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Skeletal myocyte plasticity: basis for improved therapeutic potential?

Karlheinz Hilber
Center of Biomolecular Medicine and Pharmacology, Institute of Pharmacology, Medical University of Vienna, Waehringerstrasse 13A, 1090 Vienna, Austria

Abstract

Skeletal muscle tissue exhibits a remarkable capacity to regenerate after injury and to adapt its properties in response to altered functional demands or environmental pressure. This potential renders skeletal myocytes especially attractive candidates to be used in therapeutic strategies. Besides the well-described adaptability of skeletal myocytes in terms of contractile function and metabolic profile, more recent research has revealed that the electrophysiological properties of myocytes are also subject to significant changes both under physiological conditions and in pathophysiological situations. A better understanding of skeletal myocyte plasticity, its regulation and its forced induction could improve existing therapeutic approaches and may pave the way for new therapeutic strategies.

Introduction

In adult skeletal muscle, undifferentiated progenitor cells, the so-called satellite cells, reside between the sarcolemma and the basal lamina of adult skeletal muscle fibres. After muscle injury, normally quiescent satellite cells become activated and regenerate the muscle. Moreover, when overloaded, the muscle adapts by increasing its size and strength through satellite cell-mediated mechanisms [1]. Satellite cells are, to a certain extent, committed to develop a muscle phenotype [2]; however, *in vitro*, myoblasts (descendants of activated satellite cells) can be converted into other cell types such as osteoblasts [3] or adipocytes [4]. Myoblasts are already utilised for therapeutic strategies, for example, intra-cardiac myoblast transplantation therapy after heart injury [5]. Recently, various populations of stem cells have been isolated from skeletal muscle that may provide an alternative pool of progenitor cells in addition to, and clearly distinct from, satellite cells [2,6].

Largely independent of satellite cells [7,8•] fully differentiated skeletal muscle fibres also exhibit a remarkable capacity to adapt in response to altered functional demands. Their phenotypic profile (i.e. fibre type: fast glycolytic, fast glycolytic/oxidative or slow oxidative) is affected by innervation, neuromuscular activity, exercise training, mechanical loading/unloading, hormones and ageing [9]. Fibre type conversions involve changes in molecular, structural, metabolic and contractile properties [10], and the cellular signalling mechanisms involved are beginning to be understood [11]. Besides the well-described adaptability of skeletal myocytes in terms of contractile function and metabolic profile [12], more recent research has revealed that the electrophysiological properties of myocytes also significantly change in the course of fibre type conversion. The first part of this short review will summarise this topic. The second part will highlight the relevance of skeletal myocyte

Corresponding author: Hilber, Karlheinz (karlheinz.hilber@meduniwien.ac.at).

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plasticity and its forced induction for various therapeutic approaches. The review will focus on papers published not earlier than 2005 but will also consider older papers if they are essential.

Main text

Electrophysiological adaptations in skeletal myocytes under physiological conditions

The electrophysiological properties of excitable cells, such as neurons or skeletal myocytes, are determined by the expression and function of membrane ion channels. Over the past few years, it has become increasingly clear that ion channel gene expression is dynamically controlled not only in developing, but also in fully differentiated cells of various origins. For example, the expression of various sodium channel genes is highly dynamic in neurons, where it accompanies transitions between different physiological states (e.g. low-frequency versus high-frequency action potential firing states) [13]. In contrast to neuronal tissues, little is known about ion channel plasticity in skeletal muscle. The current knowledge will be reviewed in the following section.

Sodium channels—Fast muscle fibres exhibit larger action potentials than slow fibres [14]. This is due to the higher density of voltage-gated sodium channels in fast muscle fibres (e.g. reference [15]). Moreover, fast and slow muscle fibres also clearly differ in basic functional properties of their sodium currents. For example, fast and slow sodium current inactivation occurs at more positive potentials and is less voltage-dependent in slow fibres [15,16]. Importantly, these basic differences in sodium channel expression levels and gating properties affect cellular excitability. The high channel density of fast fibres reduces the refractory period for action potential generation. Thus, fast fibres, but not slow fibres, are able to fire at high rates [17]. Moreover, the relative resistance of slow fibres to slow inactivation may enable them to remain tonically active. On the contrary, pronounced slow inactivation in fast fibres limits the duration these fibres can fire at high rates to prevent injury associated with prolonged high-frequency contraction [16]. Taken together, Ruff's exciting work has made it clear that cellular excitability substantially differs between the skeletal muscle fibre types. The molecular mechanisms underlying these differences, however, remained unknown. Using a simple *in vitro* approach, we recently showed [18] that basic functional parameters of sodium currents in differentiated skeletal myocytes of the mouse were significantly altered after their fibre type had been partly transformed from fast to slow. In accordance with Ruff's work, the slow fibre phenotype showed an increased resistance to slow inactivation. This was most probably due to enhanced expression of the cardiac sodium channel isoform $Na_v1.5$ versus the adult skeletal muscle isoform $Na_v1.4$ [18]. Importantly, these changes in the expression of sodium channel isoforms may represent a mechanism to generate differences in cellular excitability between fast and slow muscle fibres. However, convincing evidence for considerable expression of $Na_v1.5$ in adult slow skeletal muscle is still lacking. As an alternative mechanism, the different resting potentials of fast and slow fibres [19] may influence the functional properties of their sodium channels [20•], and thereby alter excitability.

Calcium channels—Similar to sodium channel expression, the expression of L-type calcium channels is also subject to changes during fibre type conversion. [21,22], using *in vivo* chronic low frequency electrical stimulation, showed that fast-to-slow fibre type conversion downregulated the expression of $Ca_v1.1$ (skeletal muscle isoform), whereas upregulated the expression of $Ca_v1.2$ (cardiac isoform) calcium channels. In accordance, significant expression of $Ca_v1.2$ was detected at protein level in adult slow skeletal muscle [22,23]. Moreover, the abundance of calcium channel auxiliary subunits (α_2, β) shows fibre type-specific differences [22]. The functional consequences of these shifts in calcium

channel expression remain unclear. The finding that not only the cardiac voltage-gated calcium channel, but also the cardiac isoform of the ryanodine receptor (RyR2), is upregulated during fast-to-slow conversion [22] suggests a possible role of cardiac-like excitation-contraction coupling in fast-to-slow transformed and slow skeletal muscle [24]. A clear functional role of calcium influx in skeletal muscle was recently exposed by [25,26] who showed that calcium influx becomes relevant for muscle contractility during ageing.

Chloride channels—Chloride channels conduct at hyperpolarised potentials and thereby influence the resting potential and excitability of skeletal muscle fibres [19]. Owing to the higher sarcolemmal chloride conductance of fast fibres, their resting potential is significantly shifted towards hyper-polarised potentials compared with that of slow fibres [19]. In accordance with a higher chloride conductance in fast fibres, slow-to-fast fibre type conversion, induced by hindlimb unloading, increases the chloride conductance in rat skeletal muscle fibres [27,28,29•] by a reduction in PKC activity, which normally silences chloride channels in slow fibres [29]. Most interestingly, an increased chloride conductance precedes the transitions of myosin heavy chain isoforms, the classical markers of skeletal muscle fibre type, during conversion [27,28]. This suggests a possible involvement of ion channel (i.e. chloride channel) activity in initiating fibre type conversions. Accordingly, inhibition of the ryanodine receptor 1 calcium channels induces a fast-to-slow conversion [30].

Besides the voltage-gated ion channels described above, also other ion channel types change their expression levels and/or properties in the course of fibre type conversion (e.g. references [31-33]). Although impacts on cellular excitability are likely, the functional consequences of these changes are less clear and not further discussed. Finally, skeletal myocytes also undergo electrophysiological adaptations in pathophysiological situations. For example, in dystrophic compared with normal mouse muscle, the functional properties of voltage-gated calcium channels are altered [34]. At present, however, it is too early to finally judge how electrophysiological adaptations contribute to the pathology of skeletal muscle diseases. By contrast, in neuronal tissues, dysregulation of ion channel expression has been causally associated with a variety of pathophysiological settings, the so-called ‘transcriptional channelopathies’ [35].

Relevance of skeletal myocyte plasticity and its forced induction for therapeutic approaches

Myoblast transplantation therapy—Intra-cardiac transplantation of skeletal myoblasts is a new therapy to regenerate the injured or diseased heart [5]. The fact that skeletal myocytes have different properties than cardiomyocytes, in addition to their limited transdifferentiation capacity after transplantation *in vivo* [36], very probably limits the efficacy of myoblast transplantation therapy. In particular, specific electrophysiological features of the skeletal myocyte (functional ion channel properties, lack of connexin 43 expression) do not allow for proper cardiac-like impulse conduction (e.g. reference [17]) and, thus, may prevent recovery of heart function by synchronous contraction of the skeletal graft with cardiac host tissue. Here, it is worthwhile to reconsider the electrophysiological differences between slow and fast muscle fibres reviewed above. In contrast to fast fibres, slow fibres exhibit some cardiac-like electrophysiological properties, that is cardiac sodium channel [18] and calcium channel [22,23] expression. It is therefore tempting to speculate that myoblasts derived from slow skeletal muscle, which, in the rat, are pre-determined to generate slow fibres [37], are better suitable for intra-cardiac transplantation than fast muscle-derived myoblasts. Indeed, in an animal model of dilated cardiomyopathy, transplanted myoblasts expressing slow, but not fast, myosin heavy chain isoforms persisted in the graft and expressed connexin 43 [38•]. In analogy, the efficacy of myoblast

transplantation to restore dystrophin in dystrophic slow skeletal muscle was significantly increased if slow instead of fast muscle-derived myoblasts were used [39]. This suggests that careful matching between donor myoblasts and host muscle is essential. The whole concept, however, requires that human satellite cells derived from slow muscle are, like in rodents [37], pre-programmed to develop slow myocytes, which has been called into question [40].

In addition, forced induction of cardiac-like electrophysiological properties in skeletal myocytes may be another strategy to improve their performance in the heart. Using a simple *in vitro* approach, we recently showed [41•] that cardiac $Na_v1.5$ sodium channel expression is induced in skeletal myocytes by paracrine action of cardiomyocytes. Importantly, this suggests that skeletal myocytes can be forced to express cardiac electrophysiological properties. However, cardiac-like impulse conduction in the skeletal graft would, besides cardiac sodium channels, also require the expression of other cardiac ion channels, for example calcium and potassium channels. An additional prerequisite would be significant electrical coupling between the transplanted cells and host cardiomyocytes that may not occur *in vivo* [36]. The latter problem could be overcome by genetic modification of myoblasts to overexpress the cardiac gap junction protein connexin 43 [42].

Future approaches of intra-cardiac myoblast transplantation may benefit from the use of factors that induce cardiac properties in skeletal myocytes (Figure 1). Such factors could be applied in the course of transplantation and/or in the initial postoperative weeks. Alternatively, it may be possible to boost the endogenous release of such factors by cardiocytes. The ultimate goal is to ‘reprogram’ myoblasts before transplantation to induce cardiomyogenic function [43]. Finally, skeletal muscle stem cells [2] other than satellite cell-derived myoblasts may be considered a promising alternative cell source for transplantation into the failing heart (Figure 1).

Skeletal muscle regeneration—Using a DNA microarray approach [44•] reported transient alterations in the transcript levels of voltage-gated ion channels to go along with the initiation of a regeneration program in skeletal muscle. Importantly, this indicates an involvement of ion channel expression changes in muscle regeneration. Moreover, the regenerative potential of dystrophic mouse muscles was shown to be positively related to their chloride conductance [45]. Consequently, aimed alteration of the electrophysiological properties of skeletal myocytes (e.g. stimulation of chloride conductance) may be a strategy to boost the regeneration of skeletal muscle.

Aimed fibre type conversion to induce therapeutic benefit—It is obvious that fibre type-specific excitability of skeletal myocytes should influence skeletal muscle diseases that are related to impaired cellular excitability (e.g. myotonias and periodic paralyses). Accordingly, it is easier to trigger myotonia in fast than in slow rat skeletal muscles [46]. If slow muscle is less susceptible to myotonia, aimed fast-to-slow fibre type conversion seems a reasonable therapeutic strategy. There is experimental evidence that also other diseases may benefit from a forced induction of the slow skeletal muscle phenotype: First, a fast-to-slow fibre shift has been suggested to alleviate the progression of muscular dystrophy in a mouse model (mdx) of Duchenne muscular dystrophy [47,48•,49•]. Secondly, promotion of the slow phenotype may protect against the development of insulin resistance and Type 2 diabetes [50,51•]. Finally, slow-to-fast fibre type conversion, accompanied by decreased exercise tolerance, is normally observed in pathophysiological situations of skeletal muscle disuse (e.g. references [1,27]). Forced fast-to-slow conversion may be considered a therapeutic strategy to counteract. In accordance, electrical stimulation of thigh muscles in patients with advanced chronic heart failure resulted in fast-to-slow conversion and significantly improved the patient's physical condition and exercise tolerance [52].

Besides electrical stimulation, various other strategies to achieve clinically relevant promotion of the slow skeletal muscle phenotype are feasible: endurance training [9], ion channel modulation [27,30], beta-2 receptor antagonists (indirect evidence deduced from [53]) and, most promising, activation of signalling pathways that promote the slow fibre phenotype [11,47,49•]. The concept depicted in this paragraph is summarised in Figure 2.

Conclusions

Besides satellite cells, also adult skeletal myocytes contribute to the enormous degree of plasticity featuring skeletal muscle. Recent research has revealed that, in addition to the well-described adaptability of skeletal myocytes in terms of contractile function and metabolic profile, also their electrophysiological properties, and thus, their excitability can change. Electrophysiological adaptations occur under physiological conditions, and in diseased muscle, where they may well contribute to the pathology of certain disease states. At present, however, studies that provide a clear causal link between dysregulation of ion channel expression and/or modulation and pathophysiological settings in skeletal muscle are lacking. It can be expected that the existing knowledge in this area will rapidly broaden in the next couple of years especially owing to DNA chip and proteomics technology. Skeletal myoblast and adult skeletal myocyte plasticity comprises great potential to be utilised in therapeutic strategies. A better understanding of skeletal muscle plasticity, its regulation and its forced induction will be necessary to tap its full therapeutic potential.

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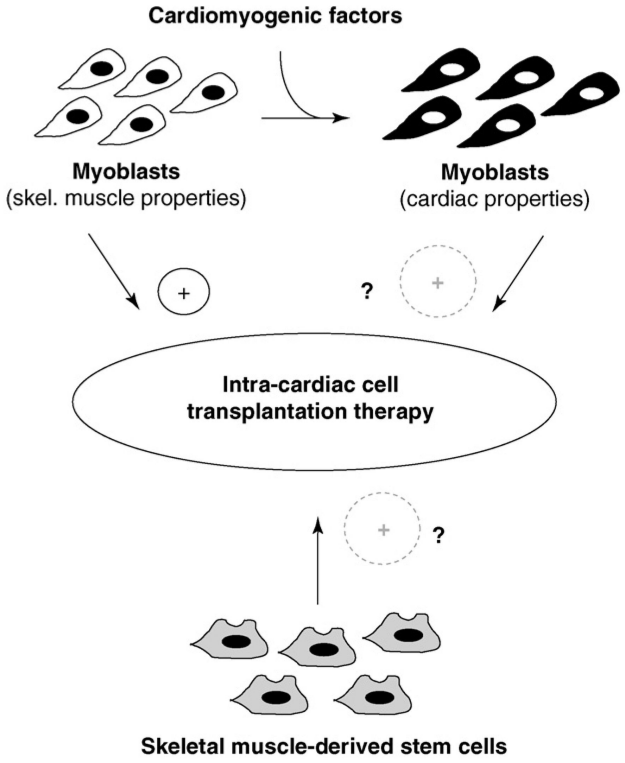

Figure 1.
New concepts for improvement of intra-cardiac cell transplantation therapy with skeletal muscle-derived progenitor cells. Skeletal myoblasts derived from satellite cells are already used for intra-cardiac cell transplantation therapy with limited success. Induction of cardiac properties in myoblasts by cardiomyogenic factors may enhance their performance in the heart. In addition, cell therapy may benefit from the use of skeletal muscle stem cells other than satellite cell-derived myoblasts.

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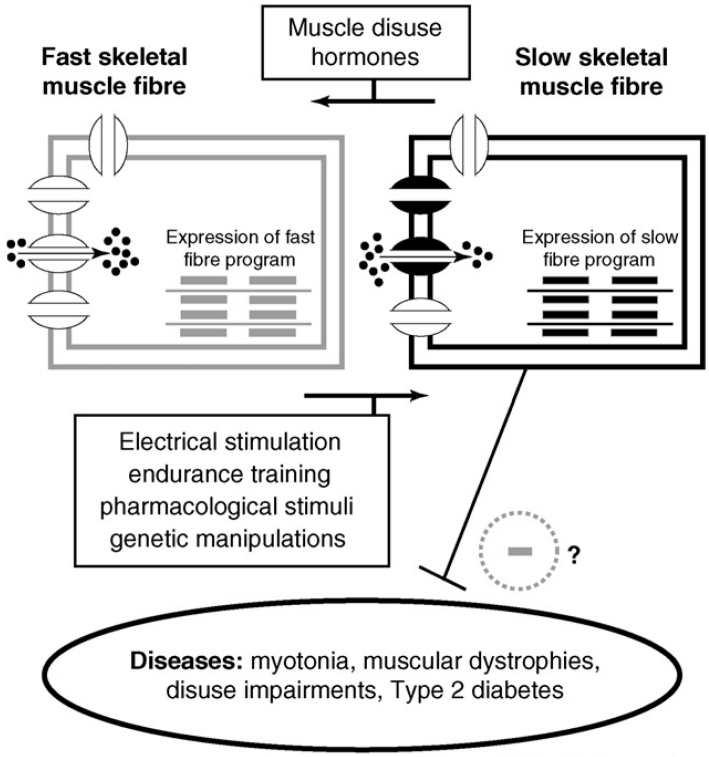

Figure 2.

Skeletal muscle fibre type conversion to induce therapeutic benefit. Slow-to-fast and fast-to-slow fibre type conversions can be induced by various stimuli. These conversions include changes in the expression and function of ion channels in the cellular membranes of skeletal muscle cells. Induction of the slow fibre phenotype may inhibit the susceptibility to, and/or the progression of, various human diseases.