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Mini review

Role of skeletal muscle proteoglycans during myogenesis

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ABSTRACT

Skeletal muscle formation during development and the adult mammal consists of a highly organised and regulated the sequence of cellular processes intending to form or repair muscle tissue. This sequence includes, cell proliferation, migration, and differentiation. Proteoglycans (PGs), macromolecules formed by a core protein and glycosaminoglycan chains (GAGs) present a great diversity of functions explained by their capacity to interact with different ligands and receptors forming part of their signalling complex and/or protecting them from proteolytic cleavage. Particularly attractive is the function of the different types of PGs present at the neuromuscular junction (NMJ). This review is focussed on the advances reached to understand the role of PGs during myogenesis and skeletal muscular dystrophies.

Contents

1. Introduction

Different processes associated with the formation and maintenance of the skeletal muscle, such as muscle development, differentiation and regeneration which actively occur in several skeletal muscle dystrophies are characterised by the dynamic expression of different molecules that robustly modulate several of the mentioned biological events.

Among the different types of macromolecules participating in skeletal muscle biology, proteoglycans (PGs) have gained tremendous attention in the past years and still there are several open questions regarding other roles during skeletal muscle physiology. The lively expression during development, repair and maintenance of skeletal muscle reflects a plethora of specific activities. These functions may vary from modulation of cytokines, proteinases, cell adhesion molecules

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and growth factors. They participate in cell adhesion and migration or unexpected functions at neuromuscular junction (NMJ) have recently appeared. At the cellular level the localisation of PGs is critical reflecting their different functions.

Structurally PGs are composed of a core protein to which the sulphated glycosaminoglycan chains (GAGs) are covalently attached. The number, length and chemical structure of these GAGs vary between the different PGs and in general, can be associated with the plasma membrane and the extracellular matrix (ECM).

The skeletal muscles contain different heparan sulphate proteoglycans (HSPGs), including the four mammalian syndecans (syndecans 1–4), glypican-1, perlecan and agrin, and chondroitin/dermatan sulphate PGs (CS/DS-PGs), such as decorin and biglycan.

This review is focused on the advances reached to understand the roles of these PGs in skeletal muscle physiology. Table 1 summarizes the multiple roles and patterns of expression of PGs during development, muscle regeneration, muscular dystrophies and at the NMJ. Other more extensive reviews on PG functions may serve to fill the gaps found here (Kresse et al., 1994; Carey, 1997; Bernfield et al., 1999; Iozzo, 1999; Filmus and Selleck, 2001; Couchman, 2003; Jenniskens et al., 2006; Filmus et al., 2008; Iozzo and Schaefer, 2010; Gillies and Lieber, 2011; Sarrazin et al., 2011).

2. Role of proteoglycans during skeletal muscle formation, differentiation and regeneration

2.1. Heparan sulphate proteoglycans

During the formation of mouse limb muscles, skeletal muscle regeneration after damage and skeletal muscle differentiation, the expression of different HSPGs is very dynamic (Jenniskens et al., 2002; Liu et al., 2002). This differential pattern of expression for membrane bound HSPGs likely reflects different functions for these complex molecules (Fig. 1).

Among the different functions described for the HSPGs is their essential role as co-receptors of transducing growth factors. Thus, fibroblast growth factor type-2 (FGF-2) forms a ternary complex in the plasma membrane with the FGF-2 receptors (FGFRs), and the HSPGs that are required for the FGF-2 dependent signalling (Rapraeger et al., 1991; Yayon et al., 1991; Olwin and Rapraeger, 1992). The hepatocyte growth factor (HGF) signals through the MET receptor (Bottaro et al., 1991) regulating proliferation, migration and differentiation of muscle precursor cells. It has been described that HGF signalling also requires HSPGs (Anastasi et al., 1997; Deakin and Lyon, 1999). Studies carried out during skeletal muscle differentiation indicate that the four syndecans are downregulated (Larrain et al., 1997a,b; Fuentealba et al., 1999; Gutierrez et al., 2006). Since FGF-2 and HGF are stimulators of skeletal muscle cell proliferation and strong inhibitors of muscle differentiation, membrane bound syndecans and glypican-1 potentially play unique, but pivotal, roles in muscle cell physiology.

HSPGs also play a critical role during skeletal muscle regeneration, a highly complex and regulated process that involves muscle precursor proliferation, migration and differentiation. Furthermore, the different localisations of the HSPGs, give them another level of complexity, besides their localisation in the ECM and plasma membrane, in this later compartment they also present a special distribution which determine some of their functions.

2.1.1. Syndecan-1

In human skeletal formation RNA transcript for syndecan-1 peaked at week 13 of gestation, after which a significant decrease was observed. However, perlecan expression levels were undetectable (Sogos et al., 1998). Similar results were found during the formation of mouse limb muscles. Syndecan-1 is expressed at day 10.5 and decreases after day 14.5, whereas perlecan increases their expression at day 12.5 of development (Olguin and Brandan, 2001). In the turkey pectoralis major muscle the peak of syndecan-1 expression is early and reached between embryonic days 18 and 20, previous than glypican (Liu et al., 2004).

Sindecan-1 and -3 are critical modulators of FGF-2 biological activity (Larrain et al., 1998; Fuentealba et al., 1999). Since FGF-2 is a potent inhibitor of skeletal muscle differentiation (Brunetti and Goldfine, 1990), the downregulation of both syndecans (Fig. 1) seems to be a key step required to silence the muscle inhibitory signal mediated by FGF-2, allowing by this way the skeletal muscle differentiation (Larrain et al., 1997a,b; Larrain et al., 1998; Fuentealba et al., 1999). Turkey derived myogenic satellite cells overexpressing syndecan-1, maintain a rounded morphology and are unable to fuse to form multinucleated myotubes after differentiation is triggered (Velleman et al., 2004).

2.1.2. Syndecan-2

Much less attention has been given to evaluate the expression of syndecan-2 in skeletal muscle. One study performed to evaluate the expression of syndecan-2 during the mouse embryo development, indicates that this occurred almost exclusively on mesenchymal cells, which would derivate mainly in connective tissue cells. No syndecan-2 was detected in epithelia, neural or muscle cells (David et al., 1993). More recent *in vitro* studies of skeletal muscle differentiation, indicate that the expression of syndecan-2 is downregulated, similar to syndecan-1 and syndecan-3, suggesting common but not necessarily overlapping functions during this process (Fig. 1) (Larrain et al., 1997a,b; Fuentealba et al., 1999; Gutierrez et al., 2006). Studies focused to evaluate the role of syndecan-2 in skeletal muscle are required.

2.1.3. Syndecan-3

During the development of mouse limb muscles, syndecan-3 increases their expression at day 12.5 of development (Olguin and Brandan, 2001). Its expression is temporally and spatially coincident with the expression of myogenin, an essential muscle regulatory factor (Rudnicki and Jaenisch, 1995).

In the adult skeletal muscle fibres, the expression of syndecan-3 is restricted to the satellite cells (Cornelison et al., 2001) and as mentioned in myoblast its expression after inducing skeletal muscle differentiation decrease quite rapidly (Fig. 1) (Fuentealba et al., 1999).

In vitro evidences indicate that in the absence of syndecan-3 the muscle differentiation process is enhanced due to a diminished sensibility to FGF-2 (Fuentealba et al., 1999). *In vivo* its absence is associated with a dystrophic–fibrotic muscle phenotype characterised by impaired locomotion, fibrosis, and hyperplasia of myonuclei and satellite cells, indicating a key role for this HSPG in satellite cell maintenance, activation and differentiation (Cornelison et al., 2001; Casar et al., 2004a,b; Cornelison et al., 2004). Myoblasts with inhibited syndecan-3 expression grafted into regenerating muscle had a normal proliferation rate but an impaired capacity to fuse and form skeletal muscle fibres (Casar et al., 2004a,b). It has been demonstrated that in the absence of syndecan-3, there is increased cell death, delayed onset of differentiation, and markedly reduced numbers of Pax7(+) satellite cells. Interestingly, syndecan-3-null satellite cell is rescued by ectopic expression of the constitutively active Notch intracellular domain and is required for Notch processing by ADAM17/tumour necrosis factor-alpha-converting enzyme (TACE) and signal transduction, supporting the idea that syndecan-3 and Notch cooperate in regulating the homeostasis of the satellite cell population and myofibre size (Pisconti et al., 2010).

2.1.4. Syndecan-4

During the formation of mouse limb muscles syndecan-4 increase their expression at day 12.5, peaked at day 13.5 of development and down regulated thereafter (Olguin and Brandan, 2001). Syndecan-4 presence in adult skeletal muscle fibres is also restricted to satellite cells, as mentioned for syndecan-3, and *in vitro* studies show that its levels are downregulated during the muscle differentiation (Gutierrez et al., 2006).

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