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Sarcoglycan subcomplex: state of the art

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More than 15 years have elapsed since the discovery of the sarcoglycan complex (SGC) [1] and the characteristics of this original complex have been fairly studied in succeeding years later [2].

In details, sarcoglycan (SG) is a component of the larger dystrophin-associated glycoproteins complex (DAGC) called DGC also [1]. The DAGC is composed of at least ten proteins links laminin2 (merosin) of the extracellular matrix and actin, stabilizing the cell membrane during muscle activity. Three subcomplex can be identified in the DAGC on the basis of different biochemical characteristic and localization: the sarcoplasmic subcomplex, made up of the dystrophin, dystrobrevin and syntrophin complex; the dystroglycan subcomplex, made up of α- and β-dystroglycan; the SGC, composed of six SG subunits (α, β, γ, δ, ε and ζ-SG). SGC subcomplex is an independent complex that is not directly associated with dystrophin and it plays a key role in signalling functions maintaining sarcolemma viability in muscle fiber membrane. As mutations in any one of SG subunits cause autosomal recessive limb-girdle muscular dystrophy (LGMD), characterized by integrity of dystrophin, SGC can be considered as associated system of DAGC and for this, it seems to be functionally as important as dystrophin.

Moreover, previous reports have demonstrated that SGs are localized in skeletal and cardiac muscle forming the costameres, also showing that these proteins are co-localized with integrins in these regions in skeletal muscle in the region of the sarcolemma over I or A bands on the basis of the fiber types, slow or fast respectively [3,4]. These results have reinforced the hypothesis of a functional connection between SGs and integrins through a bidirectional signalling [5] which seems to be important to alleviate muscle diseases and to improve the survival of a severely dystrophic mouse model of Duchenne muscular dystrophy. For this, in our opinion the study of SGs implies also the consequent analysis of the integrins in many different tissues.

Furthermore, it was demonstrated the presence of all SGs, and then of an exameric arrangement of SGC, in smooth muscle fibers of many districts [6,7] emphasizing an important correlation between SGs and frequency of contraction force [7,8].

Whereas the expression of α and γ-SG is restricted to striated muscle cells, the other SGs are widely expressed in various tissues as levels of β, δ and ε-SG were highest in lung, moderate in brain, heart, and low, but detectable in kidney and liver [9].

Then, since this complex is not considered as muscle-specific, previously we have analyzed the SGs in non-muscle tissues, as well as digestive, respiratory and urinary epithelial cells. Interestingly, our immunohistochemical results showed the presence of all SGs in all tested tissues. About this, recently, we analyzed SGC in biopsies obtained from human breast and prostate in normal and pathological conditions in order to study these proteins also in glandular epithelium. Our results showed, for the first time, that in normal conditions, staining pattern for all SGs has been detecta-

ble and distributed in both epithelial and myoepithelial cells. Moreover, observations on samples of pathological tissues have shown that immunofluorescence for all SGs appears to be severely reduced in benign diseases, and almost absent in malignant syndromes.

These results were confirmed also by data obtained on gingival epithelium in normal and pathological conditions. Particularly, our results on normal gingival epithelium showed the presence of SGC in this tissue confirming that SGs are ubiquitously distributed; in gingival epithelium, obtained from patients during inflammatory processes, due to treatment with bisphosphonates, staining pattern for SGs was decreased.

Then, SGs could play a crucial role in oncogenesis since it is possible to hypothesize that these diseases could be due to lack of SGs in epithelial cells; moreover, the invasivity of malignant syndromes could be provoke by homology of SGs sequences with that of cadherins, transmembrane glycoproteins that are essential for cell-cell adhesion [10].

Additionally, it is known that even in the central nervous system the DGC exists but differs in composition from the DGC core present in muscle for the presence of several isoforms of dystrophin and for the existence of a SGC which is made up only for ε- and ζ-SG. On this, in our previous study we have analyzed the SGs expression and localization in rat's cerebral cortex and our results showed that all SGs are present with a staining pattern in relation to the cerebral cortex area observed. In particular we think that they could be associated with synapse sites such as inhibitory GABAA Rε and D5DR receptors. Furthermore, the same analysis carried out on the brain of the WAG/Rij rats, a model of absence epilepsy, confirmed this role for SGs.

On this basis, in order to understand the real function of SGs and integrins and their relationship with contraction forces, we studied these proteins in masseter muscle which, as well known, is highly unusual compared with other muscles; in fact, in addition to normal slow and fast fibers, this muscle contains fibers types which are typical for developing or cardiac muscle. Many fibers are hybrid, and they are important for the specific functional demands of masseter; these fibers probably increase the capacity of the masseter muscle to generate a large variety of motor tasks.

First, to evaluate differences in muscles with different functions, we analyzed SGs and integrins in normal human masseter muscle compared with masseter muscle affected by unilateral right crossbite. Our results, in according to electromyographic evaluations, showed a decrease of SGs and integrins in crossbite side in respect to counterpart and to control subjects. Interestingly, in the crossbite side we observed an increase of b1D-integrin, an isoform detected in differentiating myofibers, playing a key role in muscle regeneration and appearing to have a minor role in mature skeletal muscle.

Moreover, to comprehend the different role playing by SGC and integrins and to individuate a phylogenetic diversity in the expression of these proteins, we studied these proteins also in non human species. Particularly, we obtained masseter muscle biopsies from chimpanzees and baboons, individuating different classes of dominance, high and low dominance, for baboons, and alpha and non-alpha male for chimpanzees. About chimpanzees, our results have shown a different quantitative composition of integrins in alpha male in respect to non-alpha male hypothesizing a key role for integrins and SGs in the determination of contraction force. About

baboons, Our immunohistochemical results, confirmed also by Western Blotting analysis, show that, in high dominance subjects, stainings for SGs and integrins were normal; interestingly, in low dominance subjects, stainings for these proteins were normal, lower or absent in different fibers of the same microscopic field. Thus, preliminary analysis on cell cultures of myoblasts and myotubes, at different days of differentiation, immunolabelled with antibodies against SGs and integrins, have demonstrated a similar behaviour, showing cells with an higher or lower staining for these proteins providing a first suggestion that integrins and SGs in masseter muscle play a key role regulating muscular functional activity and allowing the optimization of contractile forces of this muscle.

References

[1] Yoshida M. et al. 1994. Dissociation of the complex of dystrophin and its associated proteins into several unique groups by n-octyl β-D-glucoside. Eur J Biochem 222: 1055-1061.
[2] Holt K.H. et al. 1998. Functional rescue of the sarcoglycan complex in the BIO 14.6 hamster using delta-sarcoglycan gene transfer. Mol Cell 1: 841-848.
[3] Anastasi G. et al. 2003a. Sarcoglycans in human skeletal muscle and human cardiac muscle: a confocal laser scanning microscope study. Cells Tissues Organs. 173: 54-63.
[4] Anastasi G. et al. 2003b. Distribution and localization of vinculin-talin-integrin system and dystrophin-glycoprotein complex in human skeletal muscle. Cells Tissue Organs. 175: 151-164.
[5] Yoshida T. et al. 1998. Bidirectional signaling between sarcoglycans and the integrin adhesion system in cultured L6 myocytes. J Biol Chem 273: 1583-1590.
[6] Anastasi, G. et al. 2005. Sarcoglycan subcomplex in normal human smooth muscle: an immunohistochemical and molecular study. Int J Mol Med 16: 367-374.
[7] Anastasi G. et al. 2007 Sarcoglycan subcomplex expression in normal human smooth muscle. J Histochem Cytochem 55: 831-843.
[8] Arena S. et al. 2008. Sarcoglycan subcomplex expression in refluxing ureteral endings. J Urol 179: 1980-1986.
[9] Ettinger A.J. et al. 1997. ε-sarcoglycan, a broadly expressed homologue of the gene mutated in limb-girdle muscular dystrophy 2D. J Biol Chem 272: 32534-32538.
[10] Arco A et al. 2012. Sarcoglycans in the normal and pathological breast tissue of humans: an immunohistochemical and molecular study. 195: 550-562.

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