Advanced Drug Delivery Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Coaxing stem cells for skeletal muscle repair ☆

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ARTICLE INFO

Article history:
Accepted 7 July 2014
Available online xxxx

Keywords:
Satellite cells
Mesenchymal stem cells
Pluripotent stem cells
Muscular dystrophy
Muscle regeneration
Niche
Bioengineering

ABSTRACT

Skeletal muscle has a tremendous ability to regenerate, attributed to a well-defined population of muscle stem cells called satellite cells. However, this ability to regenerate diminishes with age and can also be dramatically affected by multiple types of muscle diseases, or injury. Extrinsic and/or intrinsic defects in the regulation of satellite cells are considered to be major determinants for the diminished regenerative capacity. Maintenance and replenishment of the satellite cell pool is one focus for muscle regenerative medicine, which will be discussed. There are other sources of progenitor cells with myogenic capacity, which may also support skeletal muscle repair. However, all of these myogenic cell populations have inherent difficulties and challenges in maintaining or coaxing their derivation for therapeutic purpose. This review will highlight recent reported attributes of these cells and new bioengineering approaches to creating a supply of myogenic stem cells or implants applicable for acute and/or chronic muscle disorders.

Contents

1. Introduction

Skeletal muscle is a vitally important tissue to normal whole body function and homeostasis. This mass of fibrous tissue makes up nearly

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Scaffolds, Cells, Biologics: At the Crossroads of Musculoskeletal Repair".

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http://dx.doi.org/10.1016/j.addr.2014.07.007
0169-409X/

half a person's body weight. The role of skeletal muscle in the body is beyond its critical involvement in movement, breathing, and posture. For instance, skeletal muscle is a major regulator of blood glucose levels, and consequently, a defect in the mechanism of muscle insulin cell signaling is the main contributor to type II diabetes [1–7]. There are other examples of metabolic diseases linked to defects in skeletal muscle including the McArdle syndrome. McArdle syndrome is caused by a mutation in the glycogen phosphorylase gene resulting in an inability to breakdown muscle glycogen which ultimately leads to rhabdomyolysis [1,2,8–12]. Therefore, skeletal muscle is a key target for therapy in metabolic diseases.

Maintenance of healthy muscle is essential for everyday organ activities, the ocular muscles that surround the eyeball, sphincter muscles for excretion of waste, and the diaphragm muscles essential for respiration. Skeletal muscle is susceptible to numerous dysfunctions that contribute to disease or pathological states including, muscular dystrophies (primary defect is in muscle), neuromuscular disorders (defect is in neural control of muscle), sarcopenia (aging associated decrements in muscle), cachexia (cancer induced muscle loss), and metabolic disorders. There are over 100 muscle diseases identified in humans (see http://www.musclegenetable.fr/ for an updated list). Skeletal muscle can also be subject to injury from mild lacerations to more severe volumetric muscle loss. Therefore, understanding the mechanisms of skeletal muscle repair is essential for development of therapies for muscle disease, injury and aging associated defects that can accelerate morbidity and mortality. In this review we will refer mostly to muscular dystrophies and aging, but mechanisms and therapeutic strategies discussed may apply to many muscle deficiencies associated with diseases, pathologies and injury.

2. Muscular dystrophy and aging

Muscular dystrophy (MD) refers to a group of genetic muscle diseases caused by inherited mutations in muscle proteins that result in progressive muscle weakness, degeneration and muscle cell death [10,13–16]. The most prevalent form is Duchenne Muscular Dystrophy (DMD), an X-linked lethal disorder that affects 1 in 5000 male live births [1,13,16–21]. DMD is caused by mutations in dystrophin, the largest gene in the human genome [18,22,23]. The absence of dystrophin protein causes the loss of cell membrane integrity, activating a cascade of cellular events that leads to degeneration of the muscle cell. Degeneration is accompanied by successive cycles of regeneration by the muscle stem cell pool, called satellite cells (SC), which eventually becomes depleted. Over time, muscle tissue is substituted with fat and connective tissue [2,6,7], muscle becomes atrophic and consequently, the capacity to restore skeletal muscle function is lost [2,11]. Clinically, DMD patients are confined to a wheelchair, and their life span is shortened due to cardio-respiratory problems. A milder dystrophic disease is Becker's Muscular Dystrophy due to mutations resulting in partial dystrophin deficiency. Dystrophin is associated with a complex of proteins, which includes three subcomplexes: the dystroglycan complex, the sarcoglycan complex and the cytoplasmic complex consisting of syntrophins and α-dystrobrevin. The dystrophin protein complex (DPC) functions by providing mechanical support to the muscle cell. The structural role of the DPC is evident from gene deletion studies on members of the DPC, many of which result in muscle degeneration, including sarcoglycan mutations causing limb-girdle muscular dystrophy.

A number of different strategies are being attempted to combat skeletal muscle disorders, which include drug, gene and cell therapy or a combination of these. Pharmacological targets include nitric oxide production, which is reduced in several muscular dystrophies [10,14]. The production of nitric oxide has been stimulated by nitric oxide donors or phosphodiesterase inhibitors which have had efficacy in animal studies and now in clinical trials [13,16,17]. Drug screens to identify ways to up-regulate the dystrophin homologue utrophin have also been of major focus in academic and commercial ventures [1,24]. Gene therapy has been heavily focused on delivering micro-dystrophin genes (due to gene packaging size limitations of appropriate vectors) into muscle using adeno-associated viruses (AAV) [1,4]. More recently, the size limitation issue of AAV has been overcome by implementing a triple-AAV vector system to successfully express full-length dystrophin in mice [25,26]. However, unexpected immune responses to dystrophin delivery observed during clinical trials is an added challenge that is being addressed now [1,9]. Partially recovering dystrophin by exon skipping appears to be an alternative approach that is generating optimistic results in the clinic [8,27].

Skeletal muscle has a remarkable ability to regenerate. However, skeletal muscle is susceptible to a drastic decline in regenerative capacity with advanced age, a phenomenon known as sarcopenia. Sarcopenia is linked to loss of muscle mass and function, and has a severely debilitating impact on quality of life in aged people. Some symptoms are shared with muscular dystrophy including a limited capacity to regenerate new muscle fibers, and the presence of inflammation. The limited capacity to regenerate is determined by cell-intrinsic and/or environment influences on the stem cells within muscle, which we will refer to in this review.

3. Stem cells and regeneration

The body's tissues show varied capacities to regenerate from nil to extensive, determined by the absence or presence of a tissue specific stem cell pool. A stem cell is defined as a cell that persists for the lifetime of the organism and continues both to reproduce itself (self-renew) and generate differentiated progeny [2,6,7,18,23]. Stem cells have been categorized in terms of their behavior and potency to differentiate into certain cell types. Most stem cells we are interested in from a therapy stance are either pluripotent, multipotent or unipotent. Skeletal muscle has a tremendous ability to regenerate due to the mobilization of its own well defined tissue-specific muscle stem cells, known as satellite cells (SC) [2,6,7,11], which are a potential target for therapeutic application in many muscle diseases, in particular muscular dystrophies [2,10,11,14]. Other stem cell populations with muscle regenerative potential have also been investigated, some of which will be discussed below. Recent new developments in muscle stem cell research may circumvent some of the therapeutic challenges confronting researchers in curing DMD and other aforementioned muscle disorders. This review focuses on some of those new developments in our understanding of the regulation and derivation of muscle stem/progenitor cells with relevance to the engineering of skeletal muscle for repair.

3.1. Satellite cells

The satellite cell (SC) population is the main cell source for muscle regeneration (see Fig. 1) and growth (fusion of newly induced muscle cells) of skeletal muscle. To replenish or substitute this finite pool of SCs with normal or gene corrected stem cells is a major focus of some DMD research (see Fig. 2). Satellite cells are located between the basal lamina and the sarcolemma of the muscle fiber. Satellite cells make up 2–7% of the nuclei in adult murine muscle, are higher in oxidative muscles and notably, reside in close proximity to blood capillaries [1,4,24]. They display several cell surface and nuclear biomarkers foremost being the expression of the paired box transcription factors Pax7 and/or Pax3 [1,4,9]. Pax7 is the canonical SC biomarker expressed across several species in both quiescent and proliferating SCs (Fig. 1). Pax3 is a paralog of Pax7 but is associated with certain anatomical located muscles including the diaphragm and trunk muscles of the body [1,8,9,27]. In fact, SCs appear to exist as heterogeneous populations isolated with different cell surface biomarkers and showing variation in their efficiency to regenerate muscles in vivo. Proof of the concept of muscle stem cell came from single myofiber transplantation studies. In one seminal study, muscle fibers with SCs were isolated and transplanted into radiation-ablated muscles of mdx/nude (immunodeficient) mice [8,

Please cite this article as: K.J.A. McCullagh, R.C.R. Perlingeiro, Coaxing stem cells for skeletal muscle repair, Adv. Drug Deliv. Rev. (2014), http://dx.doi.org/10.1016/j.addr.2014.07.007