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Collagen VI myopathies: pathogenic mechanism and therapeutic strategies

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Collagen (Col) VI is a major component of the extracellular matrix which, in skeletal muscle, is localized just outside the basement membrane. Deficiency of ColVI in humans due to mutations of *COL6* genes gives rise to Bethlem Myopathy (BM), Ullrich Congenital Muscular Dystrophy (UCMD), and Myosclerosis Myopathy. About 70 different *COL6* gene mutations have been associated to ColVI myopathies which, although present a wide range of clinical features, share a common pathogenesis. This mechanism, initially identified in the *Col6a1*$^{-/-}$ model (Irwin et al., 2003), and then in cultures from BM and UCMD patients (Angelin et al., 2007), involves a mitochondrial dysfunction due to deregulation of the permeability transition pore (PTP). The pathogenic role of PTP opening, causing the release of proapoptotic factors, has been confirmed by the normalizing effect of cyclosporine A (CsA) on the mitochondrial defect and on the increased apoptotic rate in both the mouse model and in a selected group of patients (Merlini et al., 2008).

We have recently demonstrated that the persistence of abnormal mitochondria and apoptosis are amplified by defective autophagy (Grumati et al., 2010). In fact, forced activation of autophagy by genetic, dietary and pharmacological approaches restore myofiber survival and ameliorate the dystrophic phenotype in mice. Since also muscle cells of BM and UCMD patients present a defective activation of the autophagic machinery, it will be possible to restore this activity by using a low protein diet or drugs capable to reactivate autophagy.

To monitor the effects of therapies on ColVI-related myopathies highly invasive muscle/skin biopsies have been so far utilized. We have recently obtained evidence that ColVI expression in blood macrophages from BM and UCMD patients can be detected at levels comparable to those observed in muscle biopsies and cultured skin fibroblasts (Gualandi et al., 2011). These data support the suitability of peripheral blood macrophages as a reliable, minimally invasive tool for supplementing or replacing highly invasive biopsies in the diagnosis and monitoring of ColVI myopathies.

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