Mitochondrial disorders (MDs) are caused by impairment of the mitochondrial electron transport chain (ETC). The ETC is needed for oxidative phosphorylation, which provides the cell with the most efficient energy outcome in terms of ATP production. One of the pathogenic mechanisms of MDs is the generation of reactive oxygen species.

Potential pharmacological approaches for MDs include ETC cofactors (i.e., Coenzyme Q10) and other metabolites (i.e., carnitine), antioxidants, neuroprotective drugs (i.e., tetracyclines), bezafibrate (an activator of PGC-1alpha). Controlled trials in large cohorts of patients are still needed, because therapy for mitochondrial diseases remains inadequate and mostly symptomatic. It will be important to develop a better understanding of the role of oxidative stress, since it may lead to the development of more effective treatment strategies.

1. Gene therapy; 2. Cellular therapy; 3. Pharmacological therapies

Three different therapeutic approaches are currently under study: 1. Gene therapy; 2. Cellular therapy; 3. Pharmacological therapy. The latter will be examined into the three fundamental aspects: 1. Utrophin over-expression; 2. Dystrophin re-expression; 3. Reversal of dystrophic phenotype.

1. Utrophin over-expression. Recent developments in understanding the regulatory pathways that govern utrophin expression, stimulated studies using activators of these pathways to alleviate the dystrophic symptoms in DMD animal models. Drugs used to this aim are: Interleukin 6, Agrin, Heresulin, Calcineurin. All these drugs are able to induce overexpression of the sarcolemmal utrophin in vitro and in neonatal mdx skeletal muscles. The results of these preclinical studies are promising and stimulate to implement appropriate utrophin-based drug therapies for DMD patients.

2. Dystrophin re-expression can be achieved by drug therapy -- aminoglycosides, antisense strategy and chimera-plasty -- or by cell therapy -- myoblasts and stem cells -- or by gene therapy. Aminoglycosides have been proven to cause an extensive misreading of the RNA code, allowing the insertion of alternative amino acids at the site of the mutated codon. Although it is now considered a therapeutic strategy for DMD caused by point-mutations, unfortunately it is applicable to only 1% of DMD patients.

3. Reversal of dystrophic phenotype can be achieved by the use of corticosteroids. The two main classes of steroids used are prednisone or prednisolone and deflazacort (DFZ). They are probably equally effective in stabilizing muscle strength but may have different side-effect profiles. The exact mechanism by which steroids slow the dystrophic process is yet under investigation. Corticosteroids have been found to stabilize or improve muscle strength in boys with DMD and to have beneficial effects on the different aspects of DMD, such as walking time prolongation, development of scoliosis, development of respiratory insufficiency and development of cardiac involvement. A systematic review of the Cochrane database and the personal experience on more than 200 DMD patients treated with DFZ for 20 years, let us to conclude that long term steroid therapy is able to prolong ambulation by 2 to 5 years, reduce the need for spinal stabilization surgery, improve cardiopulmonary function, delay the need for non invasive nasal ventilation and finally increase survival and quality of life of patients with Duchenne muscular dystrophy.
tains antibodies play a role by recruiting macrophages to the muscle in an ADCC process, remains unclear.

In uncontrolled studies, PM and DM respond to prednisone to some degree and for some period of time; adding an immunosuppressive drug (Azathioprine, Cyclosporine, Mycophenolate, Methotrexate) may have a steroid-sparing effect but their benefit is uncertain. In contrast, IBM is resistant to most of these therapies, most times. Controlled studies have shown that IVIg is effective and safe for the treatment of DM. The clinical benefit, which can be impressive in patients with early disease, is associated with improvement in the muscle cytoarchitecture and resolution of the aberrant immunopathological parameters, including interception of complement activation and downregulation of ICAM-1, VCAM, TGF-β, MHC-I and various immunoregulatory and structural genes. IVIg seems to be also effective in patients with PM but offers transient help to a small number of patients with IBM.

New agents currently on the market may be promising new therapies for the treatment of inflammatory myopathies. Among them include the monoclonal antibodies or fusion proteins against: a) molecules associated with T-cell-signaling pathways, such as the anti-CD52 (CAMPATH), anti-LFA/ICAM (Leukocyte Functional Antigen/Intracellular Adhesion Molecule), and anti-IL2 receptor (IL2-receptor antagonist). Further, two cytrophillin-binding drugs, Tacrolimus and Rapamycin, that prevent the IL2-induced T cell proliferation or transcription, may be candidate agents for certain conditions; b) B cells using the monoclonal antibody directed against CD20, expressed on B cells (Rituximab) or the humanized version Ocrelizumab; agents against B-cell growth factors, such as BAFF and APRIL, are in the offering; c) Complement C5 (Eculizumab), which might be appropriate for some complement-mediated disorders like DM or NAM; d) cytokines, especially agents against TNF-α, IL1 or IL1β; and e) Cellular Adhesion and T cell transmigration molecules. Such agents include Natalizumab directed against α4β1 integrin (VLA4) on lymphocytes, a drug approved for multiple sclerosis, and Fingolimod, an anti-T-cell-migration agent that traps lymphocytes in the lymphoid organs.

I-8
Muscle maturation and early pathogenic findings in spinal muscular atrophy: any clues for therapy?
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Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects motor neurons. It is caused by mutations in the survival motor neuron gene 1 (SMN1). The SMN2 gene, which is the highly homologous SMN1 copy that is present in all patients, is unable to prevent the disease. SMA patients can be classified into four groups based on age at onset and acquired milestones (type I or severe acute disease, with onset before 6 months; type II, before 18 months; type III, after 18 months and type IV, in adult life). The explanation for the neuromuscular phenotype in SMA is to assume that insufficient SMN protein causes motor neuron dysfunction and death, and that muscle atrophy is a consequence of denervation. However, investigation is ongoing to ascertain whether muscle, neuromuscular junctions, or motor neurons alone are the critical target tissue in SMA. The neuropathologic description of SMA comes largely from postnatal necropsy samples, which describe the end-stage of the disease. The human developmental period appears to play an essential role in SMA pathogenesis. With the exception of severe congenital SMA (type 0), varying age at onset in the four SMA types provides evidence of a latency period without clear manifestations in most SMA patients. Given that studies of patients’ preclinical status are lacking, the main objective of our work is to study SMA during development to gain insight into the mechanism of disease in the prenatal and presymptomatic stage. Prenatal SMN tests performed at around 11-13 weeks allowed us to identify fetuses predicted to develop SMA in families with a previous patient affected by type I disease. SMA fetuses were collected from therapeutic abortions after confirmation of a homozygous deletion of exon 7 and 8 of the SMN gene by chorionic villi DNA analysis. In these samples we systematically studied histology, cell death and gene and protein expression in spinal cord and muscle, the key tissues involved in the disease. The study of terminal peripheral nerves and neuromuscular junctions identify possible links between the two tissues in the pathogenesis of the disease. By confocal and electron microscopy we observed a variable degree of changes in the acetylcholine receptors clustering, presynaptic retention of vesicles and terminal nerve degeneration in the motor endplates of fetuses with severe SMA. Furthermore, ultrasound fetal movements were investigated at these stages. At the gestational age examined, we did not observe a qualitative early limitation of movements in fetuses with SMA. Our results support the view of SMA as a developmental disorder and the hypothesis that motor neurons, terminal peripheral nerves, neuromuscular junctions and skeletal muscle may play all together a role in the pathology of SMA. These studies may help to define therapeutic targets and delineate a possible early intervention in SMA.

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I-9
Opportunities and challenges of pharmaceutical research and development today
L. Middleton
Not arrived

I-10
Pathogenesis of muscle degeneration in periodic paralyses and DMD
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Mutations in Cav1.1 and Nav1.4 channels cause hypokalemic periodic paralysis, a dominantly inherited muscle disorder characterized by episodic weakness and chronic progressive weakness. In-vivo 23Na magnetic resonance imaging (MRI), fat-suppressed 1H-MRI (STIR), and force assessment were performed to determine intramuscular Na+ load, edema, and muscle strength in patients under different conditions. Membrane