The cytoskeleton meets the skeleton. Focus on “Deficiency of the intermediate filament synemin reduces bone mass in vivo”

Omar Skalli
Department of Life Sciences, The University of Memphis, Memphis, Tennessee

IN AN ACCOMPANYING ARTICLE in the current issue of the American Journal of Physiology: Cell Physiology, Moorer and colleagues (6a) put the limelight on synemin, which is one of the 70 intermediate filament (IF) proteins, by demonstrating that synemin knockout mice exhibit a substantial reduction in bone mass. This finding is of particular significance since the skeletal system is arguably the organ system for which we know the least about the roles of cytoskeletal IF proteins.

On their own or in specific combinations, IF proteins form cytoplasmic and nuclear filamentous networks protecting cells and tissues from mechanical and metabolic stressors. They play these roles by combining unique strain hardening properties with the ability to act as dynamic scaffolds for signaling proteins. Some IF proteins also assume cell type-specific functions by contributing to a host of cellular processes such as motility, shape specification, and organelle transport. A sobering testimony for the crucial role of IF proteins in cell physiology are the ∼70 debilitating human diseases due to mutations in genes encoding IF proteins.

Due to the large size of the IF protein family, specific IF proteins have received different degrees of attention. In this context, synemin is somewhat the victim of scientific neglect: while it was described in the early 1980s, it is not until recently that studies have begun in earnest to elucidate its roles, identify its interacting partners, and characterize its expression pattern during development and diseases (reviewed in 8). Collectively, these studies have established that compared with the other IF proteins, synemin possesses several interesting idiosyncrasies including a large molecular weight (180 and 140 kDa for α- and β-synemin isoforms, respectively, vs. 40–60 kDa for most other IF proteins), an inability to assemble on its own into IFs which can be mitigated by partnering with vimentin or desmin, an expression pattern encompassing many cell types, and binding sites for actin-associated proteins and signaling proteins (Fig. 1). In addition, recent studies have revealed that synemin-null mice display a myopathic phenotype which is unlike that of mice deficient in desmin, the most abundant IF protein in muscles (3, 5).

Pursuing the meticulous analysis of the synemin-null mice in which synemin intervenes in bone formation. They report that in synemin-null mice osteoblasts are less abundant and have decreased cyclin D1 levels relative to wild-type mice. Since cyclin D1 is involved in the G1-S cell cycle transition, these results point to a role of synemin in cell proliferation, an emerging recurrent theme in functional studies of synemin. Thus, in synemin-null mice the balance between the self-renewal and differentiation of muscle satellite cells is affected (5). Moreover, in astrocytoma cells, RNAi of synemin drastically affects cell proliferation by inhibiting the G1-S transition (9). In these cells, synemin associates with and antagonizes PP2A activity. It will be interesting to examine whether a similar mechanism also operates in osteoblasts, since PP2A is a negative regulator of osteoblastic differentiation (7).

Although synemin is self-assembly incompetent, it can co-polymerize with vimentin to form a cytoplasmic IF network. Since osteoblasts contain vimentin, it is puzzling that synemin does not form a filamentous network in these cells. Instead, it is organized as small circular cytoplasmic structures, which are hypothesized by the authors to be podosomes. Immunofluorescence studies to contrast the distribution of synemin with that of vimentin, and/or podosome-specific proteins and/or actin-
associated proteins binding to synemin, should help understand the intriguing organization of synemin in osteoblasts.

In conclusion, the results of the synemin study highlighted here make a case for the “skeletal” in “cytoskeletal” to be sometimes understood as implying an important role in skeletal physiology. These results, combined with the role of lamin A/C in the osteopenia symptomatic of a human disease, should provide the impetus to expand our very limited knowledge of the role of IF proteins in bone and cartilage.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

O.S. interpreted results of experiments; O.S. drafted manuscript; O.S. edited and revised manuscript; O.S. approved final version of manuscript.

REFERENCES