The Up-Regulation of Utrophin is not Limited to Muscular Dystrophies

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Abstract. Immunohistochemical reactivity for utrophin has been recorded in 45 biopsies from patients with various neuromuscular diseases The upregulation of utrophin on the extrajunctional sarcolemma has been found in dystrophinopathies, other muscular dystrophies, congenital myopathies, inflammatory myopathies, neurogenic muscle disorders (diabetic neuropathy, amyotrophic lateral sclerosis and spinal muscular atrophies), minimal change myopathies as well as in some normal biopsies

Utrophin, or dystrophin related protein, is encoded by a gene located on the chromosome 6, is similar in sequence to dystrophin, but with a different pattern of expression (Blake *et al* 1996)

In normal differentiated muscle utrophin is present in the neuromuscular junction, myotendineous junction, in Schwann cells, perineurium of intramuscular nerves and smooth muscle cells of blood vessels but, unlike dystrophin, it is absent in the extrajunctional muscle membrane (Karpati *et al* 1993, Helliwell *et al* 1994, Sewry *et al* 1994, Blake *et al* 1996) Expression of the protein on the muscle membrane is developmentally regulated (Clerk *et al* 1993) Dystrophin is present at the muscle membrane from the 9th week of intrauterine life up the mature state, utrophin only until the 26th week and there is a period when both dystrophin and utrophin are co-expresed in the membrane A similar expression pattern may be recorded during the regeneration of the muscle

In Duchenne muscular dystrophy, dystrophin is absent from the membrane in the vast majority of the muscle fibers (Pons *et al* 1993, Sewry *et al* 1994), only isolated "revertant" fibbers are membrane positive In this case utrophin may be found in the same localization on the membrane of (nearly) all muscle fibers and is supposed to compensate the absence of dystrophin (Karpati *et al* 1993, Helliwell *et al* 1994, Sewry *et al* 1994, Vainzof *et al* 1995, Kawajiri *et al* 1996) This up-regulation, however, does not prevent the muscle fibers from regressive alterations In both, Becker muscular dystrophy patients and carriers, a similar up-regulation of utrophin may be recorded some fibers show immunoreactivity for both proteins

The presence of utrophin on the membrane has been described in some muscular disorders other than dystrophinopathies severe childhood autosomal recessive muscular dystrophy (SCARMD) due to the deficiency of alpha- or gamma-sarcoglycan and inflammatory myopathies (Sewry *et al* 1994)

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In order to assess whether the up-regulation of utropin is limited to the above mentioned diseases we have recorded the membrane reactivity for utrophin and dystrophin in 121 biopsies of patients suffering from various neuromuscular diseases The biopsies have been processed using up to date conventional histological, histochemical and immunohistochemical methods (Lukáš and Feit 1996, Lukáš *et al* 1997) Immunoreactivity for the aminoterminal and carboxyterminal domain of utrophin and for aminoterminal, carboxyterminal and rod domain of dystrophin was tested using appropriate antibodies (Novocastra)

Diagnoses have been subdivided into the following groups dystrophinopathies, muscular dystrophies other than dystrophinopathies, congenital (structural) myopathies, inflammatory myopathies, neurogenic disorders, minimal change myopathies and normal findings The up-regulation of utrophin was recorded in 45 biopsies, and results are summarized in Table 1

Table 1

Diagnosis	Dystrophin	Utrophin
DMD	N (+) (−) C (−) R (−)	N (+) C (+) (−)
BMD	N (+) (−) C (+) (−) R (+) (−)	N (+) (−) C (+) (−)
PMD	Normal	N (+) (−) C (+) (−)
CSM	Normal	N (+) (−) C (+) (−)
Dermatomyositis	Normal	N (+) (−) C (+) (−)
Neurogenic disordes	Normal	N (+) C (+) (−)
Normal	Normal	N (+) C (+) (−)

DMD Duchenne muscular dystrophy , BMD Becker muscular dystrophy, PMD progressive muscu lar dystrophy (other than DMD / BMD), CSM congenital (structural) myopathies, C carboxyterminal domain, N aminoterminal domain, R rod (central) domain, (+) membrane positive fibres, (−) membrane negative fibres, (+) (−) both membrane positive and negative fibres

The upregulation of utrophin has been expected and is not surprising in DMD (7 cases) Revertant fibers show co-expression of both dystrophin and utrophin on the membrane

In muscles from patients with Becker variant (3 cases), dystrophin sometimes can be found on the membrane in great majority or nearly all muscle fibers and its minute deficiency may be overlooked Up-regulation of utrophin may be helpful for the correct

interpretation of the biopsy The immunoreactivity was always more pronounced and more frequent with antibodies to the aminoterminal domain of utrophin and this holds for all following neuromuscular disorders

Progressive muscular dystrophies (10 cases), myotonic dystrophy (5 cases) and dermatomyositis (4 cases) may be accompanied by the up-regulation of utrophin and this may be extended for some congenital structural myopathies (congenital fibre type disproportion – 2 cases)

Up-regulation of utrophin has also been recorded in some neurogenic lesions (4 cases) as amyotrophic lateral sclerosis, spinal muscular atrophies and diabetic neuropathy Even some normal muscles or biopsies with borderline alterations (minimal change myopathy – 10 cases) may be accompanied by up-regulation of utrophin, which means that the membrane reactivity of utrophin is no exceptional phenomenon More frequent immunoreactivity with antibodies to the aminoterminal domain of utrophin corresponds to the producers data that staining with monoclonal NCL-DRP2 against the aminoterminal domain labels neuromuscular junctions and the upregulated form of utrophin The extent of normal regulations or upregulation of utrophin in various conditions remains to be explained

References

Blake D J , Tinsley J M , Davies K E (1996) Utrophin a structural and functional comparison to dytrophin Brain Pathol **6**, 37 47

Clerk A , Morris G E , Dubowitz V , Sewry C A Dystrophin related protein, utrophin, in normal and dystrophic human fetal skeletal muscle Histochem J **25**, 554 561

Helliwell T R , Man N T , Morris G E (1994) Expression of the 43 kDa dystrophin-associated glycoprotein in human neuromuscular disease Neuromuscular Disord **2**, 101–113

Karpati G , Carpenter S Morris G E , Davies K E , Guerin C , Holland P (1993) Localization and quantitation of the chromosome 6-encoded dystrophin related protein in normal and pathological human muscle J Neuropathol Exp Neurol **52**, 119 128

Kawajiri M , Mitsui T , Kawai H Kobunai T , Tsuchihashi T , Saito S (1996) Dystrophin, utrophin and b dystroglycan expresion in skeletal muscle from patients with Becker mus cular dystrophy J Neuropathol Exp Neurol **55**, 896–903

Lukaš Z , Feit J (1996) Introducion in Bioptical Myopathology (in Czech), LF MU Brno

Lukaš Z , Draberova E , Feit J , Vojtěšek B (1997) Immunohistochemical methods in biology and bioptical diagnostics Acta Fac Med Univ Brunensis Masarykianae, Brno, (in Czech)

Pons F Nicholson L V , Robert A , Voit T , Leger J J (1993) Dystrophin and dystrophin-related protein (utrophin) distribution in normal and dystrophin-deficient skeletal muscles Neu romuscular Disord **3**, 507 514

Sewry C A , Matsumura K , Campbell K P , Dubowitz V (1994) Expresion of dystrophin associa ted glycoproteins and utrophin in carriers of Duchenne muscular dystrophy Neuromuscular Disord **4**, 401 409

Vainzof M , Passos Bueno M R , Man N , Zatz M (1995) Absence of correlation between utrophin localization and quantity and the clinical severity in Duchenne/Becker dystrophies Amer J Med Genet **58**, 305–309