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Review

Matrix metalloproteinases: Evolution, gene regulation and functional analysis in mouse models

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ABSTRACT

Matrix metalloproteinases (MMPs) are a large family of zinc-endopeptidases which play important roles in multiple physiological and pathological processes. These enzymes are widely distributed in all kingdoms of life and have likely evolved from a single-domain protein which underwent successive rounds of duplication, gene fusion and exon shuffling events to generate the multidomain architecture and functional diversity currently exhibited by MMPs. Proper regulation of these enzymes is required to prevent their unwanted activity in a variety of disorders, including cancer, arthritis and cardiovascular diseases. Multiple hormones, cytokines and growth factors are able to induce *MMP* expression, although the tissue specificity of the diverse family members is mainly achieved by the combination of different transcriptional control mechanisms. The integration of multiple signaling pathways, coupled with the cooperation between several *cis*-regulatory elements found at the *MMP* promoters facilitates the strict spatiotemporal control of *MMP* transcriptional activity. Additionally, epigenetic mechanisms, such as DNA methylation or histone acetylation, may also contribute to *MMP* regulation. Likewise, post-transcriptional regulatory processes including mRNA stability, protein translational efficiency, and microRNA-based mechanisms have been recently described as modulators of *MMP* gene expression. Parallel studies have led to the identification of *MMP* polymorphisms and mutations causally implicated in the development of different genetic diseases. These genomic analyses have been further extended through the generation of animal models of gain- or loss-of-function for MMPs which have allowed the identification of novel functions for these enzymes and the establishment of causal relationships between MMP dysregulation and development of different human diseases. Further genomic studies of MMPs, including functional analysis of gene regulation and generation of novel animal models will help to answer the multiple questions still open in relation to a family of enzymes which strongly influence multiple events in life and disease.

1. Introduction

Matrix metalloproteinases (MMPs) comprise a large family of zinc-dependent endoproteinases, collectively capable of degrading all extracellular matrix (ECM) components. MMPs (also called matrixins) are found in all kingdoms of life and belong to the metzincin superfamily of metalloproteinases, which is characterized by the presence of a catalytic zinc atom in their active center followed by a conserved methionine residue [1]. To date, at least 25 different vertebrate MMPs have been identified, 24 of which are present in humans, including two recently duplicated genes encoding MMP-23 [2].

The proteolytic activities of MMPs influence essential cellular processes like cell proliferation, migration and adhesion, as well as many fundamental physiological events involving tissue remodeling, such as angiogenesis, bone development, wound healing, and uterine and mammary involution [3,4]. However, the increasing relevance of this family of proteases mainly derives from the high number of pathological conditions where these enzymes have been implicated [5,6]. Thus, upregulation of MMPs has been reported in cancer, vascular diseases and many different types of inflammatory pathologies, supporting the need of a precise spatiotemporal regulation of MMPs to maintain a proper homeostasis of the extracellular and pericellular environment. MMP expression and activity can be regulated at different levels including gene transcription, proenzyme activation and endogenous inhibition, which act in a coordinated manner to confine the diverse MMP proteolytic activities to those conditions and locations where they are necessary. Unfortunately, these restrictive regulatory mechanisms are frequently lost in multiple pathological conditions, as assessed from studies based on the use of gain- or loss-of-function of MMPs in animal models [7]. These models have also provided important clues about the functional relevance of MMPs in a variety of physiological processes taking place in all organisms with ability to produce these proteases. In this review,

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and after a general introduction to the biochemical properties of MMPs, we will focus on genomic characteristics of this family of proteolytic enzymes, paying special attention to gene organization and evolution. Likewise, we will discuss different levels of *MMP* gene regulation with particular emphasis on the mechanisms responsible for their transcriptional control and on the presentation of data on epigenetic and post-transcriptional regulation of these protease genes. Finally, we will present the most recent information about *MMP* polymorphisms and mutations associated with human pathologies, as well as those mouse models generated by genetic manipulation which have shed light on the functional relevance of these enzymes in life and disease.

2. Matrix metalloproteinases: Classification and biochemical properties

MMPs or matrixins are synthesized as zymogens with a signal peptide which leads them to the secretory pathway. Then, these enzymes can be secreted from the cell or anchored to the plasma membrane, thereby confining their catalytic activity to the extracellular space or to the cell surface, respectively. Interestingly, recent studies have reported that several MMP family members, such as MMP-1 [8], MMP-2 [9], MMP-11 [10] and MMP-13 [11], can be found as intracellular proteins, although their functions at this subcellular location are still unclear. The archetypal MMPs consist of a propeptide (~80 amino acids) with a cysteine-switch motif, a catalytic metalloproteinase domain (~170 amino acids), a linker peptide of variable length and a hemopexin domain (~200 amino acids). Nevertheless, the family of MMPs has evolved into different groups by removing some domains or by incorporating others which are absent in the previously described basic core (Fig. 1). Thus, based on their domain organization, MMPs can be classified in four different groups: archetypal MMPs, matrilysins, gelatinases and furin-activatable MMPs.

2.1. Archetypal MMPs

Within this category, and according to their substrate specificities, we can establish three different subgroups: collagenases, stromelysins and other archetypal MMPs.

2.1.1. Collagenases

This subgroup is composed of three enzymes, MMP-1, MMP-8 and MMP-13 (also known as collagenases-1, 2, and 3, respectively) whose name reflects their ability to cleave the collagen triple helix into characteristic 3/4 and 1/4 fragments. In addition, collagenases are also able to proteolytically process other ECM proteins, as well as a number of bioactive molecules such as interleukin-8 (IL-8) [12], pro-tumor necrosis factor (TNF)-α [13], protease-activated receptor-1 [14], and several insulin-like growth factor binding proteins (IGFBPs) [15]. Removal of the hemopexin domain turns these MMPs into enzymes unable to degrade native collagen, suggesting that the cooperation between the catalytic and hemopexin domains is essential to carry out their collagenolytic activity [16]. A fourth type of collagenase (MMP-18) has been identified in *Xenopus* [17], but it does not have any known orthologue in mammals.

2.1.2. Stromelysins

Stromelysin-1 (MMP-3) and stromelysin-2 (MMP-10) show the same structural design as collagenases and can degrade many different ECM components, but they are not able to cleave native collagen. In addition, stromelysin-1 also processes several bioactive substrates including stromal-cell derived factor-1, E-cadherin, and pro-interleukin-1 beta (IL-1β) [15]. Likewise, stromelysins participate in proMMP activation through their ability to remove the propeptide domain of the three procollagenases [18] and proMMP-9 [19], generating the fully active form of these enzymes. Stromelysins are expressed by both fibroblast and epithelial cells, and are secreted to the extracellular space where they play important roles in biological

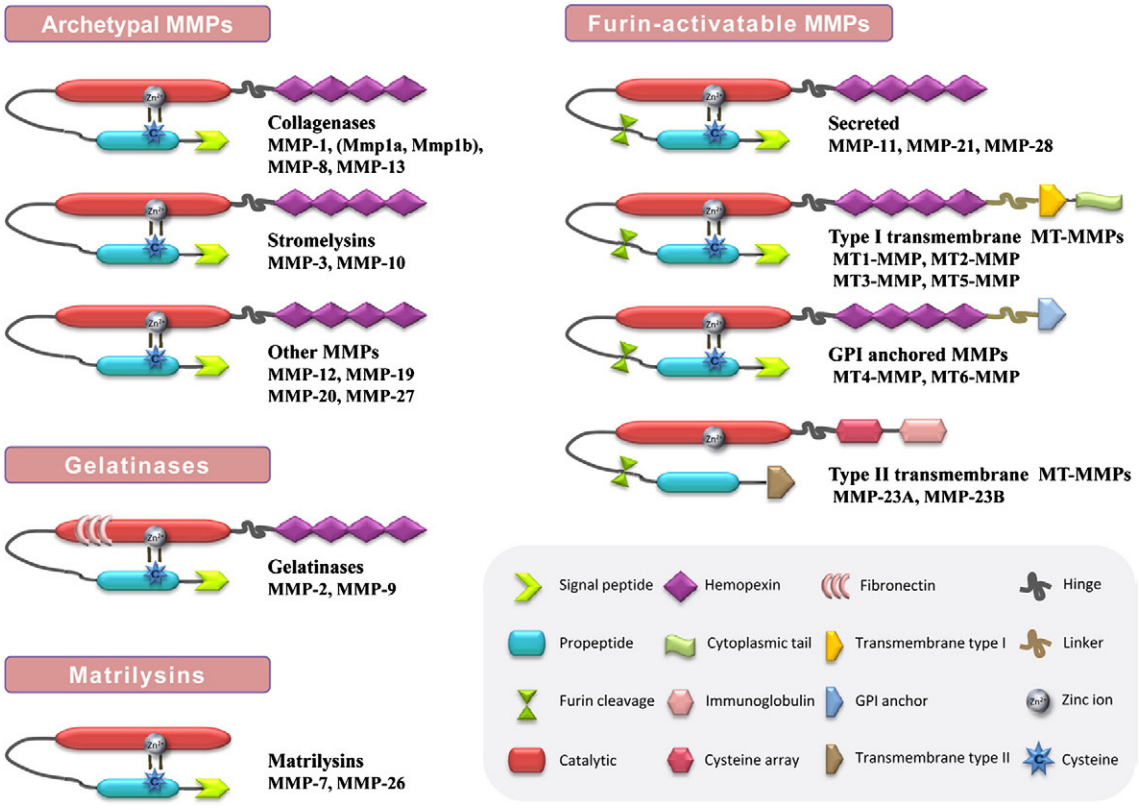

Fig. 1. The mammalian family of matrix metalloproteinases. Structural classification of MMPs based on their domain arrangement.

processes such as mammary gland development, immunity and wound healing [3]. There is another MMP called stromelysin-3 (MMP-11) which shares some structural characteristics with stromelysins but due to the presence of additional features, it is classified into the category of furin-activatable MMPs.

2.1.3. Other archetypal MMPs

There are four matrixins (MMP-12, -19, -20, -27) which cannot be classified in the previous subgroups because of their divergence in sequence and substrate specificity. MMP-12 or metalloelastase is the most potent elastolytic enzyme of the family although, as other MMPs, it can also degrade many other ECM proteins, including aggrecan, fibronectin, laminin, and type IV collagen [15]. MMP-12 is mainly expressed by macrophages [20] but it is also produced by hypertrophic chondrocytes and osteoclasts [21]. MMP-19 was first isolated from human cDNA liver libraries [22] and, afterwards, it was detected in the inflamed synovium from patients with rheumatoid arthritis [23]. This MMP is expressed in a wide variety of human tissues and exhibits a potent degradative activity against components of basement membranes, such as type IV collagen or tenascin, as well as gelatin and aggrecan [24]. MMP-20, also named enamelysin because of its first isolation from a porcine enamel organ, is secreted by ameloblasts and odontoblasts of the dental papila, which are involved in tooth enamel formation [25,26]. MMP-27 was first cloned from a chicken embryo fibroblasts cDNA library [27]. It has been reported that this chicken enzyme is able to degrade gelatin and casein, but little information is available about the activity of its human orthologue, which is highly expressed in B-lymphocytes [28].

2.2. Matrilysins

MMP-7 and MMP-26, also known as matrilysins-1 and -2, are expressed under normal and pathological conditions and have been implicated in the progression of several types of human cancers. Both proteases exhibit the simplest domain arrangement of all MMPs since they lack the carboxy-terminal hemopexin domain [29]. Matrilysins play important roles in the degradation of ECM proteins like type IV collagen, laminin and entactin [15], as well as in the processing of non-ECM proteins. Thus, MMP-7 catalyzes the ectodomain shedding of several cell surface molecules like Fas ligand [30], E-cadherin [31] and syndecan-1 [32], whereas MMP-26 has been reported to be an activator of proMMP-9 under pathological conditions [33]. In addition, matrilysins have been associated with the remodeling of the postpartum uterus and with embryo implantation [34].

2.3. Gelatinases

MMP-2 (gelatinase-A) and MMP-9 (gelatinase-B) are constitutively expressed by many cell types including fibroblasts, keratinocytes, endothelial cells, chondrocytes and monocytes in the case of MMP-2, and alveolar macrophages, polymorphonuclear leukocytes and osteoclasts in the case of MMP-9. These MMPs have an additional fibronectin domain located inside the catalytic domain, which allows the binding and processing of denatured collagen or gelatin [1], suggesting that these enzymes also play a key role in the remodeling of collagenous ECM. Thus, gelatinases degrade a broad spectrum of ECM molecules such as collagen types I, IV, V, VII, X, IX, elastin, fibronectin, aggrecan, vitronectin, laminin [15], but also many non-ECM molecules including pro-TNF-α [13], transforming growth factor (TGF)-β [35], pro-IL-1β, pro-IL-8 and monocyte chemoattractant protein (MCP)-3 [36]. Likewise, these enzymes are able to release or generate several factors with pro- or anti-angiogenic properties [37]. Both gelatinases have been associated with multiple pathologies, including cancer, bone diseases, inflammatory disorders and vascular alterations such as atherosclerosis, aortic aneurysm and myocardial infarction [5].

2.4. Furin-activatable MMPs

All MMPs belonging to this category contain a furin recognition motif inserted between the propeptide and the catalytic domain. This sequence is recognized and cleaved by convertase proteases, providing the basis for furin-dependent activation of latent enzymes prior to secretion. These furin-activatable MMPs include three secreted MMPs, six membrane-type-MMPs and two unusual type II transmembrane MMPs.

2.4.1. Secreted MMPs (MMP-11, -21, and -28)

Unlike the other secreted MMPs, these three furin-activatable enzymes are processed intracellularly by furin-like proteases and secreted as active forms. MMP-11, also known as stromelysin-3, is expressed during embryogenesis, tissue involution and wound healing, and has been proposed to play an important role in cancer [38]. Recent studies have reported that MMP-11 is induced in adipose tissue by cancer cells and contributes to tumor progression through the degradation of collagen VI, suggesting a molecular link between obesity and cancer [39]. MMP-21 is the human orthologue of *Xenopus* XMMP and it has been detected during embryo development in several organs such as kidney, intestine and skin, as well as in various epithelial cancers [40]. MMP-28, also known as epilysin, is expressed in several adult tissues such as testis, lung, heart, colon, intestine, brain and epidermis [41]. MMP-28 is also produced by several carcinomas but its functional role in transformation events has not been clearly defined. In addition, recent data have reported that epilysin may be an important mediator in certain diseases of the central nervous system, such as multiple sclerosis, where it may participate in demyelinating processes [42].

2.4.2. Membrane-type MMPs (MMP-14, -15, -16, -17, -24, and -25)

These MMPs incorporate membrane-anchoring domains that locate them at the cell surface. This feature makes these enzymes as optimal pericellular proteolytic machines, able to control the local environment that surrounds normal and tumoral cells. On the basis of their type of attachment to the plasma membrane, MT-MMPs can be classified into two groups: type I transmembrane MT-MMPs and glycosylphosphatidylinositol (GPI) MT-MMPs [43]. The first group comprises MT1-, MT2-, MT3-, and MT5-MMP (MMP-14, -15, -16 and -24, respectively). These enzymes are characterized by a long hydrophobic sequence followed by a short cytoplasmic tail which is involved in numerous cellular events, such as the activation of MERK/ERK and src-tyrosine kinase pathways or the protein trafficking to discrete regions of the cell surface [44,45]. Moreover, it has been reported that the cytoplasmic domain of MT1-MMP is essential for the regulation of protease activity through a dynamin-mediated process of internalization in clathrin-coated vesicles [46]. Besides their capacity to cleave a variety of substrates including ECM components, these membrane-associated MMPs are the major physiological activators of proMMP-2 [47]. MT-MMPs are expressed by different tissues under normal conditions, but they are also frequently upregulated in tumors. Thus, MT1-MMP expression has been associated with poor prognosis in several types of cancer [48, 49] and its overexpression strongly promotes cellular invasion and experimental metastasis [50,51]. Likewise, MT-MMPs have been involved in the formation of new blood vessels in both physiological and pathological conditions [47]. On the other hand, MT4-MMP and MT6-MMP (MMP-17 and -25, respectively) constitute the second subgroup of membrane-type MMPs which are bound to the cell surface via a GPI-anchor. MT4-MMP is expressed in brain, colon, ovary, testis, and leukocytes [52], whereas MT6-MMP is predominantly expressed in leukocytes, lung and spleen [53]. MT4-MMP has shown a low enzymatic activity against ECM components, and its contribution to ECM turnover seems to be indirectly mediated by its ability to activate aggrecanase-1 (ADAMTS-4) [54]. In contrast, MT6-MMP is able to process gelatin, collagen IV, fibronectin, fibrin, and proteoglycans [55].

Although little is known about the *in vivo* function of these proteases, recent data have detected the expression of MT4-MMP and MT6-MMP in breast and colon cancer, respectively, and, in both cases, these MMPs appear to be associated with tumor growth [56].

2.4.3. Type II transmembrane MMPs (MMP-23A and -23B)

MMP-23A and MMP-23B have identical amino acid sequence, but are encoded by distinct genes in the human genome. These proteases are unique among the matrixin family because they lack the signal peptide, the cysteine-switch motif and the hemopexin domain characteristic of all MMPs, but contain cysteine-array (CA) and immunoglobulin (Ig) domains in their shortened C-terminal tail. Besides, their type II transmembrane domain is located at the N-terminal of the propeptide. Expression analysis has demonstrated that MMP-23 is predominantly produced by ovary, testis, and prostate, suggesting that this MMP may play a specialized role in reproductive processes [57]; however, the *in vivo* functions of this protease still remain undetermined.

3. Gene evolution and genomic organization of MMPs

Comparative genomic analyses have indicated that the impressive diversity characteristic of the family of vertebrate *MMP* genes mainly derives of a series of evolutionary events that occurred during early stages of vertebrate emergence. Nevertheless, these comparative studies have also revealed a more ancient origin for these endopeptidases which predates the emergence of vertebrates. Thus, the identification of plant MMPs orthologues to both vertebrate and invertebrate MMPs clearly supports the proposal of an ancient evolutionary history for these enzymes. Moreover, the finding that MMPs in plants and invertebrates have a closer relationship between them than with vertebrate MMPs, coupled with the absence of hemopexin domains in their structure, suggests that they could be modern representatives of an ancient MMP ancestor, common to the three groups [58]. Likewise, it is tempting to speculate that the earliest forms of MMPs were based on very simple architectural designs conformed by catalytic devices without any ancillary domains. These primitive MMPs were subsequently increasing their complexity through gene fusion events that led to the incorporation of the variety of modules currently exhibited by most family members. It is also remarkable that most *MMP* genes found in vertebrates have an orthologue in *Ciona intestinalis*, one of the closest invertebrate relatives of vertebrates [59]. Thus, these enzymes likely evolved before the divergence between the vertebrate and urochordate lineages (Fig. 2). Prior to the emergence of vertebrates, the *MMP* family had remained relatively stable throughout evolution as assessed by the low number of conserved *MMP* genes present in protostomes (2 *MMPs* in *Drosophila melanogaster*) [60] and urochordates (5 *MMPs* in *C. intestinalis*) [59]. Nevertheless, it is noteworthy the presence in the sea urchin genome of at least 26 *MMP* genes with significant similarity to vertebrate *MMPs*, although they are clustered together and separated from vertebrate MMP groups. These findings suggest that *MMP* genes found in the last common ancestor to vertebrates and echinoderms underwent independent duplication and divergence, following separation of these two groups [61]. Thus, and as discussed above, it appears that *MMP* vertebrate genes were amplified from a common protostome-deuterostome ancestor (Fig. 2).

The major evolutionary event in the generation of the *MMP* gene repertoire of vertebrates was the widespread duplication of pre-existing genes (Fig. 2). In particular, most MMP subfamilies show a further expansion along the early teleost lineage. Nevertheless, it should be noted that both teleost- and tetrapod-specific duplications have occurred after the divergence of both lineages. The expansion in teleosts of *MMP* orthologues related to human *MMP7* and *MMP20*, an evolutionary event likely linked to the continuous teeth replacement in these vertebrates, is remarkable. Similarly, *MT-MMP* genes underwent

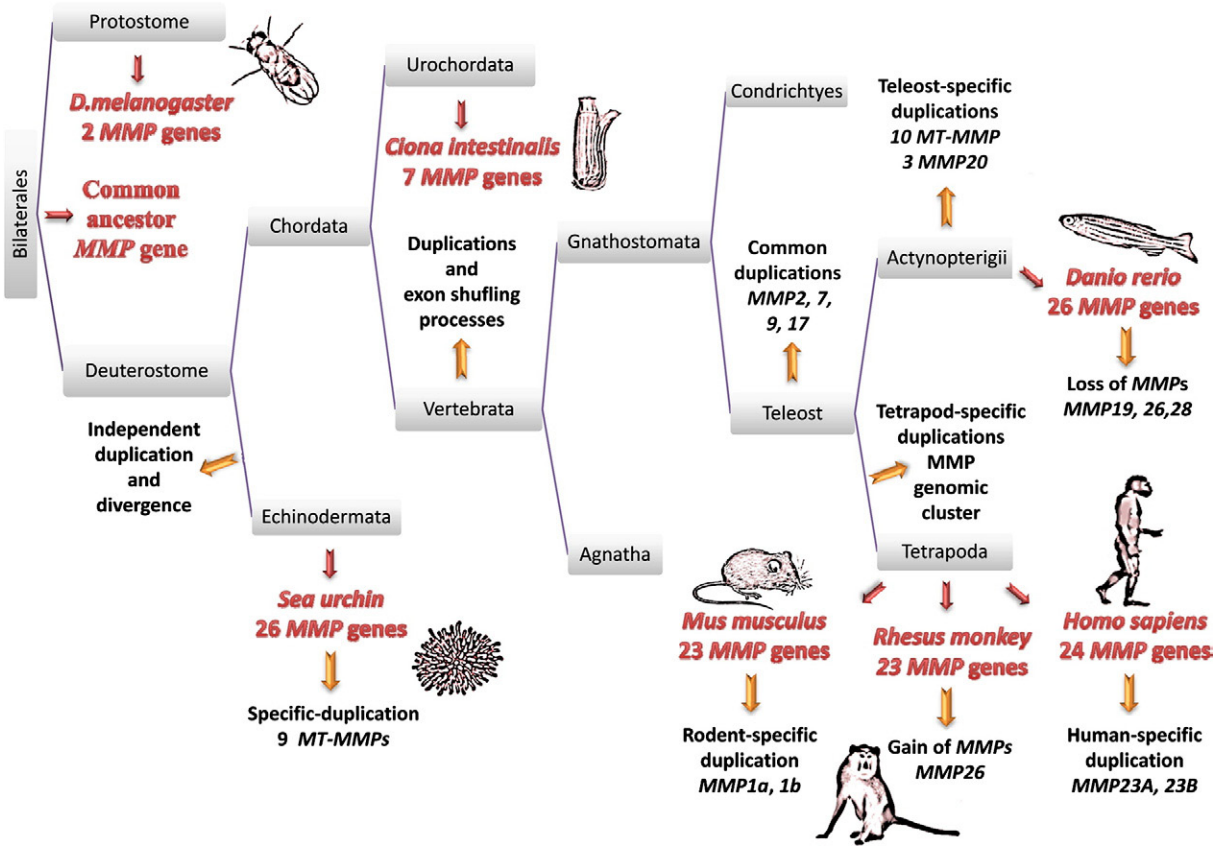

Fig. 2. Evolution of MMPs. Schematic representation of key events occurring throughout the evolutionary history of MMPs.

a greater amplification along teleost lineage, reaching a number of 10 *MT-MMPs* compared to 6 *MT-MMPs* in humans [59]. In contrast, there are no orthologues to human *MMP19*, *-26* and *-28* in the zebrafish genome, although the presence of these genes in some invertebrates strongly suggests that they have been specifically lost in the teleost lineage. Interestingly, there are several tetrapod-specific innovations within the *MMP* gene family. This is the case of *MMP26* which has only been detected in humans and other primates like chimpanzee, orangutan and rhesus monkey genomes, strongly suggesting that this small MMP is the result of a recent evolutionary event circumscribed to the primate lineage [62]. Another remarkable innovation occurred during early evolution of tetrapods is the introduction of CA and Ig-like domains in both human *MMP23* genes, since zebrafish has an orthologue for this gene which lacks these C-terminal domains. Furthermore, the identification of a single *MMP23* copy in rodent and chimpanzee genomes, suggests that the two human copies evolved from a recent duplication event in the human lineage. The presence of two almost-identical genes (*CDC2L1* and *CDC2L2*) adjacent to both human *MMP23* genes provides additional support to the idea that this region has been specifically duplicated in the human lineage [62]. Interestingly, recent studies have also found two putative *MMP23* copies in the *Xenopus* genome. The observation that one of these genes is closer to its human orthologue than to its *Xenopus* paralogue, has suggested that *MMP23* might have duplicated before the separation of amphibians and mammals, an event that was then followed by the loss of one copy of this mammalian gene, which emphasizes the relevance of genomic losses during the evolutionary history of mammals [63,64].

In any case, and beyond these specific changes affecting individual *MMP* genes, the most prominent evolutionary event among those giving rise to the current *MMP* gene families was an extensive gene tandem duplication in the tetrapod lineage (Fig. 2). Accordingly, several members of the *MMP* family have likely evolved from a single gene similar to zebrafish *MMPLe* which, in successive rounds of duplications, led to the formation of a genomic cluster of *MMPs* whose organization is preserved from amphibians to mammals. The sinteny of the common *MMP* genes within this cluster is also conserved among all species of sequenced mammals to date, from platypus to human [65]. This *MMP* cluster is not composed of the same members in the different organisms, as there are species-specific enzymes encoded in the cluster and distinct events involving loss- and gain-of-certain *MMPs* have occurred in the different genomes. Thus, the gene encoding collagenase-4 (*MMP18*) has only been identified in frog, whereas *MMP20* (coding for enamelysin) has not been found in chicken because its lack of teeth makes unnecessary the occurrence of an enzyme involved in enamel formation. Likewise, a rodent-specific duplication event has generated two *MMP1* copies, *MMP1a* and *MMP1b* [2,66]. The human cluster is located at chromosome 11q22 and contains *MMP13*, *MMP12*, *MMP3*, *MMP1*, *MMP10*, *MMP8*, *MMP27*, *MMP20*, and *MMP7* (Fig. 3). The fact that most of these MMPs are able to target protein components of the ECM, coupled with the wide number of ECM components present in most vertebrates, suggests that a co-evolution event could have played a role in this process [67]. As an illustrative example supporting this idea, there are three collagenolytic enzymes encoded in this cluster (MMP-1, MMP-8 and MMP-13) which have preferential activity against one of the three major types of fibrillar collagen: MMP-1 is mainly active against type III collagen, MMP-8 targets type I collagen and MMP-13 preferentially cleaves type II collagen [68]. *MMP* genes are not exclusively clustered in a few regions of the vertebrate genomes as they are widely distributed along the different chromosomes. This is the case of human *MMPs* which are distributed in 10 distinct chromosomes (Fig. 3). It is also noteworthy the localization of functionally related *MMP* genes in different chromosomes, as illustrated for the two gelatinase genes *MMP2* and *MMP9* which map at chromosomes 16 and 20, respectively. Moreover, the sequences encoding the catalytic and hemopexin domains of both gelatinases are not clustered together. Collectively, these observations suggest that these MMPs likely evolved in parallel, indicating that the selection pressure was distinct in the course of the diversification of this family of metalloproteinases [58].

In addition to mechanisms based on gene duplication, the evolution of *MMP* genes has also been driven by exon shuffling and duplication of protein modules to form new arrangements. In this regard, it is well known that proteases link their catalytic domains to a range of specialized functional modules generating an extraordinary diversity of specialized enzymes [69]. In the case of MMPs, some of these modules, including the hemopexin, Ig-like and fibronectin domains, act as ancillary domains that allow these enzymes to interact with other proteins and expand their functional relevance (Fig. 1). Nevertheless, evolution has also progressed in the reverse direction as illustrated by the case of the hemopexin domain which is present in most MMPs, but was specifically lost in both members of the matrilysin subfamily (MMP-7 and MMP-26) [2].

In summary, genomic studies are consistent with the idea that most part of the large complexity currently observed in MMP families of tetrapods arose during early stages of vertebrate evolution. It is also likely that these enzymes first appeared as simple proteins with a catalytic domain that, after several rounds of duplication, gene fusion and exon shuffling events, acquired a more complex structural architecture based on the introduction of additional functional domains of diverse sizes and shapes. The incorporation of ancillary domains, coupled with the subsequent parallel evolution of each member of the family, originated the increasingly specialization of these proteases. The amplification in the number of genes that has occurred from *C. intestinalis* to *H. sapiens*, together with the presence of duplicated genes in paralogous regions of the genome, suggests that one or two rounds of whole genome duplication took place. In the case of mammalian *MMP* genes, these processes of duplication and reorganization have led to a wide distribution of these genes into different chromosomes, although a number of them are clustered in a specific genome region. The large complexity arisen during *MMP* evolution made also necessary the evolutionary incorporation of precise mechanisms of regulation to control the expression and activity of these enzymes. These regulatory mechanisms, which are only partially understood, will be discussed in the next sections of this review.

4. Regulation of *MMP* gene expression

MMP gene expression is primarily regulated at the transcriptional level, which usually results in low basal levels of these enzymes in normal physiology. Most members of the *MMP* family share common *cis*-elements in their promoter sequences, which allow a tight control of cell-specific expression. As a result, *MMPs* are often co-expressed or co-repressed in response to multiple stimuli, including inflammatory cytokines, growth factors, glucocorticoids or retinoids [70]. This response at the transcriptional level occurs several hours after exposure to a stimulus, suggesting that *MMP* promoters are downstream targets within signaling pathways of early response genes, which are induced shortly after cellular stimulation and in the absence of new protein synthesis. These early response genes encode signaling proteins that phosphorylate the different transcription factors, which are then able to bind the promoters of *MMP* genes. These signaling intermediates involved in the activation of transcription factors include the nuclear factor kappa B (NF-κB), the mitogen activated protein kinases (MAPK), the signal transducers and activators of transcription (STAT) and the Smad family of proteins. These intermediates belong to signaling pathways that are activated by a large variety of ligands, such as IL-1β, TNF-α and oncostatin M. The blockade of these signaling pathways by decreasing the synthesis of some downstream mediators, by sequestering the transcription factors to prevent their binding or by inhibiting their phosphorylation, may repress the expression of *MMP* genes [71]. Some of the key transcription-binding

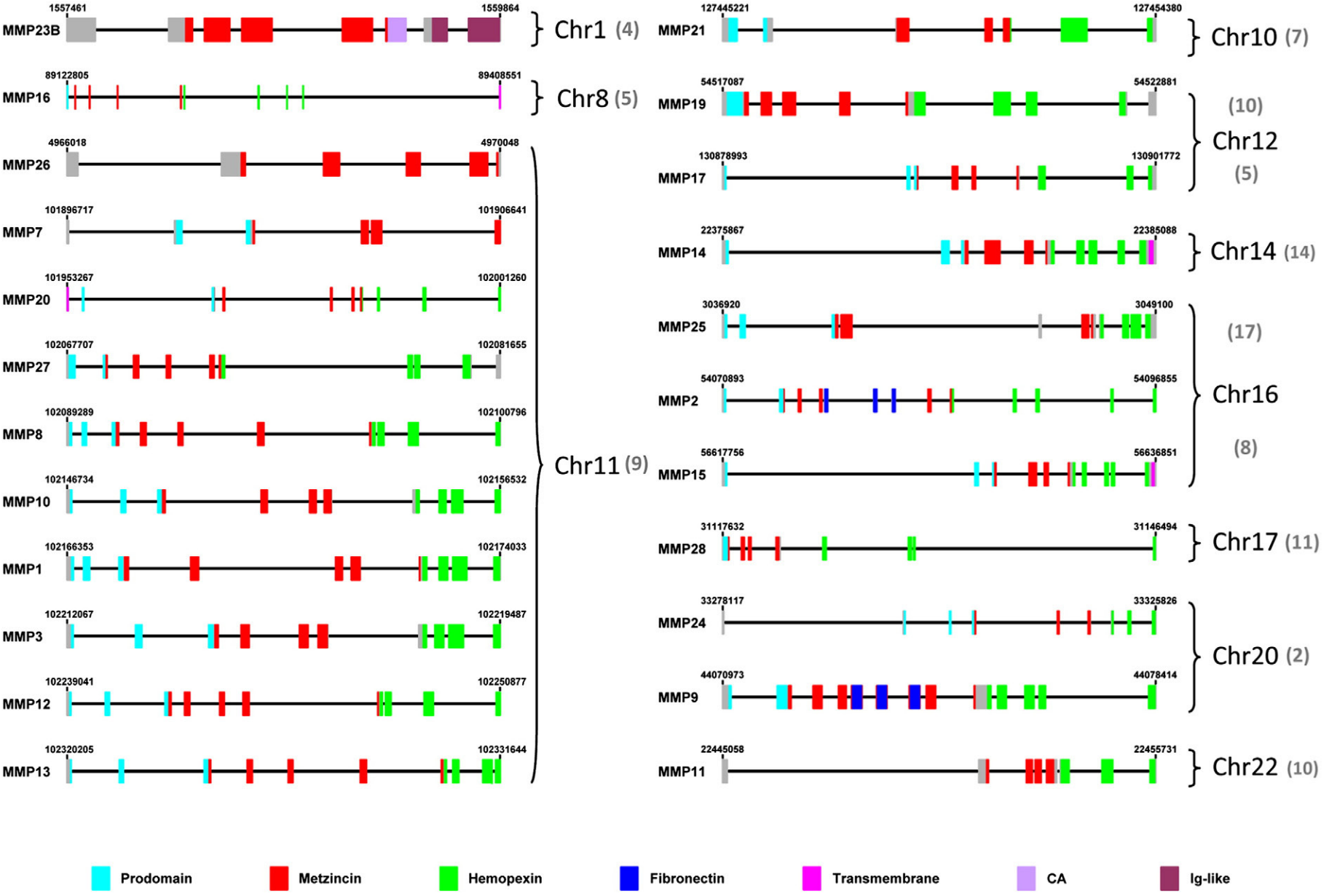

Fig. 3. Genomic organization of human *MMPs*. Exon structure of human *MMP* genes and their chromosomal location in human (black numbers) and mouse (in parentheses). Domains are shown in the indicated code colour.

sites involved in the regulation of *MMP* genes are: the activator proteins (AP) -1 and -2 sites, the polyomavirus enhancer-A binding protein-3 (PEA3) site, the NF-κB site, and the STAT site [72]. Interestingly, *MMPs* that are co-regulated in their expression under certain conditions share several transcription-binding sites in their promoter sequences, whilst functionally related MMPs, such as gelatinases (MMP-2 and -9) or collagenases (MMP-1 and -8), differ greatly in the composition of the *cis*-elements present in their respective promoter regions (Fig. 4).

4.1. AP-1 response elements

The AP-1 site appears to be the major mediator of the regulation of *MMP* genes. Thus, most *MMP* promoters harbor an AP-1 site in the proximal promoter, located close to a typical TATA box (Fig. 4). However, the composition of the AP-1 complex itself, as well as the juxtaposition of transcription factor binding sites, may determine the specificity among different genes [73]. An example of AP-1 regulation can be found in the *MMP1* promoter. Thus, it has been reported that inflammatory cytokines enhance the *trans*-activation of *MMP1* through the MAPK signaling pathway, by increasing the levels of different AP-1 proteins, such as c-*jun*, jun-B and c-*fos* [74]. In this sense, c-Jun has been described to be an independent activator of *MMP1* expression as demonstrated by its capacity to induce minimal *MMP1* promoter activity as a Jun/Jun homodimer. However, jun-B requires the interaction with other members of the AP-1 family, such as c-*fos*, to promote *MMP1* transcription [75]. Likewise, these heterodimers may form ternary complexes with additional transcription factors, thus increasing their binding capacity to the regulatory *cis*-elements [76].

4.2. PEA3 response elements

The PEA3 site binds members of the Ets family of oncoproteins. In several *MMPs*, the PEA3 site is located adjacent to the AP-1 site, and both may act cooperatively to promote MMP production by cancer cells, allowing their migration and invasiveness [77]. In this sense, although PEA3 proteins have been shown to *trans*-activate artificial promoter constructs only containing the PEA3 element, they do not usually dimerize and bind to DNA alone, but prefer to form complexes with other transcription factors, thereby enhancing their effect [78]. Consistently, PEA3 sites are able to bind multiple Ets factors and these proteins contribute to provide the required specificity. For example, Ets1 increases *MMP1* expression through c-Jun, whereas ErgB enhances the *trans*-activation of this promoter only via JunB, and Pu1 represses its induction by both c-Jun and JunB. These examples of functional interaction between Ets and AP-1 factors indicate that *MMP* gene expression may be specifically modulated in situations such as tumor cell growth and invasion, where both types of factors can be simultaneously induced [79, 80].

4.3. NF-κB response elements

The NF-κB pathway is involved in the regulation of several *MMPs*, upon activation by a number of growth factors and cytokines in pathological conditions, such as arthritis, muscular disorders and cancer [81–83]. In addition, this family of transcription factors, including NF-κB1 and 2, RelA, c-Rel, and Rel-B, can interact with other proteins to increase *MMP* expression. Thus, IL-1β-induced *MMP1* gene expression in chondrocytes requires NF-κB homodimers binding to Bcl-3 to activate *MMP1* transcription [84]. Likewise, interaction between juxtaposed sites allows the specific expression of this *MMP* in osteosarcoma and hepatoma cells after its stimulation with TNF-α, which increases the activity of both NF-κB and Sp-1 transcription factors [85].

4.4. STAT response elements

STAT proteins are transcription factors that translocate to the nucleus following tyrosine phosphorylation and dimerization [86]. This family of proteins frequently collaborates with different factors to promote gene-specific expression. Thus, epidermal growth factor (EGF)-mediated-*MMP1* transcription through STAT-3 is stimulated by the binding of c-Jun to the AP-1 element, which is located close to the STAT site [87]. It seems that the stimulation of the STAT pathway is an

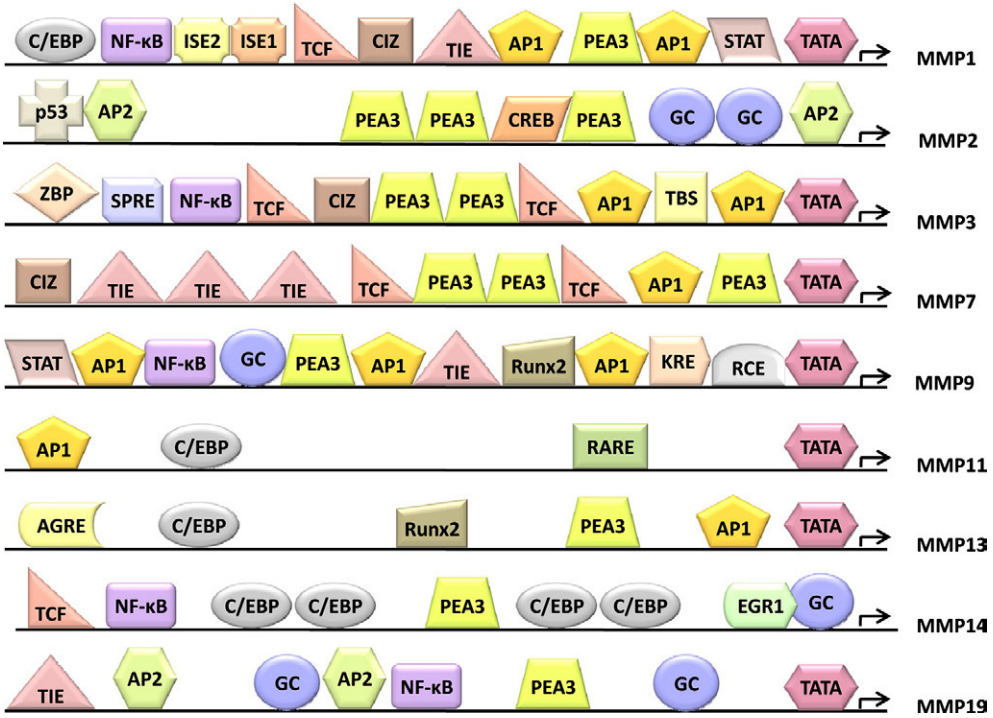

Fig. 4. Regulatory elements in the promoter regions of human *MMP* genes. Transcription start sites are indicated with a bent arrow and the main functionally validated *cis*-elements are represented within boxes. The relative positions of the different binding sites are not drawn to scale.

additional mechanism for increasing the transcription of *MMP1* in pathological conditions [71]. Similarly, a complex composed of c-Jun/Fra-1 and STAT-3 proteins has been shown to bind the promoter-proximal AP-1 site of *MMP9*, thereby confirming the existence of a STAT binding site in juxtaposition with the AP-1 site [88]. Interestingly, activation of STAT proteins does not always induce *MMP* gene expression. Thus, *MMP9* and *MMP13* expression can be repressed as a result of sequestration of co-activators, such as CBP/p300, by STAT proteins, which impair their binding to *cis*-elements on the promoters [89].

4.5. Other regulated cis-elements

MMP7 is regulated by Wnt signaling through the binding of beta-catenin and its partners like Tcf/Lef-1, to its promoter region [90]. Tcf/Lef-1 also synergizes with other factors, particularly those that bind to PEA3 or AP-1 sites, to enhance the expression of *MMP7* in colorectal tumors [91]. Similarly, soluble E-cadherin fragments increase *MMP14* expression in lung cancer cells under the control of the beta-catenin pathway [92]. On the other hand, *MMP13* expression is stimulated by p38 signaling through the recruitment of AP-1 proteins and the chondrocyte/osteoblast-specific transcription factor Runx-2, emphasizing the tissue-specific mechanisms regulating *MMP13* gene expression [93,94]. *MMP9* expression is also regulated by Runx2 binding elements, which agrees with its proposed role in bone remodeling during endochondral ossification [95]. *MMPs* are also regulated by Smads, a small family of co-regulatory proteins that can enhance or inhibit TGF-β-mediated gene expression, providing a mechanism by which TGF-β may play a dual role in the regulation of *MMP* genes during connective tissue remodeling and cancer [96–98]. As mentioned above, TGF-β counteracts the IL-1β-induced *MMP1* transcription through activation of Smad2 and Smad3, which, in turn, are able to block the binding of the CBP/p300 co-activator [99]. Opposite to *MMP1*, *MMP13* gene expression is induced by TGF-β in connective tissue cells, through the activation of Smad3 and the participation of MAPK signaling pathways [96,100]. It is also remarkable that the proximal promoters of several *MMPs* have multiple GC boxes with ability to bind Sp-1 and Sp-3 transcription factors (Fig. 4). Interestingly, some genes such as *MMP2*, *MMP14* and *MMP28*, do not harbor TATA box or other *MMP*-characteristic *cis*-regulatory elements in their proximal promoters, which can explain the fact that they are constitutively expressed and can only be occasionally induced by certain growth factors or cytokines [70]. In summary, the integration of multiple signaling pathways controlling *MMP* transcriptional regulation, provides a wide range of potential interactions between transcription factors, which may explain how tissue specificity is achieved among the different members of the MMP family.

5. Epigenetic regulation of *MMPs*

In general, MMPs have been considered as inducible genes on the basis of a series of experiments that have demonstrated that their expression is transient upon exposure to external stimuli. However, in cancer, both tumor and peritumor cells constitutively express high levels of MMPs, indicating that additional mechanisms are involved in their regulation. Thus, epigenetic mechanisms, such as DNA methylation or histone acetylation, may contribute to modulate both activation and repression of *MMP* gene expression.

Methylation of CpG islands in the promoter region of multiple genes has been widely recognized as an efficient mechanism of repressing transcription. Thus, an inverse correlation between promoter methylation of *MMP9* and expression levels has been found in lymphoma cells, providing evidence that methylation of the promoter region is functionally relevant for *MMP9* gene expression [101]. Likewise, *MMP2* hypomethylation increases its expression and contributes to cancer cell invasiveness and tumorigenesis [102]. Similarly, a colon cancer cell line defective in two key DNA methytransferases (Dmt-1 and Dmt3b) showed increased expression of *MMP3*. In addition, treatment of normal colorectal cells with DNA methyltransferase inhibitors recapitulated this effect, whereas *in vitro* methylation of the *MMP3* promoter suppresses its transcriptional activity. However, this increased expression of *MMP3* appears to be cell-specific since treatment with the same demethylating agent failed to induce *MMP3* transcription in a lymphoma cell line [103].

An additional level of epigenetic control of gene expression derives from post-translational modifications of histones through acetylation processes. Histone acetyl transferases (HAT) are the enzymes responsible for the reversible union of acetyl groups to histones (mainly H3 and H4), leaving the chromatin in a more relaxed state that allows the access of transcription factors and other transcriptional machinery to promoter regions [104]. The effect of the chromatin remodeling in the control of *MMP* expression has been reported for some *MMP* genes. Thus, Yan et al. [105] first showed that MTA1, a component of the NuRD repression complex, binds to the *MMP9* promoter causing the recruitment of histone deacetylase (HDAC) 2 and the decrease of H3/H4 acetylation levels, which finally results in a reduction of DNA accessibility and gene expression. Likewise, *MMP10* expression is repressed as a result of the recruitment of HDAC7–MEF2 complex to the MEF2-binding site present in the *MMP10* promoter [106]. Similarly, the induction of *MMP1* and *MMP13* by IL-1α and oncostatin M is almost completely abolished by two independent HDAC inhibitors [107]. Nevertheless, acetylation *per se* is not sufficient to induce *MMP1* expression in human glioblastoma cells, since treatment with HDAC inhibitors had no effect in *MMP1* mRNA levels despite an increase in local H3 acetylation at the *MMP1* promoter is observed. This finding suggests that *MMP1* transcription requires a prior activation of certain transcription factors, such as c-Jun, c-Fos, TBP, RNAPII and SET9, that bind the *MMP1* promoter and recruit CBP/p300 and RSK2 histone acetyltransferases, finally leading to a permissive state of DNA for transcription initiation [108]. In this sense, the histone acetyltransferase p300 has been recently demonstrated to play a key role in ultraviolet-induced *MMP1* promoter activity [109]. Likewise, analysis of the sequential assembly of transcription complexes on *MMP9* promoter has revealed that, after PMA-induced *MMP9* expression, transcription factors, chromatin-remodeling complexes, and co-activators are recruited to the pre-assembled *MMP9* promoter in a stepwise and coordinated manner, which is dependent on the activation of the MEK-1/ERK and NF-κB signaling pathways. Interestingly, both HDAC1 and HDAC3 are pre-assembled on the *MMP9* promoter as repressive complexes in a basal cell state, being removed upon PMA stimulation [110]. Additional studies have supported the role of transcription factors in the control of gene expression by recruiting chromatin-remodeling complexes to the promoters and the synergy among these co-activators [111,112]. Taken together, these findings show the interconnection between the diverse *MMP* gene regulatory mechanisms operating at the transcriptional level, and confirm that this complexity is increased by cell-specific induction. Nevertheless, further studies will be required to fully understand the epigenetic mechanisms that control *MMP* gene expression.

6. Post-transcriptional regulation of MMPs

Although MMPs are mainly regulated at the transcriptional level, a series of post-transcriptional events have been recently described as relevant mechanisms in the regulation of *MMP* expression. *MMP* transcripts harbor specific sequences in their 5′- or 3′-untranslated regions (UTRs), which are potential targets of different UTR-binding proteins with ability to stabilize or destabilize these mRNAs. Thus, the rat *MMP9* transcript contains several copies of AU-rich elements (ARE) within its 3′-UTR, which are important determinants for RNA turnover [113]. In this regard, it has been reported that IL-1β-induced *MMP9* expression is enhanced by the ATP analog ATPγS through an increase in the binding of the HuR stabilizing factor to the ARE motifs present in the 3′-UTR of the *MMP9* mRNA, providing protection against rapid degradation [114]. Likewise, oncogenic Ras-dependent MERK/ERK signaling maintains

high levels of MMP-9 production in transformed cells, by cooperating with α3β1 integrin which promotes mRNA stability [115]. In contrast, a decline in the *MMP9* mRNA levels has been reported to be caused by nitric oxid in mesangial cells, which is responsible for the reduction of the HuR protein content and its subsequent binding to the 3′-UTR of *MMP9* transcripts [113]. Recent studies have also shown that IL-10 contributes to improve the fibrotic processes that follow acute myocardial infarction, by reduction of *MMP9* expression via repression of HuR protein [116]. Parallel studies have revealed that cortisol induces *MMP13* steady state mRNA in osteoblasts by increasing protein binding to ARE elements in its 3′-UTR region [117].

In addition to mRNA stability, regulation of translational efficiency may be also a mechanism for controlling *MMP* expression. Thus, elevated binding of nucleolin to the 3′-UTR of human *MMP9* mRNA has been observed in fibrosarcoma cells in response to an iron chelator. Nucleolin recruits inactive *MMP9*-mRNA complexes into the rough endoplasmic reticulum, enhancing the efficiency of *MMP9* translation [118]. Likewise, more rapid *MMP9* translation has been described in murine prostate carcinoma cells where an increase in the binding of mRNA to polysomes results in elevated MMP-9 protein levels [119].

Finally, recent experimental work has demonstrated that microRNAs (miRNAs) may also participate in *MMP* regulation. Studies on the role of miRNAs in the regulation of eukaryotic genes have impressively increased over the last few years. These small RNA molecules are capable of negatively regulating gene expression at the post-transcriptional level through either translation repression or degradation of their mRNA targets. Bioinformatic analyses have predicted potential miRNA-binding sites in the 3′-UTR regions of certain *MMPs* [120]; however, to date, only one study has demonstrated that *MMPs* may be direct targets of miRNAs [121]. Indeed, the remaining reports in this field have only shown how *MMP* expression is modulated indirectly through miRNAs that target genes involved in different signaling pathways responsible for *MMP* activation. For instance, *MMP2* expression is upregulated by mir-21 in response to the high levels of phospho-Akt caused by the knockdown of *PTEN* mRNA, which is targeted by this miRNA after myocardial infarction in mice [122]. Similarly, mir-21 downregulates *TIMP3* (tissue inhibitor of metalloproteinase 3), which, in turn, leads to the activation of MMPs and the subsequent promotion of cancer cell invasiveness [123]. Likewise, MMP-13 secretion is modulated by mir-9 in human osteoarthritic processes, through the reduction of TNF-α [124]. Nevertheless, and based on the growing relevance of miRNAs in the regulation of biological processes, it is tempting to speculate that further work in this field will reveal the occurrence of additional miRNAs with ability to target specific MMPs, thus contributing to regulate their functions in the different physiological and pathological contexts in which they are implicated.

7. Mutations in *MMP* genes and human diseases

There are several hereditary disorders caused by autosomal mutations in human *MMP* genes. All of them result from the loss-of-function of the corresponding protease activity, which finally leads to marked deficiencies in the turnover of specific ECM components. The first *MMP* mutation associated with a human inherited disease was identified in two consanguineous Saudi Arabian families with nodulosis–arthropathy–osteolysis syndrome (NAO), an autosomal-recessive form of multicentric osteolysis. A genome-wide analysis had previously identified the chromosome 16 as carrier of the disease gene, and subsequent studies narrowed the critical region close to the gene encoding MMP-2 [125]. To date, several *MMP2* mutations have been reported in three different skeletal disorders, collectively known as inherited osteolysis syndromes and characterized by progressive resorption of bones. The common pathogenic mechanism in the three genetic disorders seems to be the loss of MMP-2 activity, as no detectable MMP-2 enzymatic activity can be found in serum and fibroblasts from patients homozygous for mutations in this gene. Thus, the Y244X mutation described in the above mentioned NAO syndrome introduces a premature stop codon that removes most functional protein domains [125]. The E404K mutation observed in patients with Winchester syndrome changes the key glutamate residue in the catalytic domain of the MMP-2 protein and leads to a complete loss of its peptidase activity [126]. Additionally, two *MMP2* heterozygous mutations have been reported in a patient with Torg syndrome. The first mutation, R101H, has also been found in patients with NAO syndrome and affects a residue adjacent to the key cysteine in the propeptide, thereby resulting in destabilization of the cysteine-zinc interaction. The second mutation, 1957delC, causes a frameshift which creates a truncated nonfunctional protein. In combination, the two mutations should cause the complete loss of MMP-2 activity in this patient with Torg syndrome [127]. Based on the finding that all these mutations abolish MMP-2 proteolytic activity, NAO, Winchester and Torg syndromes have been considered allelic disorders that form a continuous clinical spectrum.

Parallel studies have revealed that another genetic disease of bone metabolism is caused by mutations in a human *MMP* gene. Thus, mutations in the *MMP13* gene are responsible for the Missouri type of human spondyloepimetaphyseal dysplasia (SEMD), an autosomal dominant disorder characterized by defective growth and remodeling of vertebrae and long bones. The F56S missense mutation results in an abnormal intracellular autoactivation and autodegradation of the mutant MMP-13 protein, with the resulting MMP-13 deficiency. Nevertheless, before it is fully proteolytically degraded, the mutant protein intracellularly degrades the MMP-13 product of the wild-type allele, explaining the haploinsufficiency of the gene and thereby, the dominant phenotype of the disorder [128].

Finally, MMP-20 or enamelysin is the third MMP family member that has been implicated in a human inherited disease: autosomal-recessive amelogenesis imperfecta (ARAI). The ARAIs are a group of clinically and genetically heterogeneous disorders that affect enamel development, resulting in abnormalities in the amount, composition, and structure of enamel. To date, at least three different *MMP20* mutations have been reported in families with ARAI. The first identified mutation was found at the 3′-end of intron 6, where AG changed to TG, causing defective splicing events that introduce an upstream translation termination codon in the transcript [129]. Likewise, the W34X mutation is a single nucleotide substitution that generates a stop codon in exon 1 of *MMP20* [130]. The third characterized mutation in this gene (H226Q) changes one of the three-conserved histidine residues in the catalytic domain, thereby destroying the zinc-ligand site required for metal binding [131]. Thus, all *MMP20* mutations described to date lead to complete lack of proteolytic activity on amelogenin, the *in vivo* substrate for enamelysin.

In addition to these interesting cases of *MMP* alterations in inherited human diseases, very recent studies have shown that these genes can also be target of sporadic mutations in cancer. The first indication that *MMPs* could be mutated in cancer derived from the observation that *MMP2* was one of the so-called CAN genes found to be mutated in a small set of breast and colorectal cancers [132]. Further studies have extended the mutational analysis of *MMPs* to other malignant tumors with the finding that some family members including *MMP8*, *MMP14* and *MMP27* are mutated albeit at low frequency in different malignancies including lung carcinomas and melanoma (http://www.sanger.ac.uk/genetics/CGP/cosmic/). These yet unpublished results, together with those recently obtained in the ADAMTS family of metalloproteinases, have supported the innovative proposal that extracellular proteases are direct target of genetic mutations in cancer [6, 133]. Nevertheless, to date, no functional analysis have been reported to validate these preliminary genetic findings and further studies will be necessary to provide functional support to the putative relevance of *MMP* mutations during cancer progression.

8. *MMP* polymorphisms and human disease susceptibility

Polymorphisms in human *MMPs* can modify gene expression by altering the interaction between transcription factors and transcription-

binding sites in the corresponding promoters, resulting in higher or lower transcriptional activity and having dual roles in disease. A number of functional polymorphisms have been identified in the promoters of *MMP* genes and several of them are associated with increased susceptibility to the development of different pathologies and their prognosis (Table 1). Thus, correlations between single nucleotide polymorphisms (SNPs) and cancer susceptibility have been reported for several MMPs.

The first described SNP for *MMP1* is an insertion of a G residue at −1607 in the *MMP1* promoter which creates a binding site for Ets transcription factors adjacent to an AP-1 site located at −1602. The 2G allele leads to higher levels of *MMP1* mRNA and protein in several tumors, and is associated with increased lung and colorectal cancer susceptibility [134,135]. The association between 2G/2G genotype and poor prognosis in patients with melanoma or breast and ovarian carcinomas has also been observed, although data are inconsistent for all tumor types [136–138]. Furthermore, the −1607 1G/2G polymorphism has been implicated in other non-tumor pathologies, such as fibrotic disorders. Thus, *MMP1* is overexpressed in idiopathic pulmonary fibrosis and the frequency of 2G/2G genotype is higher in patients with this disease [139]. The 2G/2G genotype may also contribute to cirrhosis [140].

In the case of *MMP2*, three functional SNPs have been mapped in its promoter region. Two of them are C to T transitions located at −735 and −1306, which abolish Sp1 binding, with the T allele being associated with diminished promoter activity. Interestingly, these SNPs are in linkage disequilibrium with the −1306 T/−735 T haplotype resulting in a lower promoter activity comparing with the single −1306 or −735 T allele haplotypes. High risk of developing lung and esophageal cancer for −1306CC or −735 CC genotype carriers has been reported, suggesting a protective role for −1306 T and −735 T alleles. Importantly, a greater risk of lung and esophageal cancer has been associated with −1306 C/−735C haplotype [141,142]. The third SNP found in the *MMP2* promoter is a G to A transition at −1576, which disrupts estrogen receptor α binding, and also results in lower transcriptional activity [143].

A functional SNP in the *MMP3* promoter has also been described, but in this case, the insertion of an A residue at −1171 generates a 6A allele that enhances the affinity for the repressor ZBP-89 and decreases MMP-3 protein levels. This 6A allele would play a protective role in lung, oral and breast cancer, whereas the 5A *MMP3* allele is linked with an increased risk for these cancers [144–146]. Additional studies have suggested that the 6A/6A *MMP3* genotype is associated with worse rheumatoid arthritis outcome as well as with atherosclerotic processes [147,148]. On the other hand, two polymorphisms have been found in the *MMP7* promoter region, an A to G substitution at position −181 and a C to T substitution at position −153, both of them increasing the promoter activity [149]. A relationship of the −181 G allele with increased susceptibility for gastric, cervical, lung, oral and esophageal cancer has also been described [150–153].

For the *MMP8* gene, three functional SNPs (−799C/T, −381A/G and +17C/G) have been identified. The haplotype with the three less frequent alleles of these SNPs increases *MMP8* promoter activity in trophoblast cells and is associated with higher risk of preterm premature rupture of membranes [154]. Individually, the G allele of the +17 C/G SNP is linked to a decreased risk for lung cancer, and the −799 T to lower susceptibility to metastasis and better survival in breast cancer patients [155,156]. These results are in agreement with the proposal that MMP-8 has antitumor properties [157–159]. With respect to *MMP9*, a polymorphism has been observed in the promoter region located at position −1562. This variant is a C/T transition which leads to a higher promoter activity in the T allele which has been associated with increased susceptibility to atherosclerosis [160], abdominal aortic aneurysm [161] and myocardial ischemia [162]. Additionally, a microsatellite polymorphism of variable number of CA repeats (from 14 to 25 at position −131) and localized immediately adjacent to the proximal AP-1 binding site, has been described to increase the transcriptional activity of the *MMP9* gene in a manner proportional to the number of CA repeats. The *MMP9* microsatellite (≥24 CA repeats) has been associated with a higher risk of bladder cancer invasiveness [163]. This polymorphism has also been associated with susceptibility to a number of conditions, including atherosclerosis [164], multiple sclerosis [165], aneurysmal disease [166], and age-related macular degeneration [167]. For *MMP12*, an A to G substitution at position −82, located in the AP-1 binding site, has been linked to decreased expression *in vitro*. Several studies have also shown that the GG genotype is associated with increased bladder cancer invasiveness and this has been attributed to the loss of putative angiostatic effects of MMP-12 [163]. Finally, it is important to consider that *MMP* polymorphisms may not occur as independent events and could be associated with other polymorphisms in the genome.

9. Transgenic models for functional analysis of MMPs

Over the last two decades, the generation of genetically modified mouse models has become one of the most powerful strategies for studying gene function *in vivo*. Genetic engineering approaches have allowed the modulation of gene expression through gain-of-function (*transgenic*) or loss-of-function (*knock-out*) *in vivo* models. To date, many transgenic and knock-out mice (Table 2) have been generated to analyze the effects of altering MMP activity in a variety of physio-

Table 1
Functional polymorphisms in *MMP* promoters.

Gene	Polymorphism	Promoter activity	Associated pathology	
			Tumor-disease	Non-tumor disease
MMP1	−1607 1G/2G	Higher	↑ Risk: lung [134] and colorectal [135] cancer Poor prognosis: breast [136] and ovarian [137] cancer, cutaneous malignant melanoma [138]	↑ Risk: idiopathic pulmonary fibrosis [139] Poor prognosis: cirrhosis [140]
MMP2	−1575 G/A	Lower	Breast cancer [143] (*in vitro* MCF-7 cells)	
	−1306 C/T	Lower	↓ Risk: esophageal [141] and lung [142] cancer, gastric cardia adenocarcinoma [204], oral squamous cell carcinoma [205]	↓ Risk: lumbar disc disease [206]
	−735 C/T	Lower	↓ Risk: esophageal [141] and lung [142] cancer	
MMP3	−1171 5A/6A	Lower	↓ Risk: lung [144] breast [145] and oral [146] cancer	↑ Risk: atherosclerosis [147] Poor prognosis: rheumatoid arthritis [148]
MMP7	−181 A/G	Higher	↑ Risk: gastric [150], cervical [151] and oral [152] cancer, esophageal squamous cell carcinoma and non-small cell lung carcinoma [153]	Poor prognosis: atherosclerosis [149]
MMP8	−799C/T	Higher	Better prognosis: breast cancer [155]	↑ Risk: preterm premature rupture of membranes (haplotype) [154]
	−381A/G	Higher		↑ Risk: preterm premature rupture of membranes (haplotype) [154]
	+17C/G	Higher	↓ Risk: lung cancer [156]	↑ Risk: preterm premature rupture of membranes (haplotype) [154]
MMP9	−1562 C/T	Higher	↑ Risk: oral cancer [207]	↑ Risk: atherosclerosis [160, 162], abdominal aortic aneurysm [161]
	(CA)n microsatellite	Higher ≥20 CA repeats	↑ Risk: bladder cancer [163]	↑ Risk: carotid atherosclerosis [164], multiple sclerosis [165], cerebral aneurysm [166], age-related macular degeneration [167]
MMP12	−82A/G	Lower	Poor prognosis: bladder cancer [163]	

Table 2
Genetically modified mouse models of MMPs.

Genetically modified mice	Spontaneous phenotype	Pathological-induced phenotype	
		Tumoral	Non-tumoral
Haptoglobin-MMP1	Hyperkeratosis [178]	↑ Skin carcinogenesis [178]	
	Pulmonary emphysema [208]		
TypeIγ-GT-MMP2/cmyc	Chronic kidney disease [209]		
WAP-MMP3	Mammary carcinogenesis [180]		
K5-MMP3*$^{301.24}$		↓ Skin carcinogenesis [210]	
SREP-MMP9			↓ Pulmonary fibrosis [211]
MMTV-MMP14	Mammary carcinogenesis [179]		
Mmp2$^{-/-}$*/RIP-TAg*		↓ Pancreatic carcinogenesis [212]	
Mmp2$^{-/-}$*/ApoE*$^{-/-}$			↓ Atherosclerotic plaques [192]
Mmp3$^{-/-}$*/ApoE*$^{-/-}$			↑ Atherosclerotic plaques [190]
			↓ Aneurism formation [190]
Mmp7$^{-/-}$*/Apc*^{Min}		↓ Intestinal adenomas [213]	
Mmp9$^{-/-}$*/ApoE*$^{-/-}$			↓ Atherosclerotic plaques [191]
Mmp9$^{-/-}$*/K14-HPV16*		↓ Skin carcinogenesis [183]	
Mmp9$^{-/-}$*/RIP-TAg*		↓ Pancreatic carcinogenesis [212]	
Mmp11$^{-/-}$*/MMTV-ras*		↓ Mammary carcinogenesis [184]	
		↑ Number of metastasis [184]	
Mmp13$^{-/-}$*/ApoE*$^{-/-}$			↑ Atherosclerotic plaques [189]
Mmp14$^{-/-}$*/MMTV-PyMT*		↓ Lung metastasis [214]	
Mmp1a$^{-/-}$	No overt phenotype (C. Lopez-Otin, unpublished)		
Mmp2$^{-/-}$	↓ Body size [215]	↓ Tumor growth [216]	↑ Arthritis [187]
	↓ Bone density [172]	↓ Angiogenesis [216]	↓ Resolution of lung allergic inflammation [197]
	Altered mammary branching [170]	↓ Acute hepatitis [217]	
Mmp2$^{-/-}$*/Mmp9*$^{-/-}$			↓ Resolution of lung allergic inflammation [198]
Mmp2$^{-/-}$*/Mmp14*$^{-/-}$	Death at birth [176]		Resistance to EAE [193]
Mmp3$^{-/-}$	Altered mammary branching [170]	↑ Skin carcinogenesis [218]	Impaired contact dermatitis [219]
			↓ Acute hepatitis [217]
			↑ Arthritis [188]
Mmp7$^{-/-}$	↓ Innate intestinal immunity [220]		Impaired tracheal wound repair [222]
	Defective prostate involution [221]		↓ Pulmonary fibrosis [202]
			↓ EAE [195]
Mmp8$^{-/-}$		↑ Skin carcinogenesis [157]	↑ Asthma [199]
		↑ Experimental metastasis [158]	↓ Acute hepatitis [223]
			↓ EAE [194]
Mmp9$^{-/-}$	Delayed growth plate vascularization [171]	↓ Experimental metastasis [225]	↓ Aortic aneurysms [226]
	Defective endochondral ossification [171]		↓ Arthritis [187]
	Delayed myelinization [224]		↓ Acute hepatitis [217]
			Prolonged contact dermatitis [219]
			↓ Colitis [227]
Mmp9$^{-/-}$*/Mmp13*$^{-/-}$	Shortened bones [169]		
Mmp10$^{-/-}$			↑ Pulmonary inflammation and mortality [200]
Mmp11$^{-/-}$			Accelerated neointima formation after vessel injury [228]
Mmp12$^{-/-}$	Delayed myelinization [224]		↓ Pulmonary emphysema [201]
			↑ EAE [196]
Mmp13$^{-/-}$	Bone remodeling defects [168, 169]		↓ Hepatic fibrosis [229]
Mmp14$^{-/-}$	Severe abnormalities in bone and connective tissue [173]		
	Defective angiogenesis [174]		
	Premature death [173]		
Mmp14$^{-/-}$*/Mmp16*$^{-/-}$	Perinatal lethality [177]		
Mmp16$^{-/-}$	Growth retardation [177]		
Mmp17$^{-/-}$	No overt phenotype [230]		
Mmp19$^{-/-}$		↓ Skin carcinogenesis [185]	↑ Induced obesity [185]
		↑ Angiogenesis [186]	
Mmp20$^{-/-}$	Amelogenesis imperfecta [175]		
Mmp24$^{-/-}$			Absence of mechanical allodynia [231]
Mmp28$^{-/-}$			↑ Macrophage recruitment in lung [232]

logical and pathological processes. Likewise, these strategies have provided the opportunity to validate candidate substrates, which are the essential partners to uncover protease function [69].

A total of 17 out of the 23 murine *Mmp* genes have already been knocked-down. However, despite this broad landscape of gene targeting, the vast majority of these constitutive knock-out mice display subtle spontaneous phenotypes (Table 2). Among the three collagenases, only the deficiency in collagenase-3 leads to developmental defects characterized by impaired bone formation and remodeling due, in part, to the lack of appropriate type II collagen cleavage [168, 169]. However, mice deficient in collagenase-1 (C. López-Otín, unpublished data) or collagenase-2 show no overt physiological abnormalities [157]. Likewise, the absence of any of the three stromelysins does not produce major alterations, with the exception of *Mmp3*-null mice whose mammary glands show deficient secondary branching morphogenesis [170]. Deficiency in any of the two gelatinases is also characterized by certain defects in bone biology. Thus, mice deficient in *Mmp9* have delayed long bone growth and development due to impaired vascular invasion in skeletal growth plates [171]. In addition, *Mmp2* deficiency causes disruption of the osteocytic networks and reduced bone density [172]. Interestingly, the most severe phenotype among MMP knock-outs is also associated with defects in skeletal development. In this sense, targeted inactivation of the *Mmp14* gene causes multiple abnormalities in the remodeling of skeletal and connective tissues, as well as defective angiogenesis, leading to premature death by 3–12 weeks after birth

[173,174]. In addition, mice deficient in *Mmp20* have defects in tooth development due to impaired amelogenin processing [175]. Remarkably, these bone abnormalities shown in MMP knock-outs phenocopy the human skeletal syndromes caused by loss-of-function MMP mutations [125,128,129]. The remaining *Mmp*-null mice generated to date show no major physiological alterations, although it is important to emphasize that all available MMP knock-out models are constitutive, thus leading to the possibility of enzymatic compensation as a way to circumvent the absence of the targeted gene. Another possible explanation for the lack of severe phenotypes in *Mmp*-null mice is the enzymatic redundancy among different members of the family, which share many substrates *in vitro*. The recent generation of double MMP mutants has supported this hypothesis, and future studies in this direction may also argue for essential roles of certain MMPs in embryonic development, in addition to their known functions in postnatal tissue remodeling [176,177].

Despite early characterization of MMP knock-outs did not provide major evidence about the biological relevance of this family of proteases, further analyses of these mouse models challenged by a series of pathogenic conditions have revealed the essential contribution of MMPs to a broad number of pathological processes. Among them, over the last 25 years, cancer has been the central disease supporting the promising field of MMPs research. In this sense, the first transgenic mouse models overexpressing different members of the family (Table 2) validated the initial assumption for the contributory effect of these ECM degrading enzymes to tumor progression [178–180], since high levels of MMPs often correlated with poor clinical outcome in cancer patients. However, the generation of new genetically modified animal models has demonstrated that certain MMPs, such as MMP-8 or MMP-12, contribute to tumor suppression [6,157,158,181]. Furthermore, it has also been reported that other MMPs, including MMP-3 [182], MMP-9 [183], MMP-11 [184] or MMP-19 [185,186] play dual roles as pro- or anti-tumorigenic enzymes depending on tissue type and stage of the disease (Table 2). Likewise, gain- or loss-of-function mouse models have allowed the identification of some of the *in vivo* substrates for these enzymes. This is another step forward in the complex relationship between MMPs and cancer, since many non-matrix bioactive molecules, such as growth factor receptors, chemokines, cytokines, apoptotic ligands or angiogenic factors, have been identified as substrates for MMPs [37]. Altogether, these findings illustrate the diversity of MMP functions associated with cancer and provide explanations for the disappointing results of the first clinical trials based on the use of broad spectrum MMP inhibitors [72].

The increasing complexity of the *in vivo* functions of MMPs also affects many other pathological contexts, particularly those involving inflammatory conditions where MMP expression is frequently deregulated [5]. In this sense, genetically modified mice have been essential to demonstrate the relevance of these enzymes in prevalent human pathologies, such as rheumatic, pulmonary, cardiovascular and neurodegenerative disorders. Remarkably, these studies have also shown opposing and unexpected effects among different members of the MMP family on the progression of these diseases (Table 2). Thus, and somewhat surprisingly, mice deficient in *Mmp2* or *Mmp3* develop more severe arthritis than control animals [187,188]. Likewise, deficiency in *Mmp3* or *Mmp13* results in more stable atherosclerotic plaques [189,190]. By contrast, deletion of *Mmp2* or *Mmp9* reduces the formation of the plaques and attenuates cardiac fibrosis after experimental myocardial infarction [191,192]. In neuroinflammatory diseases, such as experimental autoimmune encephalomyelitis (EAE), the murine model of multiple sclerosis, MMPs also show opposite roles. Indeed, certain mouse MMPs, including Mmp-2, Mmp-7, Mmp-8 and Mmp-9 [193–195], contribute to the severity of the clinical symptoms of paralysis whereas others, such as Mmp-12 [196], play protective functions. Similarly, the role of MMPs in respiratory disorders is very complex, since it is not clear yet whether MMPs upregulation is harmful in acute and chronic lung pathologies. Genetically modified mice have demonstrated that lack of *Mmp2*, *Mmp8* or both *Mmp2*/*Mmp9* [197–199] increases the allergic response in a mouse model of asthma due to the failure in clearing inflammatory cells. In this sense, mice deficient in *Mmp10* also show more severe pulmonary inflammation and greater susceptibility to death following bacterial infection [200]. By contrast, deletion of *Mmp7* or *Mmp12* [201,202] resulted beneficial in chronic lung diseases, such as pulmonary fibrosis or emphysema.

Overall, the generation of gain- or loss-of-function mouse models has been essential to demonstrate the complex and even paradoxical roles that MMPs play in physiological and pathological processes [203]. Likewise, these approaches have allowed the *in vivo* validation and identification of specific substrates, providing a better understanding of the mechanisms involved in the development of the diseases. Therefore, it is necessary to continue analyzing and generating the remaining MMP knock-outs, but also to improve the experimental approaches through the creation of new biological models with the crossing of *Mmp*-targeted mice and transgenic animals overexpressing oncogenes that mimic human malignancies. Nevertheless, it is important to emphasize that a constitutive deletion of a gene may not have the same effect as inhibiting the enzyme in a specific spatiotemporal context during the adult life. Thus, additional *in vivo* strategies able to modulate MMPs activity, such as conditional targeting or RNA interference delivery, will be required in order to improve the extrapolation of mice experimentation to therapeutic advances in human diseases.

10. Conclusions and perspectives

The availability of the complete genome sequences of different organisms has recently allowed the identification of their entire protease complements including that of MMPs, and the establishment of novel insights into their evolutionary diversification in all kingdoms of life. The family portrait of this group of metalloproteinases has revealed that, beyond an archetypal design, they exhibit a structural diversity which allows them to participate in multiple biological and pathological functions. Over the last years, there has been a substantial change in our view of these MMP functions. Thus, the initial concept that MMPs were mainly implicated in the demolition of the structural groundwork that supports cells and generates tissue barriers has been replaced by a new vision of these enzymes as signaling scissors controlling multiple processes. The generation of animal models of gain- or loss-of-function for MMPs has been crucial for the identification of some novel and unexpected functions of these metalloproteinases. Likewise, these models have been very useful for the identification of *in vivo* substrates of MMPs and for the establishment of causal relationships between dysregulation of these enzymes and development of different human diseases. Nevertheless, the generation of new animal models is still necessary to evaluate the function of several MMP family members such as MMP-23, MMP-27 or MT6-MMP which are largely uncharacterized yet. Some of these new models will require the generation of double or even triple knock-out models to minimize the putative occurrence of functional redundancy or compensatory mechanisms between members of the MMP family. The generation of conditional mouse models to better understand the role of some enzymes, and especially MT1-MMP, in the diverse conditions in which they are presumably involved is also urgent. These genetic approaches to MMP function will also need to be complemented with strategies derived from the application of RNA interference methods to the MMP field. Genomic studies coupled to functional analysis of promoter regions of *MMP* genes have already provided important information about the molecular mechanisms controlling their expression in health and disease. Nevertheless, it will be necessary to complete these regulatory studies on MMPs and extend them to other levels of control including those based on epigenetic or miRNA-mediated mechanisms, which have acquired a great relevance in many eukaryotic genes but whose influence on the *MMP* gene family is still largely unknown. Likewise, and despite the recent progress in the identification of *MMP* mutations and polymorphisms associated with different genetic

diseases, further functional analysis will be necessary to clarify the relevance of these alterations in the context of the multiple genetic and epigenetic changes detected in complex diseases such as cancer. Hopefully, all these studies will provide new insights into the multiple questions still open in relation to a family of enzymes which had a modest irruption into the protease scene owing to their implication in tail resorption of tadpoles, and now are considered essential mediators of multiple events in all living organisms.

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