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Intermediate filaments in peripheral nervous system: Their expression, dysfunction and diseases

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ABSTRACT

Characteristics of the intermediate filament proteins (IFPs) expressed during the development and cell differentiation of peripheral neurons are here reviewed. Neurofilament triplet proteins (NFPs), peripherin, α-internexin, synemin, syncoilin, nestin, vimentin and glial fibrillary acidic protein (GFAP) are each produced by different genes. NFPs, the most extensively studied, are thought to maintain axonal caliber, thus ensuring normal axonal transport, but this network is highly disrupted in several diseases, particularly motor neuron diseases. α-internexin has been proposed as the fourth NFP subunit. The relative plasticity of the peripherin network may account for its possible role during development, when axons have to find their targets, and when axons regenerate. In addition to their expression in muscle, other IFPs, such as syncoilin and synemin, are also expressed in neuronal tissues. Syncoilin modulates peripherin filament networks. Synemin M, associated with peripherin, is present in small unmyelinated fibers, whereas synemin L is produced in large neurons with myelinated fibers positive for the light-chain neurofilament (NF-L) subunit. Nestin is an IFP expressed in dividing cells during early stages of development in the central and peripheral nervous systems, and in muscles and other tissues. After differentiation, nestin is downregulated and replaced by tissue-specific IFPs. IFPs in glial cells are primarily composed of GFAP, although vimentin is also expressed; vimentin is also widely distributed in mesenchymal derivatives and established cell lines. In the peripheral nervous system, NFPs appear early in its development and progressively replace vimentin, which is expressed before NFPs in most, if not all, dividing neuroepithelial cells. In addition, in tissues undergoing an injury response, the unique and complex cell and tissue distribution of IFPs can be markedly modified.

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1. Introduction

Intermediate filaments (IFs), along with actin-containing microfilaments and tubulin-containing microtubules, make up the three major classes of cytoskeletal filaments in multicellular organisms. IF genes can be classified according to various criteria, such as genomic structure and nucleotide sequence homology [1].

There are over 70 members in the IF protein superfamily, and these have been divided into six or seven classes, based on gene structure and sequence comparisons throughout their rod domains, and terminal head and tail domains. The rod domain promotes coiled-coil interactions between two individual IF proteins to initiate the formation of 10-nm diameter filaments. Flanking this rod domain are the N-terminal head and C-terminal tail domains that vary considerably in size and sequence within the IF classes [2]. IF proteins can self-assemble into cytoskeletal filaments, which usually appear as homogeneous apolar fibers, with diameters of 10–12 nm on visualization by negative staining and electron microscopy [3].

All major types of IF polymers have been identified as mechanical scaffolds in differentiated cell types in situ [4]. Defects in IF polymer structure or organization result in fragility states that translate into loss of cellular integrity following exposure to shearing forces [5].

There is also emerging evidence that IF proteins play additional roles that are not only cell-type-specific, but also context-dependent. Examples include the contribution of neuronal filaments to the radial growth of neurons and axonal transport [6,7].

The present review focuses on two major aspects: the expression of different neuronal IFs during their development; and their in vivo function and changes in disease and during dorsal root ganglia (DRG) regeneration.

2. Structure, expression and function of neuronal filaments

2.1. *Neurofilaments (NF-L: 68 kDa; NF-M: 160 kDa; NF-H: 240 kDa; human chromosome location: 8p21 for NF-L and NF-M; 22q12-1 for NF-H)*

Neurofilament triplet proteins (NFPs), which include a light-chain neurofilament (NF-L), a medium-chain neurofilament (NF-M) and a heavy-chain neurofilament (NF-H) are type-IV IFs and thought to be the primary components of neuronal IF [8]. All three proteins contain long stretches of polypeptide sequences rich in glutamic acid residues. NF-M and NF-H also contain multiple tandem repeats of serine phosphorylation sites, which frequently contain the peptide Lys–Ser–Pro (KSP; human NF-H contains 44 or 45 of such repeats). Phosphorylation is normally found on axonal, but not dendritic, NFs. During embryonic development, these NF subunits are sequentially expressed: first, NF-L is detected during neuronal differentiation; then the NF-M subunit during neurite formation; and finally, NF-H appears during the postnatal period of neuronal differentiation [9].

While their differential expression during embryonic development suggests potential functions of these proteins in axogenesis [10], studies from knockout mice have shown that, in the absence of NFs, axogenesis is not compromised. However, substantial developmental loss of motor axons was detected in mice lacking NF-L and in double knockout (NF-M/NF-H) mice, supporting the idea of a role for IFs in axon stabilization [11]. Mice lacking NF-L had a scarcity of IF structures and exhibited severe axonal hypotrophy, causing an up to 50% reduction in conduction velocity, a feature that would be highly detrimental in larger animal species.

Also, it appears that the NF-M, rather than NF-H, protein is required for proper radial growth of large myelinated axons. Studies with transgenic mice suggest that some types of IF accumulations, reminiscent of those found in amyotrophic lateral sclerosis (ALS), can have deleterious effects and even cause neurodegeneration. Additional evidence of the involvement of IFs in pathogenesis has come from the discovery of *NF* gene mutations linked to ALS and Charcot–Marie–Tooth disease [12,13].

2.2. *Internexin (INX: 66 kDa; human chromosome location: 10)*

α-internexin, a type-IV IF, is often expressed together with NFs and has been proposed as the fourth NF subunit [13]. It can self-polymerize in vitro and in transfected cells. It is also expressed earlier in development than NFs and is present in most neurons during their differentiation, and is the only *IF* gene expressed in adult cerebellar granule cells [14]. Several studies have suggested that α-internexin could be involved in axonal outgrowth, and its high level of expression during early neuronal differentiation as well as in oligonucleotide-based inhibition experiments in vitro further suggests such a role [15–18]. However, gene knockout experiments in mice have shown the absence of a nervous system phenotype [13]. Additional studies may be required to detect any potential subtle changes in nervous system development and maintenance.

Physiologically, α-internexin is seen as a component of inclusions in several neurodegenerative diseases, such as neuronal IF inclusion disease, Alzheimer's disease, dementia with Lewy bodies and motor neuron disease. It is also used as a diagnostic and prognostic determination tool for several types of tumors [19,20].

2.3. *Peripherin (Per1: 58 kDa; human chromosome location: 12 q12-q13)*

Of the various type-III IFs, peripherin is the only one specific to neurons. In embryos, peripherin expression is associated with the onset of terminal neuronal differentiation and present in several types of neurons (motor, sensory and sympathetic neurons) [21]. In adults, peripherin expression is limited to the peripheral nervous system (PNS) and some neurons of the central nervous system (CNS). It is often coexpressed with NFs [22], and has been shown to colocalize and interact with syncoilin and synemin M. It is interesting to note that, in dorsal root ganglia (DRG) neurons, peripherin is mainly present in small-size neurons devoid of NF-L.