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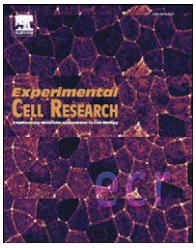

Review

Direct effects of the pathogenic mutation on satellite cell function in muscular dystrophy

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ABSTRACT

Skeletal muscle is maintained and repaired by resident stem cells called muscle satellite cells, but there is a gradual failure of this process during the progressive skeletal muscle weakness and wasting that characterises muscular dystrophies. The pathogenic mutation causes muscle wasting, but in conditions including Duchenne muscular dystrophy, the mutant gene is not expressed in satellite cells, and so muscle maintenance/repair is not directly affected. The chronic muscle wasting, however, produces an increasingly hostile micro-environment in dystrophic muscle. This probably combines with excessive satellite cell use to eventually culminate in an indirect failure of satellite cell-mediated myofibre repair. By contrast, in disorders such as Emery–Dreifuss muscular dystrophy, the pathogenic mutation not only instigates muscle wasting, but could also directly compromise satellite cell function, leading to less effective muscle homeostasis. This may again combine with excessive use and a hostile environment to further compromise satellite cell performance. Whichever the mechanism, the ultimate consequence of perturbed satellite cell activity is a chronic failure of myofibre maintenance in dystrophic muscle. Here, we review whether the pathogenic mutation can directly contribute to satellite cell dysfunction in a number of muscular dystrophies.

Contents

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Introduction

Muscle is the biggest tissue in the body by mass, normally accounting for ~40–50% of body weight in adult. Considering its roles in movement, stabilisation of the skeleton, metabolism and thermoregulation, conditions that impair skeletal muscle can cause significant morbidity, and some muscular dystrophies are amongst the most debilitating [1]. Muscular dystrophies currently comprise over 30 clinical disorders, and are characterised by progressive skeletal muscle weakness and wasting, though they vary in severity, muscle groups affected, and heart involvement [1]. They range from being relatively mild with slow progression and normal life expectancy, to the systematic loss of muscle function and disability, with life expectancy dependant on the extent of muscle weakness and allied respiratory and/or cardiac failure. Age of onset can also be used to classify muscular dystrophies: congenital muscular dystrophies (CMD) are evident at birth, while other disorders are not usually diagnosed until adolescence, adulthood, or even mid-late life.

The working unit of skeletal muscle is the myofibre: a highly specialised syncytium sustained by hundreds of post-mitotic myonuclei. Myofibres are formed by the fusion of many myoblasts during development. Post-natally, myofibres continue to grow by the addition of further myonuclei supplied by muscle satellite cells [2]. In healthy adult muscle, these resident stem cells become mitotically quiescent [3] and lie on the surface of a myofibre, beneath the overlying basal lamina [4]. In response to cues for routine myofibre homeostasis, or the more sporadic demands for hypertrophy or repair, satellite cells are activated to generate myoblasts that proliferate and eventually undergo myogenic differentiation to provide new myonuclei. Satellite cells also self-renew, thus maintaining a population of quiescent, undifferentiated precursors available to respond to repeated demand [5].

Here, we examine the evidence that in certain muscular dystrophies, the pathogenic mutation not only results in myofibre wasting, but also directly impairs satellite cell function to compromise the efficient maintenance and repair of myofibres. It should be noted that these are rare diseases, and so studies on human myoblasts from patients with muscular dystrophies are limited, necessitating extrapolation from animal studies in many cases.

Dystrophic conditions with an indirect effect on satellite cells

Where a mutated gene is primarily expressed in myofibres and is central to muscle action, it is unsurprising that its loss or dysfunction leads to myofibre damage. The dystrophin-associated protein complex (DAPC) translates force from the intracellular cytoskeleton and contractile apparatus of the myofibre, across the plasmalemma, to the extracellular matrix. Dystrophin binds F-actin at its N-terminus and various proteins of the DAPC at the C-terminus, including β-dystroglycan. In turn, β-dystroglycan associates with sarcoglycan isoforms, forming the transmembrane component of the DAPC that links to α-dystroglycan, which binds proteins of the extracellular matrix including laminin, agrin and perlecan [6]. Mutations in several genes that encode components of this complex each underlie a muscular dystrophy. Prime examples are mutations in *DMD* leading to either Becker muscular dystrophy (BMD) or Duchenne muscular dystrophy (DMD), depending on the level/functionality of the mutated dystrophin protein [7], and in *SGCA-D*, encoding four different sarcoglycan isoforms to cause Limb Girdle muscular dystrophy (LGMD) 2C-F [8].

Myofibre damage and degeneration caused by the presence of mutant dystrophin or sarcoglycan isoforms induce a regenerative response mediated by satellite cells. Since the repaired/regenerated myofibres still contain the mutated proteins however, they too are subject to the same stresses and are likely to again accumulate damage, leading to chronic rounds of degeneration and repair. The DAPC is not present in satellite cells or their myoblast progeny and so their function is not directly affected by these pathogenic mutations, meaning that they are able to repair and regenerate dystrophic muscle efficiently, at least initially. As such, the histology of DMD muscle for example, is characterised by variable muscle fibre sizes, central nucleation, and the presence of developmental myosin heavy chain isoforms: all hallmarks of ongoing regeneration. This evolving dystrophic muscle microenvironment also includes escalating endomysial fibrosis, chronic inflammation and fat infiltration, which together create an increasingly hostile milieu for effective satellite cell-mediated repair. Thus, the regenerative capacity in most muscles eventually becomes ineffective in DMD, resulting in their complete loss of function and so paralysis.

These chronic rounds of repair also lead to a progressive fall in the replicative ability of myoblasts from DMD patients, which is accelerated over that seen in normal aging [9]. Proposed causes include telomeric erosion [10], oxidative stress and transcriptional dysregulation. Many muscular dystrophies have been successfully modeled in animals, and the *mdx* mouse model of DMD exhibits chronic myofibre degeneration/regeneration cycles, as seen in man. In contrast though, near normal muscle function is maintained throughout life, which is due in part, to continued satellite cell function, since exposure to ionizing irradiation to prevent cell proliferation, leads to a more severe dystrophic phenotype [11]. The proliferative ability of most satellite cells does fall with age in mice though [12], and muscle regeneration in response to toxin damage is much less effective in older than young *mdx* and δ-sarcoglycan null mice [13]. It may be argued that since the properties of a stem cell include self-renewal, satellite cells should not become “exhausted” through excessive use. However, skeletal muscle normally has a very low rate of turnover in healthy individuals [14] and so the constant demands of a dystrophic environment are certainly atypical. Even haematopoietic stem cells have a limited regenerative ability under certain circumstances,