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Review

Ins and outs of therapy in limb girdle muscular dystrophies

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Abstract

Muscular dystrophies are hereditary degenerative muscle diseases that cause life-long disability in patients. They comprise the well-known Duchenne Muscular Dystrophy (DMD) but also the group of Limb Girdle Muscular Dystrophies (LGMD) which account for a third to a fourth of DMD cases. From the clinical point of view, LGMD are characterised by predominant effects on the proximal limb muscles. The LGMD group is still growing today and consists of 19 autosomal dominant and recessive forms (LGMD1A to LGMD1G and LGMD2A to LGMD2M). The proteins involved are very diverse and include sarcomeric, sarcolemmal and enzymatic proteins. With respect to this variability and in line with the intense search for a potent therapeutic approach for DMD, many different strategies have been tested in rodent models. These include replacing the lost function by gene transfer or stem cell transplantation, using a related protein for functional substitution, increasing muscle mass, or blocking the molecular pathological mechanisms by pharmacological means to alleviate the symptoms. The purpose of this review is to summarize current data arising from these preclinical studies and to examine the potential of the tested strategies to lead to clinical applications.

Keywords: Limb girdle muscular dystrophy; Gene; Cell and pharmacological therapy; Skeletal muscle

Contents

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1. Introduction

Muscular dystrophies (MD) are a group of genetic diseases characterized by progressive muscle degeneration and weakness. Duchenne Muscular Dystrophy (DMD), the most common form of the disease (frequency 1/3500 living males) was also the first for which the deficient gene was identified (Koenig et al., 1987). DMD is inherited through an X chromosome-linked transmission and involves mutations in the large cytoskeletal/extracellular matrix (ECM) linker protein, dystrophin (Watkins, Hoffman, Slayter, & Kunkel, 1988; Zubrzycka-Gaarn et al., 1988).

The limb-Girdle Muscular Dystrophies (LGMD) are another important subgroup of MD, responsible for up to a third of the DMD cases. LGMD are progressive myopathies grouped together on the basis of common clinical features: they all primarily and predominantly affect proximal muscles around the scapular and the pelvic girdles. However, some LGMD are severe, some are benign and others exhibit a large spectrum of severity and so the symptoms can appear anytime from childhood to adulthood. In addition, clinical characteristics such as hypertrophy of the calves or tongue, selectivity of muscle involvement and late stage cardiac complications are associated more or less specifically with each of the different forms. These variations have their source in the diversity of primary deficiencies responsible for the disease. Indeed, the emergence of an LGMD phenotype can result from mutations in any of – at least – 19 different genes (Table 1). LGMDs are divided into autosomal dominant (LGMD1) and autosomal recessive (LGMD2) forms with a lettering system denoting the chronology of locus identification (A to F for dominant and A to M for recessive LGMDs) (Bushby & Beckmann, 1995). Only three (LGMD1A to C) out of the six LGMD1 causal genes are known so far (Messina, Speer, Pericak-Vance, & McNally, 1997; Starling, Kok, Passos-Bueno, Vainzof, & Zatz, 2004) whereas all but one of the causative genes have been identified for the 13 LGMD2 (Balci et al., 2005; Bashir et al., 1998; Bönnemann et al., 1995; Brockington et al., 2001; Frosk et al., 2002; Hackman et al., 2002; Lim et al., 1995; Liu et al., 1998; Moreira et al., 2000; Nigro et al., 1996; Noguchi et al., 1995; Richard et al., 1995; Roberds et al., 1994). It is also important to keep in mind that mutations, even though sometimes strictly identical, of several LGMD deficient proteins can lead to very different phenotypes.

Considering the prevalence and the deleterious effects of MD, a therapy has actively been sought for many years. Currently, disease management is only supportive (physical therapy, assistive devices and monitoring of respiratory function and for heart complications) and is aimed at prolonging survival and improving quality of life (Bushby & Straub, 2005). Herein, we review the various approaches under current exploration for the treatment of LGMD in the fields of gene, cell and pharmacological therapies. Some lessons learned from the search for a cure for DMD have proven very useful and similar strategies have been tested. However, some protocols based on specific dystrophin characteristics cannot be used for LGMD. On the other hand, newly-acquired knowledge about the clinical symptoms, the pathophysiological mechanisms of the disease and the functions of LGMD deficient proteins has opened the way to an era of specific treatments.

2. Pathophysiologies

We present hereafter a brief review of the different proteins involved in dominant and recessive LGMD and the current understanding of how the mutations affect their functions (Table 1). For more detailed information, the reader should refer to recent reviews on each subject (e.g. Davies & Nowak, 2006; Guglieri, Magri, & Comi, 2005; Ozawa, Mizuno, Hagiwara, Sasaoka, & Yoshida, 2005; Zatz & Starling, 2005). The nature of the LGMD2 proteins is quite diverse, comprising structural proteins as well as enzymes. Their sub-cellular localizations cover most of the cellular compartments (cell nucleus, cytosol, cytoskeleton or sarcolemma). In con-