Progress in Neurobiology 155 (2017) 36–56

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Review article

The multifaceted role of metalloproteinases in physiological and pathological conditions in embryonic and adult brains

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ARTICLE INFO

Article history:
Received 1 December 2015
Received in revised form 10 July 2016
Accepted 8 August 2016
Available online 13 August 2016

Keywords:
Metalloproteinases
Brain disorders
Development
Nervous system repair
Neuroinflammation
Neurodegenerative diseases

ABSTRACT

Matrix metalloproteinases (MMPs) are a large family of ubiquitous extracellular endopeptidases, which play important roles in a variety of physiological and pathological conditions, from the embryonic stages throughout adult life. Their extraordinary physiological "success" is due to concomitant broad substrate specificities and strict regulation of their expression, activation and inhibition levels. In recent years, MMPs have gained increasing attention as significant effectors in various aspects of central nervous system (CNS) physiology. Most importantly, they have been recognized as main players in a variety of brain disorders having different etiologies and evolution. A common aspect of these pathologies is the development of acute or chronic neuroinflammation. MMPs play an integral part in determining the result of neuroinflammation, in some cases turning its beneficial outcome into a harmful one. This review summarizes the most relevant studies concerning the physiology of MMPs, highlighting their involvement in both the developing and mature CNS, in long-lasting and acute brain diseases and, finally, in nervous system repair. Recently, a concerted effort has been made in identifying therapeutic strategies for major brain diseases by targeting MMP activities. However, from this revision of the literature appears clear that MMPs have multifaceted functional characteristics, which modulate physiological processes in multiple ways and with multiple consequences. Therefore, when choosing MMPs as possible targets, great care must be taken to evaluate the delicate balance between their activation and inhibition and to determine at which stage of the disease and at what level they become active in order maximize chances of success.

Contents

Abbreviations: AD, Alzheimer's disease; ADAMs, a disintegrin and metalloproteinase; AJs, adherens junctions; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-proprionate; APP, amyloid precursor protein; AQP4, aquaporin 4; Aβ, amyloid-β peptides; BBB, blood brain barrier; BDNF, brain derived neurotrophic factor; BM, basement membrane; CAMs, cell adhesion molecules; CNS, central nervous system; CSF, cerebral spinal fluid; DG, dystroglycan; EAE, experimental autoimmune encephalomyelitis; ECM, extracellular matrix; ET-1, endothelin-1; GJs, gap junctions; IGF, insulin-like growth factor; IL-1β, interleukin-1β; IL-6, interleukin-6; LBs, Lewy bodies; LPS, lipopolysaccharide; LTP, long term potentiation; l-LTP, late phase long term potentiation; MBP, myelin basic protein; MMPs, metalloproteinases; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; MT-MMPs, membrane-type MMPs; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NVU, neurovascular unit; 6-OHDA, 6-hydroxydopamine; PARP, poly (ADP-ribose) polymerase; PNS, peripheral nervous system; PD, Parkinson's disease; PMB, parenchymal basement membrane; RNS, reactive nitrogen species; ROS, reactive oxygen species; SC, superior colliculus; SN, substantia nigra; SNAP-25, synaptosomal-associated protein 25 kDa; TIMPs, tissue inhibitors of metalloproteinases; TJs, tight junctions; TNFα, tumor necrosis factor-α; ZO-1, zona occludens-1.

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http://dx.doi.org/10.1016/j.pneurobio.2016.08.002
0301-0082/

1. Introduction

The abundant extracellular matrix (ECM) of the CNS parenchyma is an important physical scaffold to which the complex array of brain cells adheres. However, ECM is not just a purely mechanical support, but it is also vehicle for a wide range of signals, which guide cell proliferation, migration, differentiation and apoptosis during embryonic development and throughout adulthood. The ECM is mainly composed of secreted glycoproteins and proteoglycans (Bosman and Stamenkovic, 2003). By binding to a number of cell adhesion molecules (CAMs) (i.e. cadherins, integrins), these proteins convey extracellular signals inside cells and modulate processes such as cell adhesion and migration, axon and dendritic outgrowth, axon fasciculation/de-fasciculation and synaptogenesis (Fields and Itoh 1996; Dityatev and Fellin, 2009). In addition, in matured CNS, the ECM supports remodeling of established synaptic contacts and plasticity of neural circuits, as those associated with learning and memory (Dityatev et al., 2008; Wright and Harding, 2009; Faissner et al., 2010). For all these processes to be completed, the ECM is subjected to continuous and specific remodeling, which is determinant for the plasticity of cell-ECM and cell–cell contacts, availability of signaling factors (i.e. cytokines, chemokines, trophic factors) and degradation of non-permissive molecules (Yong et al., 2001). Main modulators of ECM remodeling are members of the MMPs, a family of extracellular protease widely distributed in developing and matured CNS. Thank to their structural and functional characteristics, redundancy, versatility and number of possible targets, MMPs are cardinal players in numerous and highly diversified neural physiological and pathological events.

A number of excellent reviews (Sternlicht and Werb, 2001; Yong et al., 2001; Yong, 2005, 2010; Rivera et al., 2010), some of them of recent publication (Mroczko et al., 2013; Verslegers et al., 2013; Reinhard et al., 2015; Vafadari et al., 2016), has investigated the role of MMPs in nervous system, often focusing on one or a few MMPs, or on one specific aspect (i.e. CNS activity, pathology, development, and so on). Therefore, our idea with this review has been to collect in one treatise what is known so far on the role that MMPs play in all aspects of CNS physiology and pathology, development, neurodegeneration and recovery, with particular reference to MMP-2, MMP-3 and MMP-9 (the MMPs most expressed in the CNS). All this, at the aim to come out with a comprehensive vision on their beneficial and adverse potentialities, and on how these two aspects can interchange under different conditions. To do so, we will first summarize what is known about the molecular structure of MMPs, the control of their activation and the modulation of their activity. Then, we will highlight the key role of MMPs, in the physiology of both developing and mature brain. In the next session, we will focus on MMP involvement in a number of brain pathologies (i.e. Parkinson's disease, Alzheimer's disease; multiple sclerosis, epileptogenesis and seizures, brain malignant tumors), and particular emphasis will be given to neuroinflammation and oxidative stress, as these aspects have lately received less attention compared to others. Therefore, we will highlight MMP activities in the most relevant aspects of CNS repair, to conclude with a revision of recent, and less recent, findings on the use of MMP inhibitors as possible therapeutic strategies in some of the aforementioned CNS diseases. We auspicate that the final comprehensive vision on the MMP multifaceted activities emerging from this review will help in directing future studies, which will consider these molecules as pharmaceutical targets in brain pathologies.

2. The family of MMPs

2.1. Structure, activation and inhibition

MMPs constitute a family of more than 20 members, each of which the product of a different gene, subdivided into six main subgroups based on the functional domains that characterize their structure (Fig. 1). Of the MMPs present in the brain the two collagenases, MMP-2 and MMP-9, are the most abundant. MMPs are synthesized as pro-enzymes, called zymogens. The pro-peptide domain has a conserved PRCG (V/N) PD amino acid sequence, and the cysteine contained within this sequence suppresses the proteolytic activity by interacting with a Zn^{2+} ion contained in the catalytic domain (a process called "the cysteine-switch"). In addition, in order to promote stability and enzymatic activity, the catalytic domain requires an additional Zn^{2+} and either 2 or 3 Ca^{2+} ions. C-terminal domains are quite variable and are responsible for substrate specificity. Most of the MMPs have a hinge region and a hemopexin-like domain. The gelatinases MMP-2 and MMP-9 are characterized by inclusion of three fibronectin-like repeats in their catalytic domain that interact with collagens and gelatins respectively (Sternlicht and Werb, 2001; Page-McCaw et al., 2007). The MMP-9 also bears an O-glycosylated hinge region that is responsible for the fine-tuning of its bio-availability (Van den Steen et al., 2006) (Fig. 1). The subgroup of the six membrane-type MMPs (MT-MMPs) completes the MMP family. The MT1-MMP (MMP-14) was the first to be discovered and characterized as a co-activator at the cell surface of the pro-MMP-2 in invasive cancer cells (Sato et al., 1994). For this reason, the MT1-MMP is one of the