

Role of the extracellular matrix in muscle growth and development

S. G. Velleman¹

Department of Animal Sciences, Ohio Agricultural Research and Development Center,
The Ohio State University, Wooster 44691

ABSTRACT: Skeletal muscle fibers are surrounded by an extracellular matrix. The extracellular matrix forms a complex dynamic architecture and is composed of glycoproteins, collagen, and proteoglycans. Proteoglycans have been suggested to play an important functional role in tissue differentiation. Proteoglycans affect the myogenic process by regulating collagen fibrillogenesis, modulating cell growth and the response to growth factors. The extracellular matrix communicates information back to the cell through integrin receptors. Integrins are heterodimeric transmembrane glycopro-

teins that contain extracellular, transmembrane, and cytoplasmic domains. During myogenesis, integrins play a role in both cell adhesion to the extracellular matrix and sarcomere formation. Therefore, the regulation of myoblast integrin temporal and spatial expression is critical in the formation of differentiated muscle. Although specific extracellular matrix components have been identified as being essential in myogenesis, the exact functions of these macromolecular proteins as they relate to muscle formation and growth is still not well understood.

Key Words: Connective Tissue, Muscles, Proteoglycans

©2002 American Society of Animal Science. All rights reserved.

J. Anim. Sci. 80(E. Suppl. 2):E8–E13

Introduction

Studies on skeletal muscle development have traditionally focused on myosin and actin. However, muscle secretes a network of macromolecules termed the *extracellular matrix*. The extracellular matrix is a part of three connective tissue layers (endomysium, perimysium, and epimysium) surrounding muscle fibers. Extracellular matrix is composed of proteins including collagens and proteoglycans.

There are at least 19 different vertebrate collagens with tissue-specific distributions and unique functional properties. Skeletal muscle predominantly contains fibrillar collagens Types I and III. Fibrillar collagens contain a single triple-helical domain consisting of three separate peptide chains. The three chains form a right-handed alpha helix that is linked together by interchain disulfide bonds. After collagen molecules are synthesized, they are secreted from the cell into the extracellular space and align in a quarter-stagger array. Crosslink formation between collagen microfibrils is then initiated. The crosslinks are largely responsible for the tensile strength attributed to collagen.

Proteoglycans are a diverse component of the extracellular matrix and contain a central core protein with covalently attached glycosaminoglycans. The glycosaminoglycans are polymers of disaccharide repeats that are highly sulfated, except for hyaluronic acid. The sulfation of the glycosaminoglycan gives the proteoglycan molecule a net negative charge. Typical glycosaminoglycans attached to the core protein include chondroitin sulfate, dermatan sulfate, heparan sulfate, and keratan sulfate. Proteoglycans are a multifunctional component of the extracellular matrix and play roles in regulating matrix organization, growth factor activity, and cell proliferation and differentiation. This review article will focus primarily on how proteoglycans and extracellular matrix-cell signal transduction may regulate skeletal muscle development, growth, and function.

A Brief Overview of Skeletal Muscle Development

Myogenesis involves the precise regulation of a number of developmental events, which includes cell adhesion and cell-cell recognition (Miller, 1992; Buckingham, 1994). These processes are critical in myoblast alignment and fusion into multinucleated myotubes. The formation of multinucleated myotubes is central to skeletal muscle development. Research during the past decade has significantly advanced our understanding of how myogenic precursor cells proliferate and differentiate into multinucleated myotubes. The expres-

¹Correspondence: phone: 330-263-3905; fax: 330-263-3949; E-mail: velleman.1@osu.edu.

Received July 26, 2001.

Accepted November 28, 2001.

Table 1. Characteristics of proteoglycans found in skeletal muscle

Proteoglycan	Core protein size, kDa	Glycosaminoglycan ^a	Reference
Decorin	36	CS, DS	Iozzo and Murdock, 1996
Syndecans 1–4	19–35	HS, CS ^b	Stringer and Gallagher, 1997
Glypican-1	64	HS	Stringer and Gallagher, 1997
Perlecan	400	HS	Stringer and Gallagher, 1997
Versican	370	CS	Lebaron, 1966

^aCS = chondroitin sulfate; DS = dermatan sulfate; HS = heparan sulfate.

^bSyndecans 2 and 3 contain only HS chains attached to the core protein.

sion of myogenic regulatory factors (**MRF**) is key to the process of activating the transcription of muscle-specific genes (Edmondson and Olson, 1993; Weintraub, 1993; Yablonka-Reuveni and Paterson, 2001). In addition to the MRF, the macromolecular components of the extracellular matrix are likely to play a critical role in regulating myogenesis (Fernandez et al., 1991; Florini et al., 1991; McLennan, 1993). However, little information is known about how the muscle extracellular matrix interacts with proliferating and differentiating muscle cells to influence the formation and maintenance of skeletal muscle structure.

Dynamic Expression of Proteoglycans During Skeletal Muscle Development

In skeletal muscle, chondroitin sulfate, dermatan sulfate, and heparan sulfate proteoglycans have been identified (Young et al., 1989; Fernandez et al., 1991; Brandan and Larraín, 1998). Table 1 provides a list of proteoglycans found in skeletal muscle. Fernandez et al. (1991) showed that the extracellular matrix is a complex structure and proteoglycan expression changes during embryonic chicken skeletal muscle development. As skeletal muscle proceeds through embryonic chicken maturation, a transition from a matrix rich in large chondroitin sulfate proteoglycans into a complex matrix containing smaller chondroitin sulfate, dermatan sulfate, and heparan sulfate proteoglycans occurs (Young et al., 1989). This same shift in proteoglycan expression has been reported in turkeys (Velleman et al., 1999) and mice (Young et al., 1990). Olguin and Brandan (2001) have found that the expression of myogenin, a muscle transcriptional regulatory factor, is temporally and spatially coincident with the expression of the proteoglycans syndecan-3 and decorin. Both syndecan-3 (Fuentelba et al., 1999) and decorin (Riquelme et al., 2001) have been shown to be essential in skeletal muscle differentiation. Therefore, it is likely that different types of proteoglycans expressed in skeletal muscle may have specific functions during skeletal muscle differentiation because the expression pattern of proteoglycans appears to be conserved across species.

Although the exact function of each type of skeletal muscle proteoglycan is not known as it relates to muscle growth and development, specific roles may be hypothesized. For example, the large chondroitin sulfate proteo-

glycan, versican, has been identified in numerous tissues, including skeletal muscle (Carrino and Caplan, 1989; Carrino et al., 1994). Versican has a high negative charge due to the large number of covalently attached chondroitin sulfate chains and will interact ionically with water. High levels of versican have been reported during early stages of chicken skeletal muscle myogenesis (Carrino and Caplan, 1984) and in regenerating muscle (Carrino et al., 1988). Although the exact role played by versican in developing muscle is not known, it is possible that versican may be involved with the spacing of developing muscle fibers due to its ability to ionically associate with water and to the fact that it is expressed during developmental periods when muscle fibers are forming. The dermatan sulfate proteoglycan, decorin, is a multifunctional proteoglycan regulating collagen fibrillogenesis (Vogel et al., 1984; Weber et al., 1996), cell proliferation and growth (Santra et al., 1995; Moscatello et al., 1998), and transforming growth factor- β (**TGF- β** ; Yamaguchi et al., 1990). These properties are all critical in achieving normal muscle growth, development, and function. Decorin has been detected in turkey (Velleman et al., 1997, 1999) and chicken (Lenon et al., 1991) skeletal muscle, as well as in that of other species (Brandan et al., 1991; Eggen et al. 1994). Heparan sulfate proteoglycans are localized extracellularly, or at the plasma and basement membranes. Heparan sulfate proteoglycans regulate the binding of fibroblast growth factor (**FGF**) to its high-affinity cell-signaling receptor (Aviezer et al., 1994; Brandan and Larraín, 1998). Fibroblast growth factor is a potent stimulator of muscle cell proliferation and an inhibitor of differentiation (Dollenmeir et al., 1981).

Proteoglycan Regulation of Extracellular Matrix Organization

The structural architecture of the extracellular matrix affects the response of skeletal muscle to tensile stress. In particular, the amount of collagen crosslinking and fibril organization largely determines skeletal muscle elasticity. Decorin, a chondroitin/dermatan sulfate proteoglycan, associates with fibrillar collagen, including Types I, II, and III (Vogel et al., 1984; Scott, 1988; Thiezszen and Rosenquist, 1994). Molecular modeling studies have predicted that the decorin core protein binds to collagen in the gap zone between adjacent

collagen molecules (Weber et al., 1996). In vitro studies support the notion that the interaction between decorin and collagen governs the formation of collagen fibrils (Vogel et al., 1984; Vogel and Trotter, 1987; Scott, 1988). Collagen fibrils in a decorin knockout mouse model exhibit irregular size and diameter (Danielson et al., 1997). Viability of the mice was not altered, but their skins were extremely fragile and tore with applied force. One function of decorin critical to matrix organization and function is to influence the maturation of collagen fibrils into larger fibrils and fiber networks.

The chicken Low Score Normal (LSN) genetic muscle disorder is characterized by subnormal muscle growth and function. The LSN defect is an example of a skeletal muscle alteration that can occur in the absence of normal extracellular matrix expression. Low Score Normal birds at 3 mo of age have an impaired ability to right themselves when repeatedly placed on their backs (Velleman et al., 1996). Prior to 20 d of embryonic development, LSN proteoglycan and glycosaminoglycan levels do not vary significantly from levels expressed in normal muscle (Velleman et al., 1996); however, at 20 d of embryonic development there is a dramatic increase in decorin. Subsequent to the increase in decorin, LSN collagen crosslink concentration is increased by nearly 200% at 6 wk posthatch. Although collagen crosslinking is modified, collagen concentration is not affected. Fitting with the role of decorin, this change in collagen crosslink properties affects collagen fibril organization. In terms of skeletal muscle function, the increase in collagen crosslinking results in a reduced ability to respond to tensile stress and is likely reflected in the decreased physical performance of the LSN birds.

Proteoglycan Regulation of Growth Factor Activity

Controlling the onset of skeletal muscle proliferation and differentiation is influenced by the extrinsic environment. Growth factors such as FGF and TGF- β either stimulate or inhibit skeletal muscle proliferation and differentiation. Therefore, regulating the response to growth factors has a significant impact on the progression of skeletal muscle formation from a mononucleated myoblast to a multinucleated myotube.

The response of muscle-forming cells to basic FGF is, in part, modulated by heparan sulfate containing proteoglycans. Heparan sulfate proteoglycans are a diverse group of proteoglycans with at least one covalently attached heparan sulfate glycosaminoglycan chain to the core protein; they are located extracellularly or associated with the plasma or basement membrane (Timpl, 1993). The membrane-associated heparan sulfate proteoglycans, syndecan and glypican, function as low-affinity co-receptors for basic FGF. This interaction is required for the high-affinity binding of basic FGF to its cellular receptor. If heparan sulfate is removed, basic FGF no longer functions as an inhibitor of muscle differentiation (Rapraeger et al., 1991).

Therefore, the presence of heparan sulfate proteoglycans is necessary for skeletal muscle development.

The heparan sulfate proteoglycans, syndecan-1 and glypican, have been shown to be differentially regulated during skeletal muscle differentiation (Brandan et al., 1996; Larraín et al., 1997). Syndecan expression is high early in skeletal muscle differentiation and is subsequently down-regulated, whereas glypican expression is the reverse of that observed for syndecan (Brandan et al., 1996; Larraín et al., 1997).

The syndecan family of proteoglycans are the most well-studied of the heparan sulfate proteoglycans. Syndecans are transmembrane heparan sulfate proteoglycans with at least four members interacting with a variety of extracellular matrix molecules including, but not limited to, collagen, fibronectin, and basic FGF (for review see Carey, 1997). With regard to skeletal muscle differentiation, the interaction of syndecan with basic FGF is critical for basic FGF to bind to its high-affinity cell surface receptor.

Unlike the syndecans, glypican is not a transmembrane heparan sulfate proteoglycan but is associated with the cell surface by a glycosylphosphatidylinositol linkage. Both of these proteoglycans are cofactors for basic FGF, but their function with regard to skeletal muscle differentiation and growth is not well understood. Syndecan is down-regulated during differentiation, whereas glypican expression is enhanced. The question that needs to be answered is why these proteoglycans are expressed in opposite modes, because they are both cofactors for basic FGF. Brandan and Larraín (1998) have suggested that syndecan may function as a basic FGF presenter during myoblast proliferation and glypican as a basic FGF sequester after differentiation has been initiated and prevent the inhibitory effect of basic FGF.

In support of a proteoglycan functioning as a growth factor sequester, decorin has been shown to function in this mode for TGF- β . Transforming growth factor- β binds to decorin at its core protein (Schönherr et al., 1998). When TGF- β is bound to the decorin core protein its activity is suppressed (Yamaguichi et al., 1990). Increased expression of TGF- β upregulates the expression of several extracellular matrix molecules, including decorin (Bassols and Massagué, 1998), fibronectin (Heino et al., 1989), collagen (Heino et al., 1989; Heino and Massagué, 1990), and integrins (Heino et al., 1989). Therefore, TGF- β and decorin may be key cofactors in a feedback regulatory mechanism. Decorin is a negative regulator of TGF- β and TGF- β functions as a positive regulator of extracellular matrix protein expression.

Proteoglycan Regulation of Cell Proliferation and Differentiation

The regulation of cell proliferation and differentiation are key events in the formation of skeletal muscle and determining muscle mass. In addition to decorin's modulation of collagen fibrillogenesis, decorin also functions

in the control of cell growth (Santra et al., 1995; Moscatello et al., 1998). Several independent areas of research support this function of decorin: 1) overexpression of decorin in Chinese hamster ovary cells inhibits cell proliferation (Yamaguchi and Ruoslahti, 1988); 2) expression of decorin suppresses human colon cancer cell growth (Santra et al., 1995); and 3) during human diploid fibroblast quiescence decorin is up-regulated (Coppock et al., 1993; Mauviel et al., 1995).

In LSN pectoral muscle, decorin is up-regulated late in embryonic development. Fitting with the function of decorin's regulation of cell proliferation and differentiation, LSN pectoral muscle satellite cells exhibit decreased proliferation and differentiation compared to normal satellite cells, and LSN pectoral muscle mass is 68% the weight of normal pectoral muscle at 1 wk posthatch (Li et al., 1997). Skeletal muscle satellite cells are myogenic precursor cells responsible for postnatal muscle fiber growth and muscle regeneration following injury. Satellite cells function by proliferating, differentiating, and fusing with existing muscle fibers or other differentiated satellite cells, leading to increased muscle weight. Therefore, developing a comprehensive understanding of how the extracellular matrix is involved with the regulation of myogenic satellite cell activity is of key importance to the poultry industry.

Does Extracellular Matrix-Cell Signal Transduction Affect Skeletal Muscle Development?

One of the main functions of the extracellular matrix is to communicate information back to the cell that may affect cellular gene expression, cell shape, cell migration, or cell proliferation and differentiation. The extracellular matrix communicates this information through heterodimeric transmembrane receptors termed *integrins*. Integrins are composed of noncovalently associated α and β subunits. There are numerous isoforms of each integrin subunit with tissue-specific distributions and unique functional properties. In general, integrins are transmembrane proteins that have an extracellular domain that binds to extracellular matrix proteins such as fibronectin, collagen, and laminin and an intracellular domain that binds to the cellular cytoskeletal network. When integrins bind to the extracellular matrix, they become clustered on the cell membrane and in the interior of the cell form a cytoskeletal signaling complex leading to the assembly of actin filaments (Giancotti and Ruoslahti, 1999).

During skeletal muscle formation, myoblasts align and then fuse to form multinucleated myotubes. The process of multinucleated myotube formation requires myoblast cell migration. Cell migration involves a series of complex steps including cell extension at the leading edge, formation of stable contacts between the cell and extracellular matrix, contraction of the cellular cytoskeleton, translocation of the cell, and release of the cell-extracellular matrix contact at the rear of the

cell. Central to appropriate cell migration is the adhesion of the myoblast through integrins to the extracellular matrix. Boettiger et al. (1995) have shown by blocking a myoblast-extracellular matrix integrin that both cell migration and myotube morphogenesis are inhibited. Hence, appropriate communication from the extracellular matrix through integrins plays a critical role during muscle assembly.

In vitro studies with LSN myogenic satellite cells have shown during differentiation that myotube morphology is modified (Velleman and McFarland, 1999). After 48 h of growing LSN satellite cells in culture conditions to promote the formation of multinucleated myotubes, only 10% of the myotubes had four to six nuclei, whereas in normal satellite cell cultures 70% of the myotubes had four to six nuclei (Velleman and McFarland, 1999). Subsequent studies have demonstrated that the expression of integrin is reduced in LSN satellite cell cultures during myotube formation (Velleman et al., 2000). The reduction in LSN integrin expression likely reduces the amount of cellular contact with the extracellular matrix. This results in a decrease in cell migration and cellular contact necessary to form multinucleated myotubes. Morphologically, the muscle exhibits a significant reduction in weight and yields a less desirable product.

Conclusions

Skeletal muscle proteoglycans are precisely regulated in a dynamic fashion during skeletal muscle development. Regulation of both proteoglycan synthesis and spatial distribution may play a key role in tissue morphogenesis in terms of growth factor responsiveness, cellular growth, and extracellular matrix architecture. The heparan sulfate family of proteoglycans are crucial in regulating the cellular response to basic FGF. Proteoglycans such as decorin are multifunctional and are critical in modulating TGF- β , cellular growth properties, and collagen fibril organization. How each of these proteoglycan types influences myogenesis still remains an enigma. In addition to the proteoglycans, signal transduction from the extracellular matrix to the myoblast likely plays a significant role in muscle formation and growth. Continued analysis of the skeletal muscle extracellular matrix is necessary to develop a comprehensive understanding of the myogenic process that transcends just the myofibrillar proteins.

Implications

Why should the domestic animal industries be concerned about the extracellular matrix? Selection for growth rate and muscling alters muscle fiber proportions, and likely the amount of extracellular matrix space. The extracellular matrix functions in tissue water-holding capacity, elasticity, growth factor regulation, and cellular growth properties. Both the swine and turkey industries in recent years have experienced

a meat quality problem termed pale, soft, and exudative (PSE). When cooked, meat from animals with the PSE condition has a soft texture, poor juiciness, and increased yield losses. Proteoglycans are a major determinant in tissue water-holding capacity but have not been studied with regard to PSE. If the amount of proteoglycans have been reduced in animals selected for growth rate and muscling, the reduced water-holding capacity would directly affect the juiciness and drip loss. Therefore, domestic animal industries should consider how the extracellular matrix is affected by selection.

Literature Cited

- Aviezer, D., E. Levy, M. Safran, C. Svahn, E. Buddecke, A. Schmid, G. David, I. Vlodavsky, and A. Yayon. 1994. Differential structural requirements of heparin and heparan sulfate proteoglycans that promote binding of basic fibroblast growth factor to its receptor. *J. Biol. Chem.* 269:114–121.
- Bassols, A., and J. Massagué. 1988. Transforming growth factor β regulates the expression and structure of extracellular matrix chondroitin/dermatan sulfate proteoglycans. *J. Biol. Chem.* 263:3039–3045.
- Boettiger, D., E. Enomto-Iwamoto, H. Y. Yoon, U. Hofer, A. S. Menko, and R. Chiquet-Ehrismann. 1995. Regulation of integrin $\alpha 5\beta 1$ affinity during myogenic differentiation. *Dev. Biol.* 169:261–272.
- Brandan, E., D. J. Carey, J. Larraín, F. Melo, and A. Campos. 1996. Synthesis and processing of glypican during differentiation of skeletal muscle cells. *Eur. J. Cell Biol.* 71:170–176.
- Brandan, E., M. E. Fuentes, and W. Andrade. 1991. The proteoglycan decorin is synthesized and secreted by differentiated myotubes. *Eur. J. Cell Biol.* 55:209–216.
- Brandan, E., and J. Larraín. 1998. Heparan sulfate proteoglycans during terminal skeletal muscle differentiation: Possible functions and regulation of their expression. *Basic Appl. Myol.* 8:107–114.
- Buckingham, M. 1994. Molecular biology of muscle development. *Cell* 78:15–21.
- Carey, D. J. 1997. Syndecans: Multifunctional cell-surface co-receptors. *Biochem. J.* 327:1–16.
- Carrino, D. A., and A. I. Caplan. 1984. Isolation and partial characterization of high-buoyant-density proteoglycans synthesized in ovo by embryonic chick skeletal muscle and heart. *J. Biol. Chem.* 259:12419–12430.
- Carrino, D. A., and A. I. Caplan. 1989. Structural characterization of chick embryonic skeletal muscle chondroitin sulfate proteoglycan. *Connect. Tissue Res.* 19:35–50.
- Carrino, D. A., J. E. Dennis, R. F. Drushel, S. E. Haynesworth, and A. I. Caplan. 1994. Identity of the core proteins of the large chondroitin sulphate proteoglycans synthesized by skeletal muscle and prechondrogenic mesenchyme. *Biochem. J.* 298:51–60.
- Carrino, D. A., U. Oron, D. G. Pechak, and A. I. Caplan. 1988. Reinitiation of chondroitin sulphate proteoglycan synthesis in regenerating skeletal muscle. *Development (Camb.)* 103:641–656.
- Coppock, D. L., C. Kopman, S. Scandalis, and S. Gilleran. 1993. Preferential gene expression in quiescent human lung fibroblast. *Cell Growth Differ.* 4:483–493.
- Danielson, K. G., H. Baribault, D. F. Holmes, H. Graham, K. E. Kadler, and R. V. Iozzo. 1997. Targeted disruption of decorin leads to abnormal collagen fibril morphology and skin fragility. *J. Cell Biol.* 136:729–743.
- Dollenmeier, P., D. C. Turner, and H. M. Eppenberger. 1981. Proliferation and differentiation of chick skeletal muscle cells cultured in a chemically defined medium. *Exp. Cell Res.* 135:47–61.
- Edmondson, D. G., and E. N. Olson. 1993. Helix-loop-helix proteins as regulators of muscle-specific transcription. *J. Biol. Chem.* 268:755–768.
- Eggen, K. H., A. Malstrøm, and S. O. Kolset. 1994. Decorin and a large dermatan sulfate proteoglycan in bovine striated muscle. *Biochem. Biophys. Acta* 1204:287–297.
- Fernandez, M. S., J. E. Dennis, R. F. Drushel, D. A. Carrino, K. Kimata, M. Yamagata, and A. I. Caplan. 1991. The dynamics of compartmentalization of embryonic muscle by extracellular matrix molecules. *Dev. Biol.* 147:46–61.
- Florini, J. R., D. Z. Ewton, and K. A. Magri. 1991. Hormones, growth factors, and myogenic differentiation. *Annu. Rev. Physiol.* 53:201–216.
- Fuentealba, L., D. J. Carey, and E. Brandan. 1999. Antisense inhibition of syndecan-3 expression during skeletal muscle differentiation accelerates myogenesis through a basic fibroblast growth factor-dependent mechanism. *J. Biol. Chem.* 274:37876–37884.
- Giancotti, F. G., and E. Ruoslahti. 1999. Integrin signaling. *Science (Wash DC)* 285:1028–1032.
- Heino, J., R. A. Ignatz, M. E. Hemler, C. Crouse, and J. Massagué. 1989. Regulation of cell adhesion receptors by transforming growth factor- β . *J. Biol. Chem.* 264:380–388.
- Heino, J., and J. Massagué. 1990. Cell adhesion to collagen and decreased myogenic gene expression implicated in the control of myogenesis by transforming growth factor beta. *J. Biol. Chem.* 265:10181–10184.
- Iozzo, R. V., and A. D. Murdoch. 1996. Proteoglycans of the extracellular environment: Clues from the gene and protein side offer novel perspectives in molecular diversity and function. *FASEB J.* 10:598–614.
- Larraín, J., G. Cizmeci-Smith, V. Troncoso, R. C. Stahl, D. J. Carey, and E. Brandan. 1997. Syndecan-1 expression is down-regulated during myoblast terminal differentiation. *J. Biol. Chem.* 272:18418–18424.
- Lebaron, R. G. 1996. *Versican*. *Perspect. Dev. Neurobiol.* 3:261–271.
- Lennon, D. P., D. A. Carrino, M. A. Baber, and A. I. Caplan. 1991. Generations of a monoclonal antibody against avian small dermatan sulfate proteoglycan: Immunolocalization and tissue distribution of PG-II (decorin) in embryonic tissues. *Matrix* 11:412–427.
- Li, Z., S. G. Velleman, D. C. McFarland, J. E. Pesall, K. K. Gilkerson, N. H. Ferrin, and Y. Yun. 1997. Characterization of satellite cells derived from chickens with the low score normal (LSN) muscle weakness. *Cytobios* 91:75–85.
- Mauviel, A., M. Santra, Y. Q. Chen, J. Uitto, and R. V. Iozzo. 1995. Transcriptional regulation of decorin gene expression: Induction by quiescence and repression by tumor necrosis factor- α . *J. Biol. Chem.* 270:116692–116700.
- McLennan, I. S. 1993. Localisation of transforming growth factor beta 1 in developing muscles: Implications for connective tissue and fiber type pattern formation. *Dev. Dyn.* 197:281–290.
- Miller, J. B. 1992. Myoblast diversity in skeletal myogenesis: How much and to what end? *Cell* 69:1–3.
- Moscattello, D. K., M. Santra, D. M. Mann, D. J. McQuillan, A. J. Wong, and R. V. Iozzo. 1998. Decorin suppresses tumor cell growth by activating the epidermal growth factor receptor. *J. Clin. Invest.* 101:406–412.
- Olguin, H., and E. Brandan. 2001. Expression and localization of proteoglycans during limb myogenic activation. *Dev. Dyn.* 221:106–115.
- Rapraeger, A. C., A. Krufka, and B. B. Olwin. 1991. Requirement of heparan sulfate for bFGF-mediated fibroblast growth factor and myoblast differentiation. *Science (Wash DC)* 251:1705–1708.
- Riquelme, C., J. Larraín, E. Schönherr, J. P. Henriquez, H. Kresse, and E. Brandan. 2001. Antisense inhibition of decorin expression in myoblasts decreases cell responsiveness to transforming growth factor β and accelerates skeletal muscle differentiation. *J. Biol. Chem.* 276:3589–3596.
- Santra, M., T. Skorski, B. Calabretta, E. C. Lattime, and R. V. Iozzo. 1995. De novo decorin gene expression suppresses the malignant phenotype in human colon cancer cells. *Proc. Natl. Acad. Sci. USA* 92:7016–7020.
- Schönherr, E., M. Broszat, E. Brandan, P. Bruckner, and H. Kresse. 1998. Decorin core protein fragment leu155-val260 interacts

- with TGF- β but does not compete for decorin binding to type I collagen. *Arch. Biochem. Biophys.* 355:241–248.
- Scott, J. E. 1988. Proteoglycan-fibrillar collagen interactions. *J. Biochem.* 252:313–323.
- Stringer, S. E., and J. T. Gallagher. 1997. Heparan sulfate. *Int. J. Biochem. Cell Biol.* 29:709–714.
- Thieszen, S. L., and T. H. Rosenquist. 1994. Expression of collagens and decorin during aortic arch artery development: Implications for matrix patter formation. *Matrix Biol.* 14:573–582.
- Timpl, R. 1993. Proteoglycans of basement membranes. *Experientia* 49:417–428.
- Velleman, S. G., C. S. Coy, L. Gannon, M. Wick, and D. C. McFarland. 2000. β 1 integrin expression during normal and low score normal avian myogenesis. *Poult. Sci.* 79:1179–1182.
- Velleman, S. G., X. Liu, K. H. Eggen, and K. E. Nestor. 1999. Developmental regulation of proteoglycan synthesis and decorin expression during turkey embryonic skeletal muscle formation. *Poult. Sci.* 78:1619–1626.
- Velleman, S. G., and D. C. McFarland. 1999. Myotube morphology, and expression and distribution of collagen type I during normal and low score normal avian satellite cell myogenesis. *Dev. Growth Diff.* 41:153–161.
- Velleman, S. G., R. A. Patterson, and K. E. Nestor. 1997. Identification of decorin and chondroitin sulfate proteoglycans in turkey skeletal muscle. *Poult. Sci.* 76:506–510.
- Velleman, S. G., J. D. Yeager, H. Krider, D. A. Carrino, S. D. Zimmerman, and R. J. McCormick. 1996. The avian low score normal muscle weakness alters decorin expression and collagen cross-linking. *Connect. Tissue Res.* 34:33–39.
- Vogel, K. G., M. Paulsson, and D. Heinegård. 1984. Specific inhibition of type I and type II collagen fibrillogenesis by the small proteoglycan of tendon. *J. Biochem.* 223:587–597.
- Vogel, K. G., and J. A. Trotter. 1987. The effects of proteoglycans on the morphology of collagen fibrils formed in vitro. *Collagen Relet. Res.* 7:105–114.
- Weber, I. T., R. W. Harrison, and R. V. Iozzo. 1996. Model structure of decorin and implications for collagen fibrillogenesis. *J. Biol. Chem.* 271:31767–31770.
- Weintraub, H. 1993. The MyoD family and myogenesis: Redundancy, networks, and thresholds. *Cell* 75:1241–1244.
- Yablonska-Reuveni, Z., and B. M. Paterson. 2001. MyoD and myogenin expression patterns in cultures of fetal and adult chicken myoblasts. *J. Histochem. Cytochem.* 49:455–462.
- Yamaguchi, Y., D. M. Mann, and E. Ruoslahti. 1990. Negative regulation of transforming growth factor- β by the proteoglycan decorin. *Nature (Lond.)* 346:281–284.
- Yamaguchi, Y., and E. Ruoslahti. 1988. Expression of human proteoglycan in chinese hamster ovary cells inhibits cell proliferation. *Nature (Lond.)* 336:244–246.
- Young, H. E., D. A. Carrino, and A. I. Caplan. 1989. Histochemical analysis of newly synthesized and accumulated sulfate glycosaminoglycans during musculogenesis in the embryonic chick leg. *J. Morphol.* 201:85–103.
- Young, H. E., D. A. Carrino, and A. I. Caplan. 1990. Change in synthesis of sulfated glycoconjugates during muscle development, maturation and aging in embryonic to senescent CBF-1 mouse. *Mech. Ageing Dev.* 53:179–193.