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INVITED REVIEW

Matrix metalloproteinases in neural development: a phylogenetically diverse perspective

Christopher D. Small, Bryan D. Crawford*

Department of Biology, University of New Brunswick, Fredericton, NB, E3B 6E1, Canada

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Abstract

The matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases originally characterized as secreted proteases responsible for degrading extracellular matrix proteins. Their canonical role in matrix remodelling is of significant importance in neural development and regeneration, but emerging roles for MMPs, especially in signal transduction pathways, are also of obvious importance in a neural context. Misregulation of MMP activity is a hallmark of many neuropathologies, and members of every branch of the MMP family have been implicated in aspects of neural development and disease. However, while extraordinary research efforts have been made to elucidate the molecular mechanisms involving MMPs, methodological constraints and complexities of the research models have impeded progress. Here we discuss the current state of our understanding of the roles of MMPs in neural development using recent examples and advocate a phylogenetically diverse approach to MMP research as a means to both circumvent the challenges associated with specific model organisms, and to provide a broader evolutionary context from which to synthesize an understanding of the underlying biology.

Key Words: *matrix metalloproteinases; extracellular matrix; xenopus; Drosophila; zabrafish; neural development; evolution*

Correspondence to:
Bryan D. Crawford, Ph.D., bryanc@unb.ca.

orcid:
0000-0002-0512-4649 (Bryan D. Crawford)

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Introduction

The extracellular matrix (ECM) is a complex and dynamic facet of tissue architecture known to play fundamental roles in development, wound healing, tissue homeostasis, and a plethora of pathological processes (reviewed in DeSimone and Mecham, 2013). The ECM often modulates, and sometimes comprises, the developmental and/or positional signals used by cells to establish their transcriptional state, three dimensional structure, and interactions with other cells. Cell-matrix interactions are bidirectional; presentation of extracellular ligands or even mechanical forces can direct specific changes in the cytoskeleton and transcriptional state of cells, which in turn effect specific biochemical and mechanical changes on the matrices they secrete and inhabit. These interactions are especially important in neural development; in establishing the complex patterns of cell types in the neural tube, in axonal pathfinding and migration of peripheral nervous system cells (Myers et al., 2011), and ultimately in the stability/plasticity of synapses (Dityatev et al., 2010). Although parallels between development and regeneration continue to emerge in both neural and non-neural contexts (Werner et al., 2007; Atkinson et al., 2015; Thomas et al., 2015), it remains critical to examine each process independently in order to disentangle these complementary aspects of biology in embryonic versus adult tissues. Here we will present an overview on the role of matrix metalloproteinases (MMP) in neural development in their classical function as ECM remodelling enzymes as well as in light of their emerging role as signal modulators, with particular emphasis on insights arising from non-mammalian model systems.

What are MMPs?

The most well-known effectors of ECM remodelling are the matrix metalloproteinases – an ancient and complex family of zinc-dependent endopeptidases. These secreted and/or membrane-bound proteases are characteristically comprised of an auto-inhibitory pro-domain, a zinc-binding catalytic domain, a hinge region, and a hemopexin domain that mediates protein-protein interactions. MMPs are classified based on structure and activity into collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, as well as others that do not fit neatly into these categories (Nagase et al., 2006). The first MMPs were identified by Gross and Lapiere in 1962 on the basis of their ability to degrade collagen during tail resorption in *Xenopus* tadpole metamorphosis. This seminal study revealed the importance of MMPs in developmental tissue remodelling, and established them in their canonical role as matrix remodelling effectors (Gross and Lapiere, 1962). More recently, it has become clear that developmental ECM remodelling is not the sole function of these metalloenzymes (Apte and Park, 2015). MMPs function in post-developmental ECM-related roles such as stem cell niche maintenance (Kessenbrock et al., 2015; Porlan et al. 2015) and wound healing (Caley et al., 2015; Oh et al., 2015) as well as functions unrelated to ECM such as the processing of many cell signalling molecules (Amano et al.,

2005; Larsen et al., 2006; Rodriguez et al., 2010) and even proteolysis of intracellular targets (Kandasamy et al., 2010).

MMP Evolution

Although the majority of MMP research has focused on vertebrates, MMP orthologues are present in invertebrates (Angerer et al., 2006; Huxley-Jones et al., 2007; Page-McCaw, 2008; Buckley and Jessen, 2015), and related metalloproteinases are found in plants and prokaryotes (Maidment et al., 1999; Massova et al., 1999). The evolution of complex metazoans with ever-increasing numbers of tissues and organs correlates with duplication and diversification of the ancestral matrix genes and the matrix-remodelling toolbox along with it (Hynes, 2012).

There is a general trend of expansion and specialization in MMPs associated with metazoan evolution, but there remains a surprising amount of variability in the size and composition of the MMP families across the animal kingdom ranging from the simple two MMP genes in *Drosophila* (Page-McCaw, 2008) up to the 29 found in sea urchins (Angerer et al., 2006). Mammals have roughly two dozen MMP orthologues (24 in mice, 23 in humans) (Jackson et al., 2010), and other vertebrate models generally have comparable numbers (25 in zebrafish, 26 in *X. laevis*) (Fu et al., 2009; Wyatt et al., 2009). This apparent similarity in the numerical abundance of MMP-encoding genes among vertebrates belies some potentially important and/or informative differences; the zebrafish genome, for example, includes 2 paralogues of several MMPs, but lacks orthologues of several present in mammalian genomes, making the suite of MMPs encoded by the zebrafish genome numerically similar but biochemically quite distinct from that of mammals (Wyatt et al., 2009). It is interesting to note, for example, that all the MMPs 'missing' from the zebrafish genome, with respect to the mammalian genome, are of the secreted type. Furthermore, not only are all of the membrane-type MMPs represented in the zebrafish genome, most of them are present as duplicate paralogues, whereas many of the secreted MMPs are present only as single orthologues, suggesting that there is more, and possibly divergent, functional constraint on the membrane type MMPs, favoring the retention of duplicated copies of these genes.

Although studying MMP biology in model organisms with simple MMP families allows for experiments that elucidate the function of specific proteases, the interactions among MMPs and their various substrates, inhibitors and activators in more complex systems (for example, the activation of mammalian MMP2 through the formation of a ternary complex including MMP2, MMP14 and tissue inhibitor of metalloproteinases (TIMP) 2 (Nishida et al., 2008)) can only be studied effectively in organisms possessing the more elaborate families of MMPs characteristic of vertebrates.

Endogenous MMP Inhibitors

In addition to complex regulation at the transcriptional level, the biologically relevant proteolytic activities of MMPs are modulated by extraordinarily complex post-translational modifications and interactions. Irreversible activation by proteolytic removal of the pro-domain, as mentioned above with respect to MMP2, enables these proteases to bind and cleave their substrates (Nishida et al., 2008). Subsequent to activation, MMPs can be reversibly inhibited by the formation of complexes with endogenous regulators such as TIMPs (Page-McCaw et al., 2007) and reversion-inducing-cysteine-rich protein with Kazal motifs (RECK) (Prendergast et al., 2012). Ultimately, like all proteins, MMPs must be irreversibly degraded, but the regulation of this final step in the modulation of MMP activity has not been investigated.

It is clear, however, that post-translational regulation of MMP activity by endogenous inhibitors is at least as important as their regulation at the transcriptional level. This is best illustrated by the observation that *in vitro* assays of total MMP activity in tissue homogenates dramatically underestimate the amount of activity (as well as losing all information regarding spatial distribution) as assayed by *in vivo* imaging of MMP activity in intact embryos, due to the heterogeneous distribution of inhibitors in the intact tissue (Crawford and Pilgrim, 2005). The exquisite spatial regulation of MMP activity at the cellular, or even sub-cellular scale may well be due primarily to this mechanism (Keow et al., 2011). Finally, the phenotype of mutations in MMPs can frequently be phenocopied simply by up-regulating TIMPs in a dose-dependent manner (Wang et al., 2009). These inhibitors play such a critical role controlling MMP activity in development and disease pathogenesis that any *in vitro* assay must be considered with the understanding that MMP activity removed from its tissue context is not reflective of the biologically relevant activity.

As these inhibitors are crucial regulators of MMPs, it follows that the TIMP families should evolve in parallel with the MMPs. However, current data suggests that most TIMPs are promiscuous inhibitors of MMPs, and TIMP3 at least can also inhibit non-MMP metalloproteinases (reviewed in Iyer et al., 2012). Thus TIMPs remain much less abundant than MMPs even in complex genomes; *Drosophila* has a single TIMP, while humans have four (designated TIMP-1 through TIMP-4) and zebrafish have five (Wyatt et al., 2009; Brew and Nagase, 2010). Again, this numerical comparison is simplistic as the zebrafish complement includes paralogous copies of TIMP-2 and -4, a single orthologue of TIMP-3, and appears to lack any homologues of TIMP-1 (Wyatt et al., 2009). So again, the suite of endogenous inhibitors in the fish is numerically similar but biochemically distinct from that of mammals.

MMP Expression in Neural Development and Disease

MMPs are expressed dynamically in the brain and central nervous system during development and after wounding (Agrawal et al., 2008), however the mechanisms in which these proteases participate are still poorly understood, and their *in vivo* substrates and interaction partners are poorly characterized. MMP expression in the developing central

nervous system (CNS) has been described in detail elsewhere and MMP activity has been implicated in processes including but not limited to neuronal migration, myelination, axon guidance/invasiveness, synaptic plasticity, and neurogenesis (Yong, 2005; Agrawal et al., 2008; Fujioka et al., 2012; Porlan et al., 2015). Misregulation of MMP activity is frequently associated with pathologies and this holds true in a neural context as well (Agrawal et al., 2008; Fujioka et al., 2012). MMPs have been linked to pathological permeabilization of the blood-brain barrier (Buhler et al., 2009), Alzheimer's disease (Ito et al., 2006; Py et al., 2014), Parkinson's disease (Kim and Hwang, 2011), glioma invasion (Markovic et al., 2009), neuroinflammation (Lee et al., 2014), and even parasitic infections of the CNS (Bruschi and Pinto, 2013).

The gelatinases (MMP-2 and -9) have been studied and reviewed most extensively (Verslegers et al., 2013; Hehr et al., 2005), but all classes of MMPs have been implicated in CNS development and pathology, including collagenases (Development: Tonge et al., 2013; Pathology: Ito et al., 2006; Lee et al., 2014; Lenglet et al., 2014;), stromelysins (Development: van Hove et al., 2012; Pathology: Kim and Hwang, 2011), matrilysins (Development: Le and Friedman, 2011; Pathology: Buhler et al., 2009), membrane-type MMPs (Development: Crawford et al., 2014; Gaublomme et al., 2014; Janssens et al., 2014; Pathology: Markovic et al., 2009), and unclassified MMPs (Development: Larsens et al., 2006; Werner et al., 2007; Pathology: Py et al., 2014; Liao et al., 2015). Taken together, these studies highlight the importance of MMP activity in nearly every facet of neural development. The technical constraints imposed by some model organisms and/or experimental approaches limit our understanding of the mechanisms in which these proteases participate in the nervous system. Our understanding can be enhanced by using *in vivo* models in which we can observe and/or modify MMP activities directly.

In vivo Approaches Reveal the Biologically Relevant Activities of MMPs in the Nervous System

With its pair of MMPs and single TIMP, *Drosophila* is a simple and powerful system for investigating the functional roles of MMP activity using knockout approaches (Llano et al., 2002; Page-McCaw, 2008). In the fly, MMP activity in the developing nervous system is essential for both axon pathfinding and dendritic plasticity in the brain (Kuo et al., 2005). Dendritic plasticity in response to injury requires remodelling of the connections between neurons. Similar remodelling is apparent during metamorphosis during which neuronal processes are severed, degraded and regrown to establish the the functional nervous system of the adult. In hypomorphic Mmp1 and Mmp2 mutants, larval dendrites are severed appropriately but are not degraded suggesting that MMP activity is required in this process. Inhibition of MMP activity by over-expressing TIMP recapitulates this phenotype providing further support for this hypothesis. While the power of the simple MMP/TIMP system of the fly is obvious, this same simplicity and the lack of clear orthologies to vertebrate MMPs makes generalizing from the invertebrate studies difficult.

Xenopus has been an invaluable member of the developmental biologist's arsenal for many years and techniques such as *in vivo* exposed brain experiments make it well suited for the study of MMP function in neural development. In the frog, retinal ganglion cell (RGC) axons make three pathfinding decisions before reaching their target: crossing the optic chiasma to the contralateral side of the brain, turning caudally in the mid-diencephalon, and then recognizing the optic tectum as their destination and forming synapses. Evidence for the requirement of MMP activity in this tortuous pathfinding process emerges from experiments in which narrow- or broad-spectrum MMP-inhibitors (SB-3CT or GM6001, respectively) were administered to the brain. In GM6001-treated brains, in which we expect all MMPs to be inhibited, axons do not successfully make the turn after crossing the optic chiasma. Administration of SB-3CT, which inhibits only the gelatinases, results in axons with correct pathfinding through the first two decision points, but which fail to recognize the optic tectum as their target, suggesting that orthologues of MMP-2 and/or -9 play a role in the recognition of the target, and that other MMPs are essential in the earlier pathfinding events (Hehr et al., 2005). Determining which specific member(s) of the MMP family are involved at each decision point will be challenging using this approach until more specific pharmacological MMP inhibitors become available. However other vertebrate models are emerging that allow the use of alternate approaches.

In zebrafish, RGC axons follow a comparable path to those of *Xenopus*, crossing in the optic chiasma before turning towards the optic tectum. Whole-mount *in situ* hybridization and immunostains demonstrate that Mmp14a (one of two zebrafish paralogues homologous to MT1-MMP) is expressed and localized in the developing retina and the retinotectal projections of the RGCs. Blockade of *Mmp14a* translation using morpholino oligonucleotides or exposure to broad-spectrum MMP inhibitors both result in embryos with reduced optic tectum innervation and micropthalmia. Interestingly, the mechanism behind this teratogenic effect appears to be delayed retinal neurogenesis caused by a perturbation in the cell cycle of proliferating retinoblasts suggesting that correct innervation of targets in the optic tectum, or other Mmp14a-dependent processes, play a role in the signalling events coordinating the cell cycle (Janssens et al., 2014). That MMP inhibition in zebrafish causes only a reduction in optic tectum innervation, in contrast to the complete failure of pathfinding observed in *Xenopus*, is probably a result of the accessibility of the brain to these reagents in the exposed brain preparations used in the frog, although the increased redundancy of MMPs in zebrafish may also be a factor.

The transparency of zebrafish embryos combined with increasingly sophisticated techniques for monitoring matrix remodelling *in vivo* has proven instrumental in the study of MMP activity during neural development. Mmp25b

is a membrane-bound MMP found in zebrafish, which is homologous to human MMP-25 (a.k.a. MT6-MMP or leukolysin). *mmp25b* (but not *mmp25a*) is expressed in the developing sensory nervous system of the zebrafish, specifically in Rohon-Beard (RB) neurons as well as the trigeminal, craniofacial, and posterior lateral line ganglia (Crawford et al., 2014). Morpholino-mediated knockdown of *mmp25b* expression results in aberrant pathfinding in trigeminal ganglia axons, and larvae that are uncoordinated and insensitive to touch. *In vivo* zymography (Crawford and Pilgrim, 2005; Keow et al., 2011) reveals that the proteolytic activity associated with RB cells and Type IV collagen degradation associated with the pioneering axons of the trigeminal (but not elsewhere in the embryo) is notably reduced in Mmp25b morphants (Keow et al., 2011; Crawford et al., 2014). The failure of these axons to reach their targets underscores the importance of matrix remodelling in the development of a functional nervous system in vertebrates, and is consistent with the well-established roles of the gelatinases in neural development and regeneration (Verslegers et al., 2013).

While axon pathfinding is a phenomenon that seems tailored to the classical understanding of MMPs as secreted, extracellular matrix remodelling enzymes, MMPs are also involved in other aspects of neural development including neuron maturation. MMP-28 is implicated in the myelination of maturing neurons and its expression coincides with the emergence of migrating, myelinating glial cells and declines as myelination progresses in both frog and mouse embryos (Werner et al., 2007). This pattern of MMP-28 upregulation at the onset of myelination followed by a gradual decline in neural development is recapitulated during regeneration after limb amputation in frogs. MMP-9 (Oh et al., 1999) and MMP-12 (Larsen and Yong, 2004) are expressed in cultured oligodendrocytes and knocking out these enzymes in mice results in fewer myelinated axons in the corpus callosum at embryonic stages P7 and P10. This reduction in myelination is no longer apparent at P14 implying that this delay may be due to a partial rescue by other MMPs (possibly MMP-28). Consistent with this, cultured oligodendrocyte precursor cells from MMP-knockout mice produce fewer mature oligodendrocytes, but supplementation of IGF-1 rescues these MMP-deficient cell cultures (Larsen et al., 2006). These authors also show that both MMP-9 and MMP-12 bind and cleave IGFBP-6 (a key regulator of IGF-1 bioavailability), and that knockout mice have higher levels of IGFBP-6, implicating these MMPs as additional players in this process.

Spatial and temporal coordination of MMP activity is essential to the establishment of a functional nervous system, however the complex nature of MMP families has hindered efforts to resolve the molecular mechanisms, and to link individual MMPs and their substrates *in vivo*. We can begin to circumvent these challenges by selecting model organisms with genomes encoding MMP families most suited to research questions. Choosing a model organism will entail balancing simplicity and experimental tractability versus redundancies of the MMP family and translatability to human biology. By arming MMP researchers with a toolkit of model organisms, we can test hypotheses regarding the redundant effects that have proven challenging to disentangle – *e.g.*: if we predict that MMP-X knockouts are being partially rescued by MMP-Y, we can test this by knocking out MMP-X in an organism lacking orthologues of MMP-Y. As our toolkit broadens, we are aided by the generation of increasingly-specific MMP inhibitors, and elegant *in vivo* reporters of MMP activation and activity that will doubtless prove a boon to the study of MMP biology. The field is advancing rapidly and it is an exciting time for MMP research; below we discuss three avenues we see as particularly promising.

Promising Avenues for MMP Research in Neural Development

The use of non-mammalian vertebrate models

As we have discussed above, invertebrate systems have great potential, but generate insights that are difficult to generalize to vertebrates. Model systems like the zebrafish and the frog are amenable to approaches that are not feasible in mammalian embryos, while still providing a vertebrate context and a comparable matrisome. The avian embryo has long been a favorite of neural developmental biologists and several MMPs have been identified in chickens (Buckley and Jessen, 2014), though there is a surprising dearth of research regarding their role in neural development in this model. MMP9 is known to be important in avian neurulation and neural crest cell (NCC) development, particularly with respect to the degradation of N-cadherins and laminin during NCC epithelial-mesenchymal transition (Monsonego-Ornan et al., 2012). The amenability of the chick embryo to unilateral electroporation of the neural tube with DNA constructs makes it a tractable system for manipulating expression of genes involved in development of the CNS, but this has surprisingly not been exploited in the elucidation of the roles of MMPs in neural development.

Investigation of the roles of MMPs in signaling pathways important in neural development and/or regeneration

The emerging roles of MMPs in the regulation of signal transduction pathways known to play central roles in neural development is another promising research avenue. Along with the IGF-1 pathway discussed above, the Notch and FGF signaling pathways are both of fundamental importance in many aspects of neural development (Voelkel et al., 2014; Ariza-Cosano et al., 2015). Although not in a neural context, recent work has shown that MMPs regulate Notch signaling in bone marrow stromal cell culture by cleaving Delta-like 1 and directing differentiation away from a B-lymphocyte fate (Jin et al., 2012). Similarly, work in *Drosophila* using both RNAi knockdowns and TIMP over-expression demonstrates that Mmp2 asserts spatial control over the FGF signal regulating the branching morphogenesis of the developing air sac (Wang et al., 2009). An elaborate and intricate network such as the nervous system requires exquisite spatial and temporal regulation of signaling fields during differentiation and development; it seems unlikely that MMPs would play a role in regulating these signaling pathways in other tissues but not in the development of the nervous system.

Elucidation of the role of MMPs in learning and memory

Perhaps most excitingly, it is increasingly suspected that MMPs play an important role in mediating synaptic plasticity associated with learning and memory in mammals, implicating these proteases in higher cognitive functions (Dityatev et al., 2010; Huntley, 2012; Verslegers et al., 2013). MMP9 expression and activity is required for inhibitory avoidance learning involving long term potentiation (LTP) (Huntley, 2012). Blocking MMP9 activity with inhibitors prevents memory formation after negative stimulus, strongly implicating a role for proteolytic activity in consolidating memories, perhaps by remodeling the synaptic extracellular matrix. Consistent with this, application of active-MMP-9 to dendritic spines of CA1 pyramidal neurons results in increased synaptic strength and spine enlargement as seen after LTP (Huntley, 2012). These effects can be blocked by inhibiting the translation of MMP9, suggesting that synaptic remodeling during memory formation involves the synthesis of new MMPs rather than merely activation of MMP stores. The study of MMP activity during learning and memory is an emerging field largely limited to mammalian models where it is impossible to visualize the brain without highly invasive surgery making it challenging to uncover mechanisms. The zebrafish is becoming increasingly popular in the field of learning and memory (Roberts et al., 2013) and advances in microscopy have enabled the development of techniques such as single-cell resolution, whole-brain functional imaging of developing zebrafish embryos (Ahrens et al., 2013; Feierstein et al., 2015). The ability to visualize brain and CNS development and activity in real-time in a genetically tractable model such as the zebrafish along with a suite of behavioral learning assays make this an especially attractive model for the study of MMPs in learning and memory.

Conclusion

MMPs are central components of the molecular mechanisms underlying neural cell fate, morphogenesis, migration, homeostasis, function and pathology; these mechanisms entail not only their traditional functions in ECM remodelling, but also roles in modulating cell-cell adhesion, signal transduction and perhaps poorly-understood intracellular activities. The complexity and redundancy of the MMP/TIMP systems in mammals, combined with the nervous system's prodigious capacity for adaptation and the technical challenges of studying molecular events in the mammalian CNS, conspire to make elucidation of the roles of MMPs in the nervous system extremely challenging in these models. By combining the strengths of many non-mammalian model systems, in which investigation of MMP biology is rapidly progressing, significant insights into the roles of MMPs in mechanisms central to neural development, healing and function have begun to emerge. The development of a phylogenetically diverse array of model systems for the study of neural and ECM biology provides not only a more powerful experimental toolkit, but also an evolutionary perspective on the fundamental mechanisms underlying the formation and function of animal nervous systems.

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