in parallel with certain routes of differentiation during embryogenesis. Depending on the cell type, the amount of IF proteins may differ considerably and, notably, morphologically similar but biochemically very distinct proteins all may form highly viscoelastic filament networks with multiple nanomechanical functions. Besides their primary role in cell plasticity and their established function as cellular stress absorbers, recently discovered gene defects have elucidated that structural alterations of IFs as well as the nuclear lamina can affect their involvement both in signaling and in controlling gene regulatory networks. Indeed, the IF gene family appears to be one of the most highly mutated ones in man giving rise to more than 80 different disease entities. Therefore, a deeper insight into the basic structural and functional properties of intermediate filaments is of prime importance. In particular, the surface properties, as dominated by the non-alpha-helical carboxy-terminal end domains, may vary largely. For instance, the neurofilaments present very long, unstructured and highly acidic domains on their surface as do the IF-associated proteins nestin and synemin. Hence, new concepts of how mutations may affect cellular architecture and thereby tissue physiology, and how they eventually lead to complex diseases such as cardiomyopathy and premature ageing, are absolutely essential. Our work aims to elucidate the molecular basis of filament assembly and network formation as well as the characterization of their biophysical properties.