Collagen VI myopathies: pathogenic mechanisms and novel therapeutic perspectives

P. Bonaldo
Department of Histology, Microbiology & Medical Biotechnology, University of Padova, Italy
E-mail: bonaldo@bio.unipd.it

Mutations in any of the three genes coding for the extracellular matrix protein collagen VI cause different types of muscle diseases, including Bethlem Myopathy (BM), Ullrich Congenital Muscular Dystrophy (UCMD) and Congenital Myosclerotic Muscular Dystrophy (1). Collagen VI null (Col6a1−/−) mice display a myopathic phenotype with organelle defects, mitochondrial dysfunction and spontaneous apoptosis of muscle fibers (2). Based on the findings obtained in the murine model, similar defects could be revealed in muscle biopsies and cultures of UCMD/BM patients (3). Our previous studies demonstrated that one major pathogenic event is the PTP-dependent latent mitochondrial dysfunction (4), however the cause for the accumulation of dysfunctional organelles remained unsolved.

The presence of swollen mitochondria and dilated sarcoplasmic reticulum prompted to check whether the machinery for organelle removal, the autophagic system, is affected. We found that persistence of abnormal organelles and apoptosis are caused by defective autophagy in collagen VI deficient muscles. Autophagy is a process of cytosolic ‘renovation’, which is essential for the maintenance of cell homeostasis by clearing misfolded proteins and dysfunctional organelles. Skeletal muscles of Col6a1−/− mice display impaired autophagic flux, which matches the lower induction of Beclin 1 and Bnip3 and the lack of autophagosomes after starvation. Furthermore, muscle biopsies from patients affected by UCMD or BM show reduced levels of Beclin 1 and Bnip3. Notably, forced reactivation of autophagy by either genetic (overexpression of Beclin-1), nutritional (low protein diet) or pharmacological (cyclosporin A) approaches restores myofiber survival and leads to a marked amelioration of the structural and functional defects of Col6a1−/− muscles, with normalization of the dystrophic phenotype (5, 6).

These findings indicate that defective activation of the autophagic machinery has a key pathogenic role in congenital muscular dystrophies linked to collagen VI deficiency. Altogether, our data are the first demonstration that impaired autophagy plays a pivotal role in the pathogenesis of some muscular dystrophies, thus providing new insights into the pathogenesis of muscle degeneration and opening new perspectives for treatment.

References
1. Merlini L, Martoni E, Grumati P, et al. Autosomal recessive myosclerotic myopathy is a collagen VI disorder. Neurology 2008;71:1245-53.
2. Iriwin WA, Bergamin N, Sabatelli P, et al. Mitochondrial dysfunction and apoptosis in myopathic mice with collagen VI deficiency. Nat Genet 2003;35:367-71.
3. Angelin A, Tiepolo T, Sabatelli P, et al. Mitochondrial dysfunction in the pathogenesis of Ullrich congenital muscular dystrophy and prospective therapy with cyclosporins Proc Natl Acad Sci U S A 2007;104:991-6.
4. Palma E, Tiepolo T, Angelin A, et al. Genetic ablation of cyclophilin D rescues mitochondrial defects and prevents muscle apoptosis in collagen VI myopathic mice. Hum Mol Genet 2009;18:2024-31.
5. Grumati P, Coletto L, Sabatelli P, et al. Autophagy is defective in collagen VI muscular dystrophies, and its reactivation rescues myofiber degeneration. Nat Med 2010;16:1313-20.
6. Grumati P, Coletto L, Sandri M, et al. Autophagy induction rescues muscular dystrophy. Autophagy 2011;7:426-8.

H-2
The benefits of a specialised myositis clinic

F.L. Mastaglia
Australian Neuromuscular Research Institute (ANRI), University of Western Australia, Nedlands, Western Australia
E-mail: flmast@cyllene.uwa.edu.au

A multidisciplinary referral clinic for the diagnosis and management of adult patients with inflammatory myopathy has been in operation at the ANRI in Perth since 1990. Patients are seen jointly by a neurologist, a clinical immunologist and physiotherapist and by a speech pathologist if they have swallowing problems. The diagnosis of myositis is confirmed by muscle biopsy in all cases and screening for muscle-associated and muscle-specific autoantibodies is also performed. Over 250 patients have been seen in the clinic, falling into the following categories: inclusion body myositis (32%), dermatomyositis (32%), overlap syndromes (23%), isolated polymyositis (11%), miscellaneous (2%). Muscle function is monitored by manual muscle testing (MMT) and, in selected cases myometry and isokinetic dynamometry is performed. Patients undergo regular reviews to monitor the response to treatment. This has also allowed observations to be made on the frequency of relapses in patients with dermatomyositis and polymyositis (1), and the variability in the clinical phenotype and rate of progression of muscle weakness and influence of HLA alleles in inclusion body myositis (2). Two new clinical entities have been identified: statin-associated necrotising myopathy with upregulation of MHC-I (3), and a restricted scapulopinal form of myopathy.
I wanted to know if genetic counseling (GC) had any impact. I came back I decided to visit the families who I had counseled. From muscular disorders.

I have always been worried with the social aspects related to genetic counseling of families with neuro-muscular disorders. I was very much involved in genetic counseling of families with neuromuscular disorders.

I went to UCLA in Los Angeles for my post doc and when I came back I decided to visit the families who I had counseled. I wanted to know if genetic counseling (GC) had any impact on their lives, if high risk carriers had deterred procreation. I managed to visit more than 300 families and had two surprises: the good one was to see that most mothers of Duchenne patients had understood the GC and very few children were born among those with a high genetic risk. The sad surprise was to see how abandoned were the older affected children from poor families: no wheelchair, no transportation, no conditions to attend schools, physiotherapy clinics or any treatment. They were completely isolated from social life. I decided then that being just a scientist was not enough. I had to do more for these children and I founded the Brazilian muscular dystrophy association – ABDIM – in an attempt to improve their quality of life. We rented a house, remodeled it and established a center next to the University. Now ABDIM serves more than 100 patients who come twice a week and provides them with physiotherapy, physical therapy, but also training in arts and computers: anything to improve life quality and expectancy. Anything to make them happier. In addition we have almost 1000 patients that come from all over Brazil every 3 to 6 months for follow-up. And indeed life expectancy increased significantly which is particularly important at this moment because we hope that extending their lives will allow them to benefit of new discovered treatments. I am still the President of ABDIM- not because I want it- but because so far nobody wanted to take over. More recently, I was also involved in the political decisions regarding the approval of the bill that allows research with embryonic stem cells in Brazil. On one hand, as a scientist I wanted to have in Brazil the same freedom for research as most developed countries. On the other hand I believed that approving this law would be extremely important when talking to patients and parents. As you know, when we tell parents that their child has a progressive severe disease for which the cure has not been found yet they would be willing to go any place in the world to try to find a treatment. We wanted to tell them that if the stem cells bill would be approved in Brazil we would be able to do the same research that is being done in first world countries. They would not need to go abroad. And I started to fight for it. Indeed, after many debates, the bill was definitively approved by our Supreme Court in 2008.

Finally, I had the great privilege to listen some years ago to the talk of Rita Levi Montalcini, this incredible Italian woman and Nobel prize scientist. It was during a Congress in United States. She started her talk saying that she had taken a taxi in Italy to reach the airport and the driver looked at her and said: I know you. You are a famous person. Then she asked: Why? Because of my Nobel Prize? No he replied, for your social work. I don’t have the pretension to compare myself with Rita Levi. She is the woman I most admire on earth. But when I received the email from Giovanni Nigro I was reminded of her and I felt incredibly rewarded for doing social work. Initially from patients, from their families, and now from you my dear Italian friends for awarding me this prize.

Thank you very much!

References
1. Phillips B, Zilko P, Garlepp MJ, et al. Frequency of relapses in polymyositis and dermatomyositis. Muscle Nerve 1999;21:1668-72.
2. Needham M, James I, Corbett A, et al. Sporadic inclusion body myositis: Phenotypic variability and influence of HLA-DR3 in a cohort of 57 Australian cases. J Neurol Neurosurg Psychiatry 2008;79:1056-60.
3. Needham M, Fabian V, Knezevic W, et al. Progressive myopathy with upregulation of MHC-I associated with statin therapy. Neuromusc Disord 2007;17:194-200.
4. Rojana-Udomsart A, Hollingsworth PN, Walters SE, et al. Paraspinal and scapular myopathy in scleroderma. J Clin Neuromusc Disord 2010;11:213-22.