Intermediate filaments in development and disease: Mediators of a cell type-specific switch in cell elasticity

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Intermediate filament (IF) proteins constitute, in addition to microtubules and actin filaments, a third independent and prominent cytoplasmic filament system in all metazoan species (1). IF proteins are fibrous coiled-coil forming proteins, with a length for an individual coiled coil of about 45 nm, exposing non-α-helical "tail" domains away from the filament axis. Therefore, they are ideal candidates for enforcing the dynamic formation of complex networks from individual filaments and their collective adaption to new physiological situations. Moreover, IFs are engaged in the integration of various types of cellular structures such as mitochondria and the nucleus into the cytoskeleton via versatile crossbridging factors of the plakin family, i.e. plectin, desmoplakin and BPAG1 (2).

In mammals, epithelial cells characteristically express keratins. During embryogenesis, when ectodermal cells switch to become mesenchymal cells, they replace keratins by vimentin. In contrast to keratins, vimentin can co-assemble with a variety of very unique IF proteins that are expressed in a cell type-specific mode such as nestin, an IF protein that needs other IF proteins in order to form filaments and that carries a huge non-α-helical "tail" domain of 1620 amino acids. Muscle cells turn on the desmin gene in addition to a two other IF proteins, synemin and syncoilin, which carry complex "tail" domains too. Both synemin and syncoilin are expressed in three splice forms with increasingly longer "tail" domains, which are assumed to instrumental in "networking" with other components of the sarcomer such as the dystrophin-glycoprotein complex. Furthermore, nestin - that is up to now still considered as a stem cell marker mostly - is also found in muscle to some extent, in particular in vascular smooth muscle cells during vascular remodelling. In mature muscle, its expression is induced in response to injury.

Since different cell types, such as epithelial cells, myoctes and neurones, are subjected to quite different tkinds of mechanical stress, it is plausible that IF proteins are part of the cellular repertoire to establish distinct cell shapes and generate specific elastic properties. This hypothesis is supported by recent work on desmin disease mutations that cause myofibrillar myopathies. In this context we investigated the influence of point mutations on filament assembly, association with chaperones, and network properties such as the "strain stiffening" behaviour, which is characteristic for IFs, as well as the behaviour of mutated proteins in transfected cells (3, 4). Last but not least, we are following concepts how IFs may contribute to epithelial-mesenchymal-transitions (EMT) as well as cellular changes observed in metastatic cells during tumorigenesis. Besides their "stress absorber" role, IFs do provide a large charged surface to the cell, which may function as a hub for various protein modules, including signalling complexes as well as parts of the proteolytic machinery of the cell.

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