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HIGHLIGHTS

Matrilin-2, an extracellular adaptor protein, is needed for the regeneration of muscle, nerve and other tissues

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Abstract

The extracellular matrix (ECM) performs essential functions in the differentiation, maintenance and remodeling of tissues during development and regeneration, and it undergoes dynamic changes during remodeling concomitant to alterations in the cell-ECM interactions. Here we discuss recent data addressing the critical role of the widely expressed ECM protein, matrilin-2 (Matn2) in the timely onset of differentiation and regeneration processes in myogenic, neural and other tissues and in tumorigenesis. As a multiadhesion adaptor protein, it interacts with other ECM proteins and integrins. Matn2 promotes neurite outgrowth, Schwann cell migration, neuromuscular junction formation, skeletal muscle and liver regeneration and skin wound healing. Matn2 deposition by myoblasts is crucial for the timely induction of the global switch toward terminal myogenic differentiation during muscle regeneration by affecting transforming growth factor beta/bone morphogenetic protein 7/Smad and other signal transduction pathways. Depending on the type of tissue and the pathomechanism, Matn2 can also promote or suppress tumor growth.

***Key Words:** Schwann cells; neurite outgrowth; neuromuscular junction (NMJ); multiple sclerosis; TGF-β/BMP-7/Smad signaling; myogenic differentiation; Trf3; tumor suppression*

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Matrilin-2 Modulates the Extracellular Matrix (ECM) Assembly

Matrilins are multidomain extracellular adaptor proteins showing partially overlapping tissue distribution (Deák et al., 1999). They function in the ECM organization as they form homo- and heterooligomers and interact with many other ECM molecules *via* their von Willebrand factor A-like (VWA) domains to assemble into a filamentous pericellular network connected to collagen fibrils and proteoglycans (Klatt et al., 2011).

Matn2 is the largest matrilin, because its two VWA domains are connected by 10 epidermal growth factor (EGF)-like modules (**Figure 1A**) (Deák et al., 1999). Matn2 secreted by many cell types is deposited in varying amounts in almost every tissue. Thus, Matn2 was detected in loose and dense connective tissues, subepithelial basement membrane (BM), uterus, heart, skeletal and smooth muscle, skin, peripheral and central nervous system (CNS) (Piecha et al., 1999; Klatt et al., 2011; Jonas et al., 2014). Matn2 binds weakly to cells *via* α1β1 integrin (reviewed in Klatt et al., 2011). It forms filaments by interacting with itself and with other ECM proteins (*e.g.*, collagens, fibrillin-2, fibronectin and laminin-111-nidogen-1 complex) to perform an adaptor function in the supramolecular organization of the ECM (**Figure 1A**).

Matn2 deficiency is not lethal in transgenic mice and does not interfere with survival under laboratory conditions (Mátés et al., 2004), but it may severely decrease the survival of animals under natural, wild conditions, because, as discussed below, skeletal muscle and peripheral nerve regeneration is markedly delayed in Matn2$^{-/-}$ mice and they also have serious defects in skin wound healing, other tissue repair processes and tumor suppression (Ichikawa et al., 2008; Malin et al., 2009; Deák et al., 2014; Fullár et al., 2014).

Matn2 Deposited by Myoblasts is Required for the Timely Onset of the Myogenic Regulatory Program

Matn2 is found in connective, neuronal (see later) and myogenic tissues of skeletal muscles (Piecha et al., 1999; Deák et al., 2014). Among connective tissues, Matn2 immunostaining is strong around blood vessels and in the perimysium and epimysium, while it decreases in the endomysium of muscle fibers during development (Deák et al., 2014). Apart from fibroblasts, the gene is expressed in myogenic cell types and upregulated during myogenic differentiation in culture or in regenerating skeletal muscles. In parallel with the increasing Matn2 deposition by proliferating, differentiating and fusing myoblasts and myotubes, characteristic changes can be seen in the ECM assembly. Whereas proliferating C2 myoblasts deposit Matn2 in fine granules, the secreted Matn2 assembles with fibronectin and collagen-1 into an elaborate filamentous network, which is linked to focal adhesions and the BM of multinucleated myotubes. As Matn2 expression declines during myofiber maturation, the protein is stored in higher oligomers in the endomysium.

Silencing of Matn2 delayed C2 myoblast differentiation by hampering the gene induction for Trf3, Nfix, myogenic regulatory factors (MyoD, myogenin), the Cdk inhibitor p21 and muscle proteins (Deák et al., 2014). Downregulation of the same marker genes was confirmed in *Matn2*$^{-/-}$ fetal limbs and

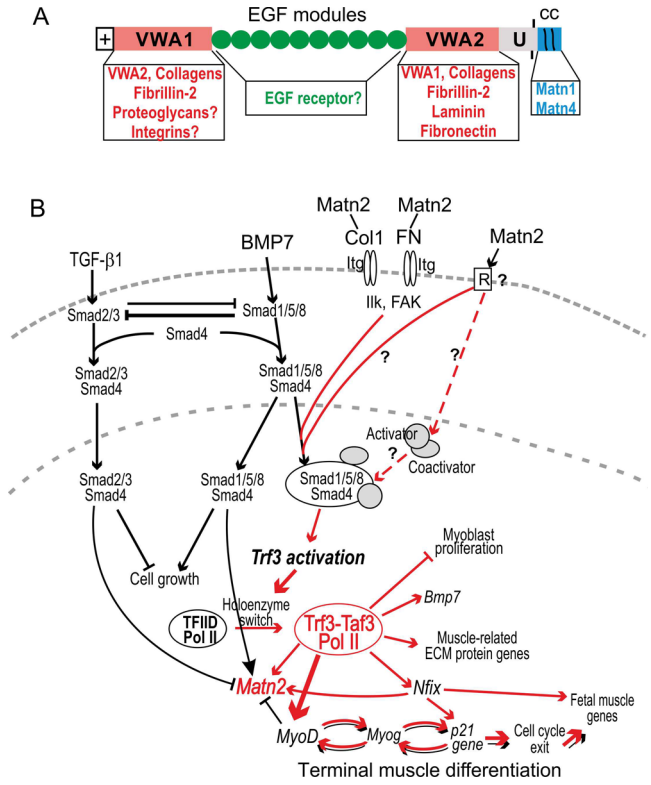

Figure 1 Model for the role of Matn2 in myoblast differentiation.
(A) Modular structure of the Matn2 monomer and its interacting partners. cc: Coiled-coil oligomerization domain; EGF: epidermal growth factor; U: unique sequence; VWA: von Willebrand factor A-like. (B) The schematic modified after Deák et al. (2014) illustrates in red color the key role of Matn2 signaling in the induction of Trf3 and in the subsequent timely onset of the Trf3/Taf3-dependent myogenic regulatory cascade. Matn2 may bind directly and signal through an unidentified receptor (R) to modify the formation of Smad multiprotein complexes *via* a cross talk between the Matn2 and bone morphogenetic protein 7 (BMP-7) signaling pathways or *via* the induction of activators or coactivators (broken red line). Alternatively, binding of the Matn2 adaptor protein to other extracellular matrix (ECM) molecules, such as fibronection (FN) or collagen-1 (Col1), may modify their integrin-mediated signaling. FAK: Focal adhesion kinase; Ilk: integrin-linked kinase; Itg: integrin; Pol II: RNA polymerase II; TFIID: transcription factor II D; TGF-β: transforming growth factor beta; Trf3: TBP-related factor 3.

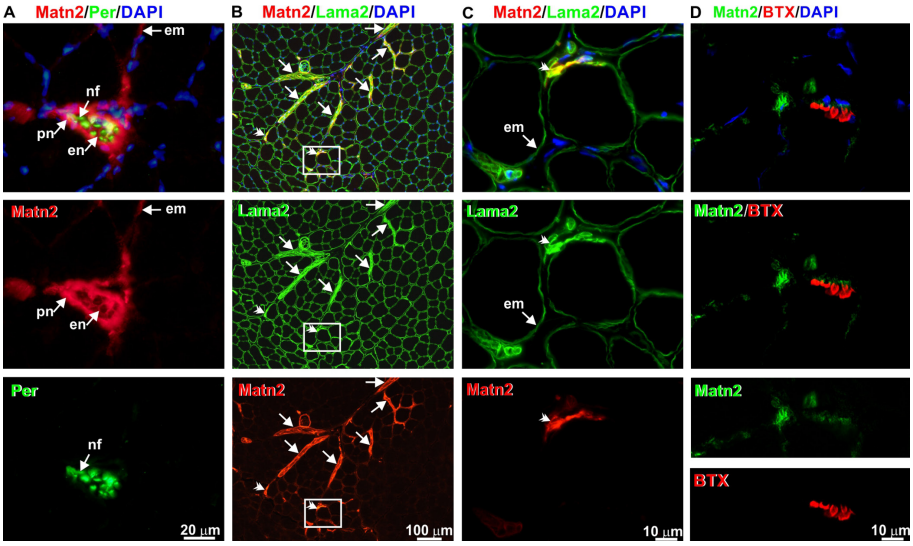

Figure 2 Matn2 distribution in the nerve tissue of skeletal muscles.
(A) Matn2 deposition in perineurium (pn) and endoneurium (en) around individual nerve fibers (nf), which are visualized by periferin (Per) staining in cryosections of rat soleus muscle. (B) Matn2 colocalizes with laminin α2 (Lama2) around nerves (arrows) and in neuromuscular junction (NMJs) (double arrowhead) in double-stained cryosections of mouse tibialis anterior. (C) Magnification of the inserts of panel B illustrates Matn2 accumulation at the NMJ (double arrowhead). (D) Matn2 is expressed in the presynaptic region of the NMJ in close proximity to the postsynaptic area shown here by α-bungarotoxin (BTX) staining. em: endomysium.

in *Matn2*$^{-/-}$ primary myoblast cultures differentiating *ex vivo*, with the largest drop in the Trf3 level (361-fold in fetal limbs). In differentiating myoblasts the Trf3/Taf3 complex replaces the TFIID complex, thereby switching of the core transcription machinery to selectively turn on the MyoD-dependent myogenic regulatory program, while turning off other programs (Deato et al., 2008). Nfix is a key activator of fetal-specific muscle genes (Messina et al., 2010). Thus, in the absence of Matn2, the lack of Nfix and Trf3 expression hampered the induction of the myogenic regulatory program, which is directed by MyoD acting in a positive feedback loop with myogenin and p21 (Deák et al., 2014). Matn2 and Nfix also seem to activate the expression of one another in a positive feedback regulation, while the declining Matn2 expression in late differentiation steps is likely due to repression at elevated MyoD level.

Thorough analysis revealed mild muscular dystrophy (fiber size heterogeneity, fiber splitting and central myonuclei) in both untreated and notexin-treated regenerating muscles of *Matn2*$^{-/-}$ mice as well as delayed myoblast differentiation, necrosis, inflammation and fibrosis in regenerating Matn2-deficient muscles (Deák et al., 2014).

Recent reports clarified that muscle mass is controlled by an interplay between the opposing transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP) signaling pathways competing for *Smad4* (Sartori et al., 2014). Receptor-bound TGF-βs act through Smad2/3 to inhibit muscle differentiation and growth, whereas BMP signaling *via* Smad1/5/8 is a dominant positive regulator of muscle growth. In keeping with these findings, TGF-β1 inhibited myogenesis in the control and rescued C2 myoblast cell lines by repressing Matn2 expression, thereby inhibiting the induction of Trf3, Nfix and the downstream myogenic regulatory cascade (Deák et al., 2014). It also inhibited the

phosphorylation of the Smad1/5/8 BMP signaling intermediate. By contrast, BMP-7 increased the dose-dependent activation of the *Matn2* promoter by Nfi proteins in cotransfections. Matn2 deficiency also hampered the activation of BMP-7, focal adhesion kinase and integrin α5 genes during muscle development and impaired Erk2 phosphorylation, indicating that Matn2 can directly or indirectly influence several signaling pathways.

Taken together, the data suggested a model for the key role of Matn2 in the timely onset of the myogenic regulatory program (**Figure 1B**) (Deák et al., 2014). Based on its adaptor function, Matn2 deposited by myoblasts may directly or indirectly (through interaction with other ECM proteins) bind to integrins and/or other cell surface receptors to modulate the TGF-β/BMP-7/Smad and other signaling pathways. The extracellular Matn2-elicited signal, possibly by modulating the multiprotein Smad complex formation, is crucial for the induction of *Trf3* and for the subsequent Trf3/Taf3-dependent global switch toward terminal muscle differentiation *via* selective activation of the MyoD- and Nfix-directed regulatory cascade in a feedback loop with Matn2. TGF-β1 may inhibit myogenic differentiation at least in part by repressing *Matn2* expression, thereby compromising the Trf3-dependent global transition of the regulatory program.

In the absence of Matn2 Trf3 is not induced, but signaling by other ECM proteins or by BMP alone may activate MyoD and the myogenic cascade at a lower level and with some delay compared to that upon Trf3 induction (**Figure 1B**, black arrows), thereby leading to delayed myogenesis. Such compensatory mechanisms can explain why only mild dystrophy, but no major defects were observed by light microscopy in the development of muscles and other tissues of Matn2-deficient mice (Mátés et al., 2004; Deák et al., 2014).

Important Role of Matn2 in Neural Regeneration

Matn2 is expressed in the peri-, epi- and endoneurium of peripheral nerves, developing dorsal root ganglia (DRG) and Schwann cells (SCs) (Piecha et al., 1999; Malin et al., 2009). Matn2 can stimulate axonal outgrowth of DRG neurons and SC adhesion and migration both *in vitro* and *in vivo* (Malin et al., 2009). Interestingly, Matn2 substrate enhanced the rate of migration even more than laminin and fibronectin, which are known to support SC migration. Matn2 expression is increased in terminal SCs (TSCs) during development, ceases in adults and gets upregulated again during peripheral nerve regeneration. Axonal growth and SC migration were impaired in DRG culture of *Matn2*$^{-/-}$ mice, but were rescued by adding exogenous Matn2. Matn2 accumulated in the endoneuronal tube promoted axonal outgrowth similarly to laminin after peripheral nerve injury. *Matn2*$^{-/-}$ mice, however, showed impaired functional recovery due to belated axonal growth. These observations substantiate that Matn2 is required for peripheral nerve regeneration. Further studies should reveal the molecular mechanism, how Matn2 aids axonal outgrowth and SC migration, and whether Matn2 signaling can facilitate regeneration-related gene expression. Utilization of Matn2 as coating substrate may improve the recovery from nerve injury in reconstructive surgery.

Interestingly, neural components of skeletal muscles exhibit stronger Matn2 staining than myogenic tissues (Deák et al., 2014). Thus, Matn2 deposition is high around nerves and neuromuscular junctions (NMJ) (**Figure 2**). Whereas myoblast proliferation occurs in the absence of innervation, the maturation of newly formed myofibers is highly dependent on nerves. Notexin treatment keeps the nerves of the skeletal muscle intact, but it destroys the motor endplates of nerve terminals. During notexin-induced regeneration of rat soleus muscle, the NMJs reestablished in large number between the newly formed myofibers and nerve terminals 4 days post-injury exhibited elevated Matn2 signal in close proximity to the α-bungarotoxin-stained acetylcholine receptors in the postsynaptic membrane (Deák et al., 2014). Matn2 deposition was high around TSCs, which form a cap around the presynaptic area of NMJs. Matn2 immunostaining of NMJs remains high during regeneration.

TSCs function in muscle fiber reinnervation by extending processes to form bridges from denervated junctions to local innervated muscle fibers. The Matn2-rich matrix produced by TSCs at NMJs may enhance the attachment and extension of these cells, thereby facilitating reinnervation. TGF-β/BMP-7/Smad signaling may be involved in this process, as various TGF-β isoforms show a distinct and characteristic expression in motoneurons and SCs (McLennan and Koishi, 2002). Furthermore, denervation dramatically increased the atrophy in Smad4$^{-/-}$ muscles, whereas BMPs reduced the denervation-induced muscle atrophy (Sartori et al., 2014). It should be tested whether TGF-β/BMP-dependent regulation of Matn2 deposition may aid axonal outgrowth and the reestablishment of NMJs.

MATN2 is also expressed in CNS neurons and upregulated in multiple sclerosis (Jonas et al., 2014). Matn2 deposition also increased by axons or neurons in response to immune-mediated axon damage in acute spinal cord lesions in experimental autoimmune encephalomyelitis (EAE) and it correlated with the disease severity, while the symptoms were much less severe in *Matn2*$^{-/-}$ mice. Acting as a damage-associated molecule and signaling through TLR4, Matn2 activates the proinflammatory genes in macrophages. By promoting inflammation, it exacerbates axonal damage in the acute phase of EAE. It remains to be tested, however, whether Matn2 can facilitate axonal growth in the recovery phase of EAE, similarly to its function in peripheral nerve regeneration. The apparently opposing roles of Matn2 in the two systems are possibly performed by different forms of the protein. Thus, high oligomers of Matn2 integrated stably in the ECM of the endoneuronal tube may promote axonal growth, whereas Matn2 likely released in soluble or monomer form by proteases from the ECM of the inflamed tissue may act as a TLR4 ligand and worsens the autoimmune axonal injury.

Important Role of Matn2 in the Regeneration of Other Tissues

In human skin, MATN2 secreted by keratinocytes and fibroblasts is deposited at the basal side of the dermal-epidermal BM (Piecha et al., 1999; Klatt et al., 2011). It was reported that transcriptional regulation of *MATN2* by the ΔNp63/BMP-7/Smad signaling pathway can modulate skin wound healing in human keratinocytes (Ichikawa et al., 2008). BMP-7 or its upregulation by ΔNp63 increased the expression of *MATN2* and p21, which was hampered in Δ*Np63*-silenced cells. Silencing of *SMAD4* also hampered the upregulation of *MATN2* and *p21*. Silencing of *MATN2* and Δ*Np63* facilitated the migration of keratinocytes into the wound. Supporting these data, serious defects were observed in skin wound healing in *Matn2*$^{-/-}$ mice (Deák et al., 2014). Thus, extracellular Matn2 deposition under the control of the TGF-β/BMP-7 signaling pathways can also modulate repair processes in the skin.

Matn2 has also been implicated in the early steps of stem cell-driven liver regeneration (Szabó et al., 2007). Expressed by oval/progenitor cells, but not by differentiated hepatocytes, Matn2 contributed to BM assembly around the tubules formed by oval cells. Knockdown experiments confirmed that vitamin K2-induced upregulation of Matn2 enhanced the regeneration and oval

cell proliferation (Lin et al., 2014). In another study, autoimmune or chemically induced liver injury increased Matn2 expression in hepatic stellate cells, but Matn2-deficiency did not affect the fibrotic process in C56BL/6 mice (Hintermann et al., 2015).

Notably, vitamin K2 also upregulates Matn2 and collagen synthesis in osteoblastic cells *via* the steroid and xenobiotic receptor (Ichikawa et al., 2006).

Role of Matn2 in Cancer

Matn2 expression is increased (*e.g.*, hepatocellular carcinoma (HCC), liver cirrhosis, melanoma), or decreased in tumors (*e.g.*, cervical cancer, colon polyps, human endometrium) (reviewed in Klatt et al., 2011). Depending on the type of tissue and the pathomechanism, Matn2 may promote or suppress tumor growth. Elevated MATN2 expression in cirrhosis and HCC is likely related to the neovascularization of the tumor (Szabó et al., 2008). In a recent report, keratinocyte growth factor treatment reduced the malignant phenotypes of cutaneous squamous skin carcinomas, and suppressed the upregulation of *MATN2* and other tumor growth-related genes by decreasing the expression of its receptor through ERK1/2 signaling (Toriseva et al., 2012). The expression may also reflect the status/nature of the tumor. For example, MATN2 may serve as a biomarker distinguishing between indolent and clinically aggressive subsets of pilocytic astrocytoma (Sharma et al., 2006).

The pathomechanism has been best studied in an animal model of HCC, where Matn2 functions as a tumor suppressor (Fullár et al., 2014). *Matn2*$^{-/-}$ mice spontaneously develop atypical microscopic foci in the liver in 129/SV genetic background. Matn2 deficiency can drive the liver into a pro-proliferatory state facilitating tumor development. Several signal transduction pathways are altered, including spontaneous phosphorylation of EGF receptor, Erk1/2, GSK-3β and retinoblastoma protein and the subsequent increase in β-catenin and decrease in p21 level. Consequently, *Matn2*$^{-/-}$mice are more susceptible to diethylnitrosamine-induced hepatocarcinogenesis than wild type mice based on the tumor number and size. The authors hypothesized that Matn2, *via* its several EGF modules, may interfere with the binding of the real EGF ligand to its receptor. Subsequently, Matn2-deficiency may increase the binding capacity of EGF receptor to its real ligand, resulting in increased activation.

Conclusion and Future Perspectives

The extracellular adaptor protein Matn2 plays a critical role in the differentiation and repair processes of skeletal muscles, peripheral nerves, liver and skin, but it has also been implicated in tumor growth or suppression. Matn2-elicited signaling is connected to TGF-β/BMP-7/Smad signaling in muscle and skin, and it is responsible for the timely initiation of the Trf3/Taf3-dependent global switch toward terminal muscle differentiation. Matn2 also seems to affect and mediate other signaling pathways in muscle, liver and other tissues. It awaits further studies to reveal: 1) the exact mechanism of Matn2 action in reinnervation, peripheral nerve and liver regeneration; 2) the interacting partners and the receptors that Matn2 directly or indirectly binds; 3) the molecular mechanism of signal transduction that affects TGF-β/BMP-7/Smad signaling and initiates the core promoter transition; 4) the contribution of Matn2 to autoimmune diseases of the CNS and perhaps other tissues; 5) the pathomechanisms explaining the opposing role of Matn2 in tumorigenesis.

As Matn2 is expressed in many committed proliferating cell types, it may have a general function in early steps of cell differentiation and regeneration by modulating the ECM assembly and ECM-cell communication. Uncovering the underlying molecular mechanisms would allow the development of new therapeutic strategies to facilitate tissue repair processes, tumor diagnosis or treatment.

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