Skeletal muscle features in myotonic dystrophy and sarcopenia: do similar nuclear mechanisms lead to skeletal muscle wasting?

M. Malatesta
Dipartimento di Scienze Neurologiche, Neuropsicologiche, Morfologiche e Motorie, Sezione di Anatomia e Istologia, Università di Verona, Italy

Abstract

In the cell nucleus, the gene primary transcripts undergo molecular processing to generate mature RNAs, which are finally exported to the cytoplasm. These mRNA maturation events are chronologically and spatially ordered, and mostly occur on distinct ribonucleoprotein (RNP)-containing structures. Defects in the mRNA maturation pathways have been demonstrated in myotonic dystrophy type 1 (DM1) and type 2 (DM2) whose characteristic multisystemic features are caused by the expansion of two distinct nucleotide sequences: (CTG)n in the DMPK gene on chromosome 19q13 in DM1, and (CCTG)n in the ZNF9 gene on chromosome 3q21 in DM2. By combining biomolecular and cytochemical techniques, it has been shown that the basic mechanisms of DMs reside in the accumulation of CUG- or CCUG-containing transcripts in intranuclear foci where several RNA-binding proteins necessary for the physiological processing of pre-mRNA are sequestered. Moreover, a nucleoplasmic accumulation of splicing and cleavage factors has been found in DMs. This suggests that the dystrophic phenotype could depend on a general alteration of the pre-mRNA post-transcriptional pathway. Interestingly, the accumulation of pre-mRNA processing factors in the myonuclei of DM1 and DM2 patients is reminiscent of the nuclear alterations typical of sarcopenia, i.e., the loss of muscle mass and function which physiologically occurs during ageing. Consistently, in an in vitro study, we observed that satellite-cell-derived DM2 myoblasts show cell senescence alterations and impairment of the pre-mRNA maturation pathways earlier than the myoblasts from healthy patient. These results suggest possible common cellular mechanisms responsible for skeletal muscle wasting in sarcopenia and in myotonic dystrophy.

Correspondence: Manuela Malatesta, Dipartimento di Scienze Neurologiche, Neuropsicologiche, Morfologiche e Motorie, Sezione di Anatomia e Istologia, Università degli Studi di Verona, Strada Le Grazie 8, 37134 Verona, Italy. Tel: +39.045.8027157 - Fax: +39.045.8027163. E-mail: manuela.malatesta@univr.it

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cally relocating also into nuclear RNP domains where they generally do not occur (unpublished results). This accumulation could hamper the functionality of the splicing machinery and slow down the intranuclear molecular trafficking thus reducing the metabolic activity of myonuclei, consistent with recent findings demonstrating a reduced protein synthesis in DM1 and DM2 myoblasts.29,35

Skeletal muscle features in sarcopenia

During ageing, the skeletal muscle undergoes a progressive loss of mass, strength and function, in the process known as sarcopenia.30,31 Sarcopenia affects healthy, physically active subjects: the rate of muscle loss in humans has been estimated to range 1 to 2% per year after age of fifty. Therefore, sarcopenia represents a great risk factor for frailty, loss of independence and physical disability in elderly, since it is associated with decreased functional performance, higher risk of falls and motor function impairment. The mechanisms underlying age-related skeletal muscle wasting and weakness are probably manifold and still remain to be fully elucidated;34 however, although no specific therapy is presently available to counteract its onset or progress, studies performed on humans and other mammals have stressed the importance of physical exercise as an effective, although still debated, approach to prevent or limit the age-related muscle mass loss.35-36

Interestingly, the sarcopenic process is characterised by structural and functional alterations of the skeletal muscle that are reminiscent of myotonic dystrophy. In fact, the aged muscle shows grouped atrophy, fibre size variability and centrally located nuclei.17 In addition, factors involved in the post-transcriptional processing of pre-mRNA have been found to accumulate not only in the nucleoplasmic RNP-containing structures where they usually locate but also in ectopic nuclear domains.37-38 This intranuclear accumulation/deocalization of RNP structures containing splicing and cleavage factors has been found not only in the skeletal muscle but also in other tissues (e.g., liver, brain) of aged mammals.40-41 Moreover, aged cells undergo malfunctions of the degradation systems both in the cytoplasm42 and in the nucleus43,44 with accumulation of crosslinked insoluble molecules (including non-coding RNAs) which hampers the intracellular transport mechanisms. This suggests that in ageing cells the entire production chain of mRNA, from its synthesis to the cytoplasmic export, becomes less efficient, likely contributing to the reduced capability of cells to positively react to metabolic stimuli, which typically occurs in elderly. This loss of responsive

Concluding remarks

A recent in vitro study49 reported that satellite-cell-derived myoblasts from DM2 patients show cell-senescence alterations (e.g., cytoplasmic vacuolisation, reduction of the proteosynthetic apparatus, accumulation of heterochromatin and impairment of the pre-mRNA maturation pathways) earlier than the myoblasts from healthy subjects; moreover, when grown in a different differentiation medium DM2 myoblasts fuse into multinucleated myotubes exhibiting structural defects similar to those observed in senescent myotubes from healthy patients.50 The early occurrence of senescence-related features in satellite cell-derived myoblasts suggests that satellite cells from DM2 patients have a reduced regeneration capability, which would contribute to the muscular dystrophic phenotype.

The cytochemical and ultrastructural evidence demonstrates that the skeletal muscle of DM patients shares intriguing similarities with the muscle from aged individuals in several nuclear features, especially in the altered nuclear RNP-containing structures involved in pre-mRNA transcription and splicing. This opens interesting perspectives on the role of the RNP nuclear components in the onset of muscle cell dysfunctions and encourages comparative studies aimed at detecting common cellular mechanisms at the basis of skeletal muscle wasting.

Finally, it is worth noting that the analysis in situ of the organization and molecular composition of nuclear domains is a powerful tool not only for getting information about the DNA/RNA pathways which govern cellular metabolism, but also for detecting the occurrence of cell dysfunctions related to pathological phenotypes.51-53

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