Review

The Role of the Metzincin Superfamily in Prostate Cancer Progression: A Systematic-Like Review

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Abstract: Prostate cancer remains a leading cause of cancer-related morbidity in men. Potentially important regulators of prostate cancer progression are members of the metzincin superfamily of proteases, principally through their regulation of the extracellular matrix. It is therefore timely to review the role of the metzincin superfamily in prostate cancer and its progression to better understand their involvement in this disease. A systematic-like search strategy was conducted. Articles that investigated the roles of members of the metzincin superfamily and their key regulators in prostate cancer were included. The extracted articles were synthesized and data presented in tabular and narrative forms. Two hundred and five studies met the inclusion criteria. Of these, 138 investigated the role of the Matrix Metalloproteinase (MMP) subgroup, 34 the Membrane-Tethered Matrix Metalloproteinase (MT-MMP) subgroup, 22 the A Disintegrin and Metalloproteinase (ADAM) subgroup, 8 the A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) subgroup and 53 the Tissue Inhibitor of Metalloproteinases (TIMP) family of regulators, noting that several studies investigated multiple family members. There was clear evidence that specific members of the metzincin superfamily are involved in prostate cancer progression, which can be either in a positive or negative manner. However, further understanding of their mechanisms of action and how they may be used as prognostic indicators or molecular targets is required.

Keywords: metzincin; prostate cancer; Matrix Metalloproteinase; Tissue Inhibitor of Metalloproteinases; A Disintegrin and Metalloproteinase; A Disintegrin and Metalloproteinase with Thrombospondin Motifs

1. Introduction

Prostate cancer (PrCa) is one of the major causes of cancer-related morbidity in men worldwide [1,2]. The early stages of PrCa are androgen-dependent, but during PrCa progression, the tumors become independent of androgens [1,3]. The detection of PrCa is difficult, with symptoms often not being apparent until metastasis has occurred [1]. The use of the Prostate-Specific Antigen (PSA) test is considered a gold standard, yet remains flawed, with a considerable false-positive rate [1,4]. The survival rates for men diagnosed with PrCa have increased, although the treatment options can have significant side effects [1,2]. An increased understanding of the etiology of this disease provides the potential to develop more specific detection methods and/or alternative treatment modalities.

The metzincin superfamily represents a large group of proteases named after a specialized structural component, a zinc ion-binding methionine turn sequence within their catalytic domain [5–7]. The superfamily can be divided into families and subgroups on the basis of other structural and functional features (Figure 1). The Matrixin family consists of the soluble Matrix Metalloproteinase (MMP) and Membrane-Tethered Matrix Metalloproteinase (MT-MMP) subgroups that are principally regulated by the Tissue Inhibitor of Metalloproteinases (TIMP) family, and the Astracin family comprises the BMP1/TLL and Meprin subgroups, whereas the Adamalysin family consists of the A Disintegrin...
and Metalloproteinase (ADAM) and A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTS) subgroups [8]. The metzincins are well-known for their roles in development and disease, largely through remodeling of the extracellular matrix (ECM) [9–13].

Figure 1. Structure of the metzincin superfamily members found in humans and their key regulators. Schematic representation of the structural components of the metzincin subgroups found in humans, grouped by family, along with the Tissue Inhibitor of Metalloproteinases (TIMP) family of regulators.

Members of the metzincin superfamily have been increasingly implicated in cancer progression, including a key role in the metastatic process via their ability to remodel the ECM of tumors [13–15]. However, the exact role varies, with some being tumor-promoting, others having an antitumorigenic function and others seemingly not playing a role [13,14,16–18]. The metzincin superfamily is therefore of interest as a potential source of biomarkers and/or targets for therapeutic interventions, although the results of the clinical trials to date have been discouraging [19]. However, given the pressing need for both biomarkers and therapeutics in PrCa, it is timely to conduct this systematic-like review in order to synthesize the role of the metzincin superfamily in this disease.

2. Results

Extensive database searching was undertaken to identify studies that investigated the role of metzincin superfamily members in PrCa progression, as described in Materials and Methods. This identified 205 articles that are presented in five tables, each covering a specific subgroup of the metzincin superfamily or their regulators—specifically, the Matrixin family subgroups MMPs and MT-MMPs, the TIMPs and the Adamalysin family subgroups ADAMs and ADAMTSs. A number of studies involved more than one of these groups and so are included in more than one table. No articles on the BMP/TLL or Meprin subgroups within the Astracin family were identified.
2.1. Soluble Matrix Metalloproteinases (MMPs)

The most extensively studied metzincin superfamily subgroup are the soluble MMPs, with 138 articles included (Table 1). Generally, MMPs have been demonstrated to act in a protumorigenic manner—particularly, MMP-2, MMP-7 and MMP-9, which have been the most widely studied of this subgroup.

Table 1. Studies on soluble Matrix Metalloproteinases (MMPs) in prostate cancer (PrCa).

| Authors               | Year | MMP          | PrCa Platform | Role                                                                                                                                 |
|-----------------------|------|--------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Aalinkeel et al. [20] | 2004 | MMP-9 *      | Yes—Prostate cell lines | MMP-9 expression increased in metastatic PrCa lines. Enforced expression of MMP-9 increased invasiveness, whereas ablation of expression decreased invasiveness. |
| Aalinkeel et al. [21] | 2011 | MMP-9        | Yes—Prostate cell lines | Enforced expression of MMP-9 increased invasiveness, whereas ablation decreased invasiveness, with no change in migration.            |
| Adabi et al. [22]     | 2015 | MMP-2        | Yes—Prostate cell lines | MMP-2 polymorphism not associated with PrCa risk or degree of metastasis.                                                        |
| Albayrak et al. [23]  | 2007 | MMP-1        | Yes—Prostate cell lines | MMP-1 polymorphism not associated with PrCa risk.                                                                                    |
| Assikis et al. [24]   | 2004 | MMP-9        | Yes—Prostate cell lines | MMP-9 expression low in PrCa.                                                                                                        |
| Babichenko et al. [25]| 2014 | MMP-9*       | Yes—Prostate cell lines | MMP-9 expression negatively correlated with Gleason score and proliferation index.                                                   |
| Baspinar et al. [26]  | 2017 | MMP-9        | Yes—Prostate samples  | MMP-9 expression increased in samples with high metastatic potential scores and staging. Increased MMP-9-positive neutrophils in highly disseminated PrCa correlated with angiogenic potential. |
| Bekes et al. [27]     | 2011 | MMP-9        | Yes—Prostate cell lines | Polymorphism in MMP-7 (but not MMP-1, 2 and 13) correlated with increased PrCa risk. Active forms of MMP-2 and 9 present in late stage PrCa in mouse model, but MMP-3 not expressed and MMP-7 only focal expression. |
| Bialkowska et al. [28]| 2018 | MMP-1, 2, 7 and 13 | Yes—Prostate samples  | MMP-13 expression not changed in PrCa compared to healthy controls. Expression of MMP-9 (but not MMP-2, 3, 7, 13 or 19) negatively correlated with overall, recurrence-free and disease-specific survival. |
| Bok et al. [29]       | 2003 | MMP-2, 3, 7& 9 | Yes—Mice          | MMP-2 expressed significantly in more advanced PrCa tumors, and MMP-9 significantly less. MMP-9 expression in osteoclasts contributed to PrCa tumor growth in the bone through increased angiogenesis. |
| Bonaldi et al. [30]   | 2015 | MMP-13       | Yes—Prostate samples  | Expression of MMPs significantly increased in the epithelium than the stroma, and of MMP-7 and 9 (but not MMP-1) with Gleason score.  |
| Boxler et al. [31]    | 2010 | MMP-2, 3, 7, 9, 13 and 19 | Yes—Prostate samples  | Expression of MMP-2 and 9 negatively correlated with survival. Tumor-derived microvesicles induced MMP-9 expression that correlated with increased migration and resistance to apoptosis. |
| Brehmer et al. [32]   | 2003 | MMP-2 and 9*  | Yes—Prostate samples  | MMP-1 and 9 differentially expressed following co-culture with metastatic PrCa.                                                    |
| Brunini-Cardoso et al. [33] | 2010 | MMP-9        | Yes—Mice and rats  | MMP-1 and 13 expression higher in more aggressive sublines Low serum MMP-2 (but not MMP-9) associated with increased risk of disease progression. |
| Cardillo et al. [34]  | 2006 | MMP-1, 7 and 9* | Yes—Prostate samples  |                                                                                                                                   |
| Carozzi et al. [35]   | 2016 | MMP-2 and 9  | Yes—Prostate samples  |                                                                                                                                   |
| Castellana et al. [36] | 2009 | MMP-2, 3, 7, 9 and 13* | Yes—Prostate cell lines |                                                                                                                                   |
| Coulson-Thomas et al. [37] | 2010 | MMP-1 and 9* | Yes—Prostate cell lines |                                                                                                                                   |
| Daja et al. [38]      | 2003 | MMP-1 and 13* | Yes—Prostate cell lines |                                                                                                                                   |
| De Cicco et al. [39]  | 2008 | MMP-2 and 9*  | Yes—Prostate samples  |                                                                                                                                   |
| Authors                     | Year  | MMP     | PrCa Platform                                   | Role                                                                 |
|-----------------------------|-------|---------|------------------------------------------------|----------------------------------------------------------------------|
| Di Carlo et al. [40]        | 2010  | MMP-2 and 9 | Yes—Prostate samples/urine                     | Active MMP-9 in urine (but not MMP-2) decreased in PrCa versus benign prostatic hyperplasia. |
| Dong et al. [41]            | 2001  | MMP-9   | Yes—Prostate cell lines and mice               | Pro-MMP-9 expression levels enhanced during PrCa co-culture, including in bone implants in mice. |
| dos Reis et al. [42]        | 2009  | MMP-1, 2, 7 and 9 | Yes—Prostate samples              | Polymorphisms in MMP-1, 2 and 9 (but not MMP-7) lower in PrCa versus controls. Polymorphism in MMP-2 more frequent in PrCa, including in higher Gleason scores, compared to those in MMP-9 that were associated with lower scores. |
| dos Reis et al. [43]        | 2010  | MMP-2   | Yes—Prostate samples                           | Polymorphism in MMP-1, 2 and 9 (but not MMP-7) lower in PrCa versus controls. |
| dos Reis et al. [44]        | 2008  | MMP-1, 2, 7 and 9 | Yes—Prostate samples              | Polymorphisms in MMP-1, 2 and 9 (but not MMP-7) lower in PrCa versus controls. |
| Eiro et al. [45]            | 2017  | MMP-2, 9 and 11 | Yes—Prostate samples                  | MMP-2 expression lower and MMP-11 higher in cancer-associated fibroblasts in PrCa. |
| El-Chaer et al. [46]        | 2020  | MMP-1   | Yes—Prostate samples/ Serum                     | Genotype adjusted MMP-1 expression higher in PrCa compared to benign prostatic hyperplasia. |
| Eryilmaz et al. [47]        | 2019  | MMP-2 and 9 | Yes—Prostate samples                         | MMP-2 expression associated with increased PrCa risk. |
| Escaff et al. [48]          | 2010  | MMP-1, 2, 7, 9, 11 and 13 * | Yes—Prostate samples              | Increased expression of MMP-11 and 13 associated with significant probability of biochemical recurrence. |
| Escaff et al. [49]          | 2011  | MMP-1, 2, 7, 9, 11 and 13 * | Yes—Prostate samples              | Expression of MMP-2 in fibroblasts and MMP-9 in mononuclear inflammatory cells associated with PrCa. |
| Escaff et al. [50]          | 2011  | MMP-1, 2, 7, 9, 11 and 13 * | Yes—Prostate samples              | Expression of MMP-9 and 13 in fibroblasts. MMP-13 in tumor cells associated with biological recurrence. |
| Favaro et al. [51]         | 2012  | MMP-2   | Yes—Prostate samples                           | MMP-2 expression increased in periacinar retraction during PrCa. |
| Fernandez-Gomez et al. [52] | 2011  | MMP-1, 2, 7, 9, 11 and 13 * | Yes—prostate samples              | Expression of MMP-2 negatively associated with high tumor grade, MMP-7 expression negatively associated with Prostate-Specific Antigen (PSA), whereas MMP-13 expression positively associated with PSA. |
| Festuccia et al. [53]       | 1996  | MMP-2 and 9 | Yes—Prostate samples/ Serum           | MMP-2 and 9 highly expressed in PrCa. High MMP-9 expression and activity relative to MMP-2 associated with high Gleason grade. Serum MMP-2 higher in patients with PrCa and higher in those with metastasis. |
| Gohji et al. [54]           | 1998  | MMP-2   | Yes—Prostate samples/ Serum                   | MMP-2 consistently secreted by PrCa, whereas MMP-9 secretion sporadic. |
| Gravina et al. [55]         | 2013  | MMP-2 and 9 * | Yes—Prostate cell lines              | MMP-7 expression associated with increased invasiveness. |
| Grindel et al. [56]         | 2014  | MMP-7   | Yes—Prostate cell lines                       | MMP-9 knockdown resulted in increased adhesion and cell spreading. |
| Gupta et al. [57]           | 2013  | MMP-9   | Yes—Prostate cell lines                       | MMP-9 activity increased in malignant PrCa tissue compared to benign. |
| Hamdy et al. [58]           | 1994  | MMP-9   | Yes—Prostate samples                           | MMP-2 and 9 expression higher in PrCa tissue. MMP-7 levels and MMP-7/TIMP-1 ratio higher in advanced PrCa, and correlated with pathological stage, lymph node metastasis, histological differentiation, as well as vascular and lymphatic invasion. |
| Hanqing et al. [59]         | 2003  | MMP-2 and 9 | Yes—Prostate samples              | MMP-2 and 9 expression increased in PrCa versus controls. |
| Hashimoto et al. [60]       | 1998  | MMP-7 (matrilysin) * | Yes—Prostate samples              | MMP-2 and 9 expression increased in PrCa versus controls. |
| Authors                  | Year  | MMP          | PrCa Platform                  | Role                                                                                                                                                                                                 |
|-------------------------|-------|--------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Incorvaia et al. [62]   | 2007  | MMP-2 and 9  | Yes—Prostate samples          | Circulating MMP-9 (but not MMP-2) showed significant correlation with PSA.                                                                                                                                  |
| Jaboin et al. [63]      | 2011  | MMP-7        | Yes—Prostate samples          | MMP-7 polymorphism associated with PrCa recurrence.                                                                                                                                                    |
| Jedroszka et al. [64]   | 2017  | MMP-2, 3 and 9 | Yes—Prostate samples         | Expression of MMP-2, 3 and 9 increased in Gleason grade 8 and 9 tissues.                                                                                                                                   |
| Jernbacken et al. [65]   | 2006  | MMP-2 and 9 * | Yes—Prostate cell lines       | MMP-9 expression increased in PrCa, but MMP-2 expression not detected.                                                                                                                                   |
| Jung et al. [66]        | 1998  | MMP *        | Yes—Prostate samples          | MMP levels decreased but MMP/TIMP ratio increased in PrCa.                                                                                                                                              |
| Jung et al. [67]        | 2003  | MMP-2 and 9  | Yes—Rats                     | Expression of MMP-9 (but not MMP-2) increased in advanced PrCa.                                                                                                                                       |
| Jung et al. [68]        | 1997  | MMP-1 and 3 * | Yes—Prostate samples          | Platelet MMP-2 levels increased in metastatic versus localized PrCa.                                                                                                                                      |
| Jurasz et al. [69]      | 2003  | MMP-2        | Yes—Prostate samples/Serum    | MMP-13 highly expressed in PrCa tissue and associated with Gleason score.                                                                                                                                  |
| Kalantari et al. [70]   | 2019  | MMP-13       | Yes—Prostate samples          | PrCa conditioned medium increased MMP-1 expression in fibroblasts.                                                                                                                                     |
| Kaminski et al. [71]    | 2006  | MMP-1        | Yes—Prostate cell lines       | Serum MMP-2 increased in PrCa and bone metastasis, but not correlated with PSA.                                                                                                                            |
| Kanoh et al. [72]       | 2002  | MMP-2        | Yes—Prostate samples/Serum    | MMP-7 expressed in PrCa.                                                                                                                                                                                  |
| Knox et al. [73]        | 1996  | MMP-7        | Yes—Prostate samples          | MMP-1 and 2 expressed in PrCa, but only MMP-2 expression increased following implantation.                                                                                                               |
| Koshida et al. [74]     | 2004  | MMP-1 and 2  | Yes—Prostate cell lines       | Expression of MMP-2 and 9 in high grade tumors and associated with Gleason score.                                                                                                                       |
| Kuniyasu et al. [75]    | 2000  | MMP-2 and 9  | Yes—Prostate samples          | Increased MMP/E-cadherin ratio correlated with increased stage.                                                                                                                                     |
| Kuniyasu et al. [76]    | 2003  | MMP-2 and 9  | Yes—Prostate samples          | High MMP-9 expression associated with poor prognosis.                                                                                                                                                  |
| Larsson et al. [77]     | 2020  | MMP-9        | Yes—Prostate samples, Prostate cell lines and mice | MMP-9 expressed in PrCa tissue.                                                                                                                                                                           |
| Latil et al. [78]       | 2003  | MMP-9        | Yes—Patient samples           | Plasma MMP-3 (but not MMP-2) increased in PrCa.                                                                                                                                                           |
| Lein et al. [79]        | 1999  | MMP-2 and 3 * | Yes—Prostate samples/Serum    | MMP-9 gene repositioned in PrCa and MMP-2 in both PrCa and hyperplasia.                                                                                                                                  |
| Leshner et al. [80]     | 2016  | MMP-2 and 9 * | Yes—Prostate samples          | MMP-1 promoter polymorphisms not a risk factor for PrCa.                                                                                                                                               |
| Liao et al. [81]        | 2018  | MMP-1        | Yes—Prostate samples/Serum    | Expression of MMP-2 gene decreased and MMP-9 unchanged, but MMP-9 protein higher in cancerous tissue, with no change in MMP-2 protein.                                                                 |
| Lichtinghagen et al. [82]| 2002  | MMP-2 and 9 * | Yes—Prostate samples          | Expression of MMP-2 and 11 decreased, and MMP-9 increased in PrCa, but no correlations with grade, stage or PSA.                                                                                      |
| Lichtinghagen et al. [83]| 2003  | MMP-1, 2, 7, 9 and 11 * | Yes—Prostate samples          | Expression of MMP-2, 7 and 9 increased with PrCa progression. MMP-2 knockout mice showed reduced tumor burden, prolonged survival, decreased lung metastasis, and decreased blood vessel density. Knockout of MMP-7 or MMP-9 did not impact tumor growth or survival but affected blood vessel formation. |
| Littlepage et al. [84]  | 2010  | MMP-2, 7, 9 and 13 * | Yes—Mice                     | MMP-9 expression increased in metastatic cancer.                                                                                                                                                        |
| Liu et al. [85]         | 2017  | MMP-9        | Yes—Prostate samples and prostate cell lines | MMP-2 and 9 secretion, including of the active form of MMP-2, increased in neoplastic tissue.                                                                                                           |
| Lokeshwar et al. [86]   | 1993  | MMP-2 and 9 * | Yes—Prostate samples/Serum    | MMP-2 secretion, including of the active form of MMP-2, increased in neoplastic tissue.                                                                                                         |
Table 1. Cont.

| Authors                     | Year | MMP          | PrCa Platform          | Role                                                                 |
|-----------------------------|------|--------------|------------------------|----------------------------------------------------------------------|
| London et al. [87]          | 2003 | MMP-9        | Yes—Prostate cell lines| Ablation of MMP-9 caused decreased tumor invasion, migration, and growth. |
| Lynch et al. [88]           | 2005 | MMP-7 (matrilysin) | Yes—Rat               | MMP-7 expression increased at tumor/bone interface. MMP-7 knockout mice showed reduced tumor-induced osteolysis. |
| Marin-Aguilera et al. [89]  | 2015 | MMP-9        | Yes—Prostate samples   | MMP-9 upregulated in PrCa and correlated with poorer overall survival.  |
| Maruta et al. [90]          | 2010 | MMP-10       | Yes—Prostate samples   | MMP-10 expression correlated with stage, cell renewal and vascular invasion. |
| Medina-González et al. [91] | 2020 | MMP-2, 9, 11 and 13 * | Yes—Prostate samples | Expression of MMP-2 and 9 increased (but MMP-11 and 13 unchanged) in PrCa. |
| Miyake et al. [92]          | 2010 | MMP-2 and 9  | Yes—Prostate samples   | MMP-2 and 9 expression correlated with stage, recurrence, proliferation, and invasion. |
| Montironi et al. [93]       | 1995 | MMP-2 (type IV collagenase) * | Yes—Prostate samples | MMP-2 protein expression identified in cells in contact with the stroma |
| Montironi et al. [94]       | 1996 | MMP-2 and 3 and 13 * | Yes—Prostate samples   | MMP-2 expression correlated with progression. |
| Morgan et al. [95]          | 2005 | MMP-2, 3 and 13 * | Yes—Prostate samples | Plasma levels of MMP-2 and 9 (but not MMP-13) increased in metastatic PrCa. |
| Moses et al. [96]           | 1998 | MMP-2 and 9  | Yes—Prostate samples   | Active MMP-2 and 9 in urine were independent predictor of organ-confined PrCa. |
| Muñoz et al. [97]           | 2017 | MMP-2 and 9  | Yes—Prostate samples/Ur ine | No difference in urine levels of MMP-2 or MMP-9 species in PrCa. |
| Nabha et al. [98]           | 2006 | MMP-9        | Yes—Mice               | MMP-9 knockout resulted in no difference in tumor incidence, growth or microvascularity. |
| Nagle et al. [99]           | 1994 | MMP-7 (matrilysin) | Yes—Prostate samples   | MMP-7 expression in PrCa located in dilated ducts when inflamed and atrophic glands. |
| Nalla et al. [100]          | 2010 | MMP-9        | Yes—Prostate cell lines| Ablation of MMP-9 reduced migration and invasion and induced apoptosis. |
| Neuhaus et al. [101]        | 2017 | MMP-3, 7, 13 and 20 * | Yes—Prostate samples | Decreased MMP-3/TIMP ratio in PrCa, but other MMPs not altered. |
| Oguic et al. [102]          | 2014 | MMP-2 and 9  | Yes—Prostate samples   | Higher MMP-2 and 9 expression in positive surgical margins. MMP-9 expression associated with biochemical recurrence. |
| Ok Atilgan et al. [103]     | 2020 | MMP-9        | Yes—Patient samples    | MMP-9 expression positively associated with WHO grade, tumor stage, extracapsular extension, positive surgical margin lymphovascular, perineural invasion and decreased disease-free survival. |
| Ouyang et al. [104]         | 2001 | MMP-7 (matrilysin) | Yes—Rats              | MMP-7 expressed in premalignant and malignant tissue. |
| Ozden et al. [105]          | 2013 | MMP-1 and 9 * | Yes—Prostate samples   | MMP-1 expression in tumors correlated with higher grades and Gleason scores. MMP-9 expression in normal glands correlated with low PSA and Gleason scores. |
| Pajouh et al. [106]         | 1991 | MMP-7 (matrilysin) | Yes—Prostate cell lines| MMP-7 expressed in invasive metastatic primary human PrCa. |
| Pang et al. [107]           | 2004 | MMP-13       | Yes—Prostate samples and prostate cell lines | MMP-13 expressed in PrCa. |
| Pettaway et al. [108]       | 2008 | MMP-2 and 9  | Yes—Prostate samples   | MMP-2 and MMP-9/E-cadherin ratio increased at tumor edge and correlated with disease, biochemical recurrence, and pathological stage. MMP-9 expression higher in PrCa patients related to Gleason score and age, but not PSA, metastasis, or survival. |
| Pouyanfar et al. [109]      | 2016 | MMP-9        | Yes—Prostate samples   | Enforced MMP-7 expression led to increased invasion. |
| Powell et al. [110]         | 1993 | MMP-7 (matrilysin) | Yes—Prostate cell lines and mice | |
| Authors                  | Year | MMP        | PrCa Platform | Role                                                                                                                                 |
|--------------------------|------|------------|---------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Prior et al. [111]       | 2010 | MMP-2      | Yes—Prostate samples | Increased MMP-2 levels in urine/blood associated with PrCa progression.                                                                 |
| Reis et al. [112]        | 2012 | MMP-2 *    | Yes—Prostate samples | MMP-2 expression reduced in PrCa samples but increased in higher grades.                                                                 |
| Reis et al. [113]        | 2015 | MMP-2&9 *  | Yes—Prostate samples | MMP-2 and 9 expressed in most PrCa but no prognostic value.                                                                                                                                  |
| Reis et al. [114]        | 2011 | MMP-9 *    | Yes—Prostate samples | Higher MMP-9 expression associated with increased PSA and recurrence, but not Gleason score.                                                                                                 |
| Riddick et al. [115]     | 2005 | MMP-2, 10, 23 and 25 * | Yes—Prostate samples | Increased expression of MMP-10 and 25, but MMP-2 and 23 decreased in PrCa.                                                                                                                    |
| Ross et al. [116]        | 2003 | MMP-2 *    | Yes—Prostate samples | MMP-2 expressed in more advanced PrCa and correlated with prognostic variables.                                                                                                               |
| Sakai et al. [117]       | 2005 | MMP-2 and 9 | Yes—Prostate samples | Increased expression of MMP-2 and 9 in peripheral zone cancers compared to transitional zone.                                                                                                 |
| San Francisco et al. [118]| 2004 | MMP-9      | Yes—Prostate cell lines | MMP-9 expression not changed in PrCa.                                                                                                                                                    |
| Sauer et al. [119]       | 2004 | MMP-2 and 9 | Yes—Prostate cell lines and Serum | MMP-9 serum levels increased in PrCa patients and correlated with grade, but tissue MMP-9 activity not related to stage or grade. MMP-2 activity correlated with disease progression. |
| Schäfer et al. [120]     | 2012 | MMP-9      | Yes—Prostate cell lines and mice | Enforced MMP-9 expression enhanced tumor regression and impacted metastasis. MMP-9 polymorphism and increased expression associated with PrCa, with polymorphism related to pathological stage and prognostic group, and expression with survival. |
| Schveigert et al. [121]  | 2013 | MMP-9      | Yes—Prostate samples | MMP-9 polymorphism associated with developing PrCa.                                                                                                                                          |
| Sehgal et al. [122]      | 1998 | MMP-9      | Yes—Mice | Ablation of MMP-9 reduced metastatic potential. Expression of MMP-1 (but not MMP-2 or MMP-9) decreased in more metastatic PrCa.                                                                     |
| Sehgal et al. [123]      | 2003 | MMP-1, 2 and 9* | Yes—Prostate cell lines | MMP-9 expression not associated with Gleason score 4 and 5.                                                                                                                                     |
| Serretta et al. [124]    | 2018 | MMP-3      | Yes—Prostate samples | MMP-9 polymorphism associated with increased risk of advanced PrCa.                                                                                                                             |
| Sfar et al. [125]        | 2007 | MMP-9      | Yes—Prostate samples | MMP-9 polymorphism associated with increased risk of developing PrCa.                                                                                                                           |
| Sfar et al. [126]        | 2009 | MMP-9      | Yes—Prostate samples | Increased MMP-9 expression in PrCa cells co-cultured with dermal lymphatic microvascular endothelial cells.                                                                                      |
| Shah et al. [127]        | 2016 | MMP-9      | Yes—Prostate cell lines | MMP-2 polymorphism not associated with PrCa risk.                                                                                                                                             |
| Shajarehpoo Salavati et al. [128] | 2017 | MMP-2      | Yes—Prostate sample | MMP-2 polymorphism associated with PrCa risk.                                                                                                                                                 |
| Shi et al. [129]         | 2017 | MMP-9      | Yes—Prostate samples/Urine | MMP-9 detected in urine of PrCa patients.                                                                                                                                                      |
| Silva et al. [130]       | 2015 | MMP-2      | Yes—Prostate samples | Increased MMP-2 expression in reactive stroma. MMP-2 polymorphism associated with PrCa risk but not staging.                                                                                   |
| Srivastava et al. [131]  | 2012 | MMP-2 *    | Yes—Prostate samples | MMP-2 expression increased in higher PrCa grades. MMP-2a expressed in glandular epithelial cells and increased in PrCa samples with high Gleason score.                                           |
| Stearns et al. [132]     | 1996 | MMP-2      | Yes—Prostate samples and prostate cell lines | MMP-2 localized to malignant cells, with increased MMP-2/TIMP-2 ratio associated with high grade and stage.                                                                                   |
| Stearns et al. [133]     | 1996 | MMP-2      | Yes—Prostate samples | Serum MMP-7 level significantly higher in docetaxel-resistant PrCa and associated with poor survival.                                                                                         |
| Still et al. [134]       | 2000 | MMP-2 *    | Yes—Prostate samples | MMP-2 expression increased in higher PrCa grades.                                                                                                                                             |
| Szarvas et al. [135]     | 2018 | MMP-7 (matrilysin) | Yes—Prostate samples | MMP-2 polymorphism not associated with PrCa risk. MMP-2a expressed in glandular epithelial cells and increased in PrCa samples with high Gleason score.                                           |
Table 1. Cont.

| Authors          | Year | MMP    | PrCa Platform               | Role                                                                 |
|------------------|------|--------|----------------------------|----------------------------------------------------------------------|
| Trudel et al.    | 2008 | MMP-2 *| Yes—Prostate samples       | MMP-2 expression in basal epithelial cells and stromal cells associated with shorter disease-free survival. |
| Trudel et al.    | 2003 | MMP-2  | Yes—Prostate samples       | MMP-2 expression in malignant cells associated with disease-free survival. |
| Trudel et al.    | 2010 | MMP-9  | Yes—Prostate samples       | MMP-9 expression correlated with Gleason score but not disease-free survival. |
| Tsuchiya et al.  | 2009 | MMP-1  | Yes—Prostate samples       | MMP-1 promotor polymorphisms (and increased expression) associated with pathological stage but not PrCa susceptibility or progression. |
| Upadhyay et al.  | 1999 | MMP-2 *| Yes—Prostate samples       | MMP-2 localization altered in PrCa. MMP-2 (but not MMP-9) expressed in malignant cells. |
| Vallbo et al.    | 2005 | MMP-2 and 9 | Yes—Rat               | MMP-1 expression significantly increased in PrCa and associated with higher Gleason score, metastasis and pathological stage, as well as reduced overall and recurrence-free survival. |
| Wang et al.      | 2014 | MMP-1  | Yes—Prostate samples       | MMP-1 expression significantly increased in PrCa and associated with higher Gleason score, metastasis and pathological stage, as well as reduced overall and recurrence-free survival. |
| Wiesner C        | 2007 | MMP-9  | Yes—Prostate cell lines and mice | Epithelial cells secreted little MMP-2 or MMP-9, whereas pro-MMP-2 (but not MMP-9) secreted by stromal cells. |
| Wilson et al.    | 2002 | MMP-2 and 9 | Yes—Prostate samples and prostate cell lines | Expression of MMP-2 and 9 increased in malignant samples. |
| Wilson et al.    | 1993 | MMP    | Yes—Prostate cell lines and mice | MMP isoforms differentially altered in PrCa. Increased expression of MMP-2&9 in high grade samples. |
| Wood et al.      | 1997 | MMP-2 and 9 * | Yes—Prostate samples | MMP-7 expression elevated in PrCa. |
| Xie et al.       | 2016 | MMP-7 (matrilysin) | Yes—Mice               | MMP-2 polymorphisms increased in PrCa patients. MMP-2 expressed in PrCa, but not altered across different types. |
| Xu et al.        | 2010 | MMP-9  | Yes—Prostate cell lines and mice | Expression of MMP-9 (but not MMP-2) increased in malignant samples. |
| Yaykašli et al.  | 2014 | MMP-2 *| Yes—Prostate samples       | Expression of MMP-2 and 9 increased in PrCa. Expression of MMP-1 increased in more metastatic lines. Ablation of MMP-1 decreased invasion and migration. Expression of MMP-26 (but not MMP-9) increased in PrCa. Blocking of either reduced invasion. |
| Zellweger et al. | 2005 | MMP-2  | Yes—Prostate samples       | Expression of MMP-1 increased in more metastatic lines. Ablation of MMP-1 decreased invasion and migration. MMP-2 expressed in stromal cells and MMP-7 expressed in epithelial cells. Differential expression between cell lines. |
| Zhang et al.     | 2002 | MMP-2 and 7 * | Yes—Prostate samples and prostate cell lines | Expression of MMP-9 (but not MMP-2) increased in malignant samples. |
| Zhang et al.     | 2004 | MMP-2 and 9 | Yes—Prostate samples and prostate cell lines | MMP-1, 2 and 9 expression significantly higher in PrCa. MMP-2 expression correlated with TMN grade and Gleason score. |
| Zhang et al.     | 2008 | MMP-2 and 9 | Yes—Prostate samples and prostate cell lines | MMP-2 expression enhanced when PrCa co-cultured. |
| Zhao et al.      | 2018 | MMP-1  | Yes—Prostate cell lines    | Expression of MMP-1 increased in more metastatic lines. Ablation of MMP-1 decreased invasion and migration. Expression of MMP-26 (but not MMP-9) increased in PrCa. Blocking of either reduced invasion. |
| Zhong et al.     | 2008 | MMP-1, 2 and 9 | Yes—Prostate samples | MMP-2 expression enhanced when PrCa co-cultured. |
| Zhu et al.       | 1999 | MMP-2 and 9 | Yes—Prostate cell lines   | MMP-2 expression enhanced when PrCa co-cultured. |

* Included in at least one other table.

The strongest evidence for protumorigenicity relates to MMP-9. Multiple publications have identified an increased expression in PrCa [59,61,78,83,109,113,129,153,156], including positive associations with more advanced PrCa [67,75,84,103] and, specifically, with higher grade/stage [26,34,53,92,138] and enhanced metastatic properties [20,21,58,65,85,146], as
well as increased recurrence [92,102] and poorer prognosis [35,77,89]. Others show no association [24,47,48,52,118], and a small number show negative associations [25,31,40] with PrCa progression, indicating that MMP-9 is not universally important. However, functional studies serve to confirm its significant role, particularly in PrCa spreading, with MMP-9 ablation repeatedly shown to decrease its invasion and/or migration [57,87,100,148]. Interestingly, no differences in tumorigenesis were observed in a mouse MMP-9 knockout model [98], suggesting that expression within the tumor is important for this enzyme.

Many studies similarly showed an increased expression of MMP-2 in PrCa [49,53,59,61,62,91,150,153,156]. This also generally correlated with more advanced PrCa [32,75,84,92,94,119,132,133,141,146], including metastatic disease [54,69], as well as increased risk [47] and decreased survival [35,52,136]. In contrast, other publications showed no association [67,79,97] or a negative association [52,82,83,112,115]. In this case, a mouse MMP-2 knockout model exhibited reduced tumor burden [84], suggesting expression within the tumor is not necessarily essential for MMP-2.

Several publications have also demonstrated increased MMP-7 in PrCa [34,56,73,84,99,104,147,151], including correlations with metastasis [106] and chemoresistance [135]. However, others have identified no change in expression in PrCa [42] or, indeed, a negative correlation with disease [52], including when examining the levels of the active form of this enzyme [29,101]. For MMP-7, gene polymorphisms may be important in terms of the risk of the disease [28] and recurrence [63], while the relative levels of the inhibitors may also influence the impact of MMP-7 on PrCa progression [60]. An enforced expression of MMP-7 in PrCa cells has been shown to mediate an increased invasion [110], while a mouse MMP-7 knockout model exhibited reduced tumor-induced osteolysis [88], indicating the source of this enzyme may not be critical.

For other MMPs, there was some limited evidence that they also may play a cancer-promoting role. This includes the association of expression with PrCa for MMP-3 [64,68,79,101], MMP-10 [90,115], MMP-23 [115] and MMP-25 [115], as well as MMP-26, for which some functional evidence also exists [155].

Finally, other MMPs appear to be less significantly involved in PrCa. Thus, most studies reported no association between PrCa and MMP-1 in terms of the expression [31,48,52,68,74,83], activation [29] or polymorphism [28,44,60,63,64,68,74,81,88,90,110,155]. However, other studies have reported associations between expression and PrCa [46], including grade/stage [105,139] and metastatic properties, with MMP-1 ablation shown to reduce invasion [154]. Similarly, MMP-13 expression has typically not been associated with PrCa [31,48,84,91,95], but some studies do provide evidence of this [50,52,70]. Publications investigating MMP-11 also range from identifying no correlation [91] to a negative correlation [83] to a positive correlation [45,48], while the only study on MMP-23 points toward a negative correlation [115].

2.2. Membrane-Tethered Matrix Metalloproteinases (MT-MMPs)

Thirty-four articles were identified detailed the role of membrane-type MMPs in PrCa (Table 2). The majority of these related to MT1-MMP (formerly MMP-14). There were conflicting reports about whether MT1-MMP was upregulated [38,65,158] or downregulated [78,112] in PrCa, which may be partially explained by studies describing its expression as being variable across the stages of PrCa progression [67,83,101,140], with PrCa cells eliciting altered MT1-MMP expression in surrounding noncancer cells [34,36,37,151]. However, functional studies have consistently shown MT1-MMP to contribute to a more invasive/migratory phenotype [158–162] and, potentially, tumor growth [163,164].
| Authors                  | Year | MT-MMP                  | PrCa Platform                                                                 | Role                                                                                           |
|-------------------------|------|-------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Aalinkeel et al. [20]   | 2004 | MT1- and MT4-MMP *      | Yes—Prostate cell lines                                                      | MT4-MMP expression higher in metastatic PrCa cell lines.                                       |
| Bair et al. [159]       | 2005 | MT1-MMP                 | Yes—Prostate samples and prostate cell lines                                  | Ablation of MT1-MMP decreased migration and invasion.                                          |
| Bonfil et al. [163]     | 2007 | MT1-MMP                 | Yes—Prostate samples and prostate cell lines                                  | MT1-MMP expressed in PrCa bone metastasis. Enforced expression of MT1-MMP enhanced tumor growth and osteolysis. |
| Cao et al. [158]        | 2008 | MT1-MMP                 | Yes—Prostate cell lines                                                      | MT1-MMP expression increased in PrCa. Enforced expression of MT1-MMP induced epithelial to mesenchymal transition associated with metastatic ability. |
| Cardillo et al. [34]    | 2006 | MT1-MMP *               | Yes—Prostate samples                                                          | MT1-MMP expression increased in epithelial and stromal tissues in PrCa.                        |
| Castellana et al. [36]  | 2009 | MT1-MMP *               | Yes—Prostate cell lines                                                      | MT1-MMP protein levels high in PrCa microvesicles.                                            |
| Cheng et al. [165]      | 2017 | MT6-MMP                 | Yes—Prostate samples/Serum                                                    | MT6-MMP expression upregulated in serum and tissue in PrCa.                                    |
| Chu et al. [166]        | 2006 | MT3-MMP                 | Yes—Prostate cell lines and mice                                              | MT3-MMP expressed in PrCa tumors, especially in lymph node metastases. MT1-MMP expressed in the stromal cells during co-culture with metastatic PrCa cells, extending into the ECM MT1-3-MMP (but not MT2-MMP) expressed highly, particularly processed versions, in aggressive PrCa cell lines. MT1-MMP expression increased in more invasive PrCa subline. High levels of MT3-MMP associated with advanced tumor stage and metastasis. Ablation of MT3-MMP decreased migration. MT1 and 5-MMP expressed in most PrCa cell lines and prostate tissue, with variable expression in metastatic lines and malignant tumors, with no correlation to tumor classification. MT6-MMP expression up-regulated in high grade prostate intraepithelial neoplasia but decreased with PrCa progression, with MT6-MMP expressing cells prone to apoptosis. |
| Coulson-Thomas et al. [37]| 2010 | MT1-MMP *               | Yes—Prostate cell lines                                                      | MT1-MMP expression increased in more invasive PrCa subline.                                    |
| Daja et al. [38]        | 2003 | MT1-, MT2- and MT3-MMP *| Yes—Prostate cell lines                                                        | MT3-MMP expression upregulated in serum and tissue in PrCa.                                    |
| Jennbacken et al. [65]  | 2006 | MT1-MMP *               | Yes—Prostate cell lines                                                      | MT1-MMP expression increased in more invasive PrCa subline.                                    |
| Jiang et al. [167]      | 2017 | MT3-MMP                 | Yes—Prostate samples and prostate cell lines                                  | MT1-MMP expression increased in more invasive PrCa subline.                                    |
| Jung et al. [168]       | 2003 | MT1- and MT5-MMP        | Yes—Prostate samples and prostate cell lines                                  | MT1-MMP expression increased in more invasive PrCa subline.                                    |
| Khamis et al. [169]     | 2016 | MT6-MMP                 | Yes—Prostate samples and prostate cell lines                                  | MT1-MMP expression increased in more invasive PrCa subline.                                    |
| Latil et al. [78]       | 2003 | MT1-MMP *               | Yes—Patient samples                                                           | MT1-MMP expression decreased in PrCa tissue. MT6-MMP expression increased in high-grade prostatic intraepithelial neoplasia but reduced in invasive cancer. |
| Lee et al. [170]        | 2006 | MT6-MMP                 | Yes—Prostate samples                                                          | MT1-MMP expression observed in PrCa, but no correlation with grade, stage, or serum PSA.        |
| Lichtinghagen et al. [83]| 2003 | MT1-MMP *               | Yes—Prostate samples                                                          | MT1-MMP expression observed in PrCa, but no correlation with grade, stage, or serum PSA.        |
| Lin et al. [171]        | 2013 | MT3-MMP                 | Yes—Prostate samples                                                          | MT3-MMP single nucleotide polymorphisms associated with PrCa aggressiveness.                   |
| Lin et al. [172]        | 2016 | MT3-MMP                 | Yes—Prostate samples                                                          | MT3-MMP expression associated with PrCa aggressiveness.                                         |
Table 2. Cont.

| Authors                  | Year | MT-MMP       | PrCa Platform       | Role                                                                 |
|--------------------------|------|--------------|---------------------|----------------------------------------------------------------------|
| Littlepage et al. [84]   | 2010 | MT1-MMP *    | Yes—Mice            | Broad MMP inhibitor reduced tumor burden. MT1-MMP ablation reduced susceptibility to immune-mediated killing. MT1-MMP expression increased in more metastatic PrCa lines. MT1-MMP expression decreased in PrCa but increased in benign prostatic hyperplasia. |
| Liu et al. [173]         | 2010 | MT1-MMP      | Yes—Prostate cell lines | MT1-MMP ablation reduced susceptibility to immune-mediated killing. |
| Nagakawa et al. [174]    | 2000 | MT1-MMP      | Yes—Prostate cell lines | MT1-MMP expression increased in more metastatic PrCa lines. MT1-MMP expression decreased in PrCa but increased in benign prostatic hyperplasia. |
| Neuhaus et al. [101]     | 2017 | MT1-MMP *    | Yes—Prostate samples | Enforced MT1-MMP expression increased invasion. |
| Nguyen et al. [161]      | 2011 | MT1-MMP      | Yes—Prostate cell lines | MT1-MMP expression decreased in PrCa but increased in benign prostatic hyperplasia. |
| Reis et al. [112]        | 2012 | MT1-MMP *    | Yes—Prostate samples | MT1-MMP under-expressed in PrCa. MT1-MMP expression increased invasion. MT5-MMP expression correlated positively with Gleason score. MT1-MMP expression enhanced tumor migration. |
| Riddick et al. [115]     | 2005 | MT2-, MT5- and MT6-MMP * | Yes—Prostate samples | Enforced MT1-MMP expression enhanced tumor migration. MT1-MMP expression in apical regions in PIN and PrCa. Ablation of MT1-MMP enhanced cell migration. MT1-MMP localized in benign glands changing to cytoplasmic staining and then heterogenous as PrCa progressed. Increased vasculature when MT1-MMP co-localized with MMP-2. |
| Sabbota et al. [160]     | 2010 | MT1-MMP      | Yes—Prostate cell lines | MT1-MMP expression increased in tumor cells. Enforced expression increased tumor growth in mice. MT1-MMP inhibition decreased cell migration, but not growth. MT1 and 3-MMP expressed in stromal and epithelial cells in PrCa. |
| Sroka et al. [175]       | 2008 | MT1-MMP      | Yes—Prostate samples and prostate cell lines | MT1-MMP expression increased in tumor cells. Enforced expression increased tumor growth in mice. MT1-MMP inhibition decreased cell migration, but not growth. MT1 and 3-MMP expressed in stromal and epithelial cells in PrCa. |
| Udayakumar et al. [176]  | 2003 | MT1-MMP      | Yes—cells and patients | MT1-MMP expressed in stromal and epithelial cells in PrCa. MT6-MMP highly expressed in PrCa samples. Inhibition of MT6-MMP decreased invasion. |
| Upadhyay et al. [140]    | 1999 | MT1-MMP *    | Yes—Prostate samples | MT1-MMP expression increased in tumor cells. Enforced expression increased tumor growth in mice. MT1-MMP inhibition decreased cell migration, but not growth. MT1 and 3-MMP expressed in stromal and epithelial cells in PrCa. |
| Wang et al. [164]        | 2009 | MT1-MMP      | Yes—Prostate cell lines and mice | MT1-MMP expression increased in tumor cells. Enforced expression increased tumor growth in mice. MT1-MMP inhibition decreased cell migration, but not growth. MT1 and 3-MMP expressed in stromal and epithelial cells in PrCa. |
| Zarrabi et al. [162]     | 2011 | MT1-MMP      | Yes—Prostate cell lines | MT1-MMP expression increased in tumor cells. Enforced expression increased tumor growth in mice. MT1-MMP inhibition decreased cell migration, but not growth. MT1 and 3-MMP expressed in stromal and epithelial cells in PrCa. |
| Zhang et al. [151]       | 2002 | MT1- and MT3-MMP * | Yes—Prostate samples and prostate cell lines | MT1-MMP expression increased in tumor cells. Enforced expression increased tumor growth in mice. MT1-MMP inhibition decreased cell migration, but not growth. MT1 and 3-MMP expressed in stromal and epithelial cells in PrCa. |
| Zhao et al. [155]        | 2003 | MT6-MMP *    | Yes—Prostate samples and prostate cell lines | MT1-MMP expression increased in tumor cells. Enforced expression increased tumor growth in mice. MT1-MMP inhibition decreased cell migration, but not growth. MT1 and 3-MMP expressed in stromal and epithelial cells in PrCa. |

* Included in at least one other table.

A single study reported that MT2-MMP is downregulated in PrCa [38], but in contrast, MT3-MMP expression was increased and correlated with enhanced aggressiveness/metastatic potential [38,166,167,172]. Likewise, MT6-MMP expression was generally observed to be increased in PrCa [155,165], including one study that indicated a correlation with the PrCa grade [115]. The sole functional study suggested that this MT-MMP also makes a contribution to enhanced invasion [155].

2.3. Tissue Inhibitors of Metalloproteinases (TIMPs)

The TIMPs represent direct regulators of the metzincin superfamily—particularly, members of the MMP subgroup (Table 3). Fifty-three studies investigated the role of TIMPs in PrCa progression, which collectively indicated that these proteins typically act to suppress PrCa progression. For TIMP-1, the expression was generally reduced in PrCa [66,82,95,123,146,177], including specifically in the transition from benign to neoplastic disease [25,55,178], and was also decreased in the recurrent [113] and metastatic [179] forms of the disease. However, some studies reported increased expression in more advanced/aggressive/malignant forms [20,38,48,60,68]. This difference may in part be due to its known upregulation by inflammatory cytokines [180] that might independently impact
the expression in more advanced PrCa, as well as the mode of analysis, with the protein and mRNA levels not always in correlation [82].

**Table 3.** Studies on the Tissue Inhibitor of Metalloproteinases (TIMPs) in PrCa.

| Authors                  | Year  | TIMP          | PrCa Platform                  | Role                                                                 |
|--------------------------|-------|---------------|--------------------------------|----------------------------------------------------------------------|
| Aalinkeel et al. [20]    | 2004  | TIMP-1, 3 and 4 * | Yes—Prostate cell lines      | TIMP-1 and 4 (but not TIMP-3) expressed higher in more metastatic PrCa cells. TIMP-3 mouse knockout exhibited enhanced PrCa tumor growth and invasion. TIMP-1 expression down-regulated in the transition to PrCa. |
| Adissu et al. [181]      | 2015  | TIMP-3        | Yes—Mice                      |                                                                  |
| Ashida et al. [178]      | 2004  | TIMP-1        | Yes—Prostate samples          |                                                                  |
| Babichenko et al. [25]   | 2014  | TIMP-1 *      | Yes—Prostate samples          |                                                                  |
| Baker et al. [182]       | 1994  | TIMP-1 and 2 * | Yes—Prostate samples          |                                                                  |
| Brehmer et al. [32]      | 2003  | TIMP-1 and 2 * | Yes—Prostate samples          |                                                                  |
| Daja et al. [38]         | 2003  | TIMP-1 *      | Yes—Prostate cell lines       |                                                                  |
| De Cicco et al. [39]     | 2008  | TIMP-1 and 2 * | Yes—Prostate samples/Serum    |                                                                  |
| Deng et al. [183]        | 2006  | TIMP-3        | Yes—Prostate cell lines       |                                                                  |
| Escaff et al. [48]       | 2010  | TIMP-1, 2 and 3 * | Yes—Prostate samples          |                                                                  |
| Escaff et al. [49]       | 2011  | TIMP-1, 2 and 3 * | Yes—Prostate samples          |                                                                  |
| Fernandez-Gomez et al. [52] | 2011 | TIMP-1, 2 and 3 * | Yes—Prostate samples          |                                                                  |
| Gong et al. [184]        | 2015  | TIMP-1        | Yes—Prostate samples and prostate cell lines |                                                                  |
| Gravina et al. [55]      | 2013  | TIMP-1, 2 and 3 * | Yes—Prostate cell lines       |                                                                  |
| Gustavsson et al. [185]  | 2008  | TIMP-2 and 3 * | Yes—Prostate cell lines and mice |                                                                  |
| Hashimoto et al. [60]    | 1998  | TIMP-1 *      | Yes—Prostate samples          |                                                                  |
| Hoque et al. [186]       | 2005  | TIMP-3        | Yes—Prostate samples/Urine    |                                                                  |
| Jerónimo et al. [187]    | 2004  | TIMP-3        | Yes—Prostate samples          |                                                                  |
| Jung et al. [66]         | 1998  | TIMP-1 *      | Yes—Prostate samples          |                                                                  |
| Jung et al. [68]         | 1997  | TIMP-1 *      | Yes—Prostate samples          |                                                                  |
| Kamińska et al. [188]    | 2019  | TIMP-2        | Yes—Prostate cell lines       |                                                                  |
| Authors             | Year  | TIMP | PrCa Platform                        | Role                                                                 |
|---------------------|-------|------|--------------------------------------|----------------------------------------------------------------------|
| Karan et al. [189]  | 2003  | TIMP-3 * | Yes—Prostate samples and prostate cell lines | TIMP-3 not expressed in PrCa cell lines, only in benign prostatic hyperplasia. TIMP-1 expression downregulated in metastatic PrCa. |
| Kim et al. [179]    | 2012  | TIMP-1 * | Yes—Prostate samples | TIMP-2 over-expressed in PrCa tissue. |
| Kuefer et al. [190] | 2006  | TIMP-2 * | Yes—Prostate samples and prostate cell lines | TIMP-3 promoter more highly methylated in PrCa versus controls. TIMP-2 administration decreased tumor growth. |
| Kwabi-Addo et al. [191] | 2010 | TIMP-3 | Yes—Patient samples | |
| Lee et al. [192]    | 2012  | TIMP-2 | Yes—Prostate cell lines and mice | |
| Lein et al. [79]    | 1999  | TIMP-1 * | Yes—Prostate samples | TIMP-1 plasma concentration significantly higher in PrCa and correlated with tumor stage. |
| Leshner et al. [80] | 2016  | TIMP-2 and 3 * | Yes—Prostate samples | TIMP-2 and 3 genes do not reposition during PrCa progression. |
| Lichtinghagen et al. [82] | 2002 | TIMP-1 * | Yes—Prostate samples | TIMP-1 protein, but not mRNA, decreased in PrCa tissue. |
| Lichtinghagen et al. [83] | 2003 | TIMP-1, 2 and 3 * | Yes—Prostate samples | Expression of TIMP-2 and 3 (but not TIMP-1) decreased in PrCa tissue, with TIMP-2 correlating with stage. |
| Liu et al. [177]    | 2005  | TIMP-1 | Yes—Prostate samples | TIMP-1 protein levels decreased in PrCa samples, being located in secretory cells. |
| Lokeshwar et al. [86] | 1993 | TIMP * | Yes—Prostate samples | TIMP expression high in normal, but not neoplastic prostate. |
| Morgia et al. [95]  | 2005  | TIMP-1 * | Yes—Prostate samples | TIMP-1 expression reduced in patients with metastatic PrCa. |
| Oh et al. [193]     | 2011  | TIMP-1 | Yes—Prostate samples | Elevated plasma TIMP-1 correlated with decreased survival in metastatic PrCa. |
| Ozden et al. [105]  | 2013  | TIMP-1 * | Yes—Prostate samples | TIMP-2 expression in normal glands associated with lower Gleason grade. |
| Pulukuri et al. [194] | 2007 | TIMP-2 | Yes—Prostate samples and prostate cell lines | Re-expression of TIMP-2 reduced tumor invasion. |
| Reis et al. [112]   | 2012  | TIMP-2 * | Yes—Prostate samples | Reduced TIMP-1 expression associated with recurrence, whereas TIMP-2 expression negative in all cases. |
| Reis et al. [113]   | 2015  | TIMP-1 and 2 * | Yes—Prostate samples | TIMP-1 under-expressed in PrCa samples but over-expressed in benign samples. |
| Reis et al. [114]   | 2011  | TIMP-1 * | Yes—Prostate samples | TIMP-3 and 4 expression negatively correlated with Gleason score. |
| Riddick et al. [115] | 2005 | TIMP-3 and 4 * | Yes—Prostate samples | TIMP-2 expression correlated with advanced PrCa. |
| Ross et al. [116]   | 2003  | TIMP-2 * | Yes—Prostate samples | TIMP-1 expression in blood cells upregulated in PrCa. |
| Ross et al. [195]   | 2012  | TIMP-1 | Yes—Prostate samples | TIMP-1 expression reduced in metastatic PrCa subline. |
| Sehgal et al. [123] | 2003  | TIMP-1 * | Yes—Prostate cell lines | TIMP-3 expression down regulated in PrCa versus normal due to promoter hypermethylation. |
| Shinojima et al. [196] | 2012 | TIMP-3 | Yes—Prostate samples | |
| Srivastava et al. [131] | 2012 | TIMP-2 * | Yes—Prostate specimens | TIMP-2 GC polymorphism associated with PrCa progression not initiation, as well as cancer risk. |
| Stearns et al. [180] | 1995 | TIMP-1 * | Yes—Prostate cell lines | TIMP-1 expressed in PrCa cells. |
| Still et al. [134]  | 2000  | TIMP-2 * | Yes—Prostate specimens | MMP-2/TIMP-2 ratio increased in tumors of higher grade and stage. |
Table 3. Cont.

| Authors                | Year | TIMP       | PrCa Platform                                      | Role                                                                 |
|------------------------|------|------------|----------------------------------------------------|----------------------------------------------------------------------|
| Trudel et al. [136]    | 2008 | TIMP-2 *   | Yes—Prostate specimens                            | Higher TIMP-2 expression associated with longer disease-free survival. TIMP-1 and 2 expressed in stromal inversely correlated with Gleason score, with reduced expression in metastatic PrCa samples. TIMP-3 promoter methylation low, and unchanged between PrCa and benign samples. |
| Wood et al. [146]      | 1997 | TIMP-1 and 2 * | Yes—Prostate samples                           | TIMP-1 and 2 expressed in stromal inversely correlated with Gleason score, with reduced expression in metastatic PrCa samples. TIMP-3 promoter methylation low, and unchanged between PrCa and benign samples. |
| Yamanaka et al. [197]  | 2003 | TIMP-3     | Yes—Prostate samples                             | TIMP-2 polymorphism under-represented in PrCa patients. TIMP-1 and 2 expressed in both stromal and epithelial cells in PrCa, with no difference between fibroblasts and smooth muscle cells. Tendency for higher TIMP-2 expression in cells derived from malignant PrCa tissue. |
| Yaykaşlı et al. [149]  | 2014 | TIMP-2 *   | Yes—Prostate samples                             | TIMP-2 polymorphism under-represented in PrCa patients. TIMP-1 and 2 expressed in both stromal and epithelial cells in PrCa, with no difference between fibroblasts and smooth muscle cells. Tendency for higher TIMP-2 expression in cells derived from malignant PrCa tissue. |
| Zhang et al. [151]     | 2002 | TIMP-1 and 2 * | Yes—Prostate samples and prostate cell lines | Enforced TIMP-3 expression inhibited proliferation, survival, migration, invasion, and adhesion of cells, with reduced incidence and size of tumors in mice. |
| Zhang et al. [198]     | 2010 | TIMP-3     | Yes—Prostate samples, Prostate cell lines and mice | Enforced TIMP-3 expression inhibited proliferation, survival, migration, invasion, and adhesion of cells, with reduced incidence and size of tumors in mice. |

* Included in at least one other table.

For TIMP-2, the included studies typically reported a reduction in expression in PrCa [55,83,112,182,188], including a negative correlation of the expression to tumor grade [105,146] and metastasis [146], with promoter hypermethylation representing one mechanism by which the expression could be lost [188]. There were also a number of conflicting studies [116,151,185,190]. However, functional investigations have demonstrated that TIMP-2 administration reduced the tumor growth [192], and enforced TIMP-2 expression reduced the tumor invasion [194].

The publications on TIMP-3 provided a similar picture, with most showing a reduced expression in PrCa [20,55,189,196], including a negative correlation with the grade [115], and with promoter hypermethylation again representing a key mechanism [191], although a couple of studies were in disagreement with this interpretation [49,52]. The functional investigations were quite definitive, however, with the ablation of TIMP-3 in mice leading to enhanced tumor growth and invasion [181] and enforced expression decreasing the proliferation, survival, migration and invasion [198], as well as increasing apoptosis and chemosensitivity [183].

Finally, there were only two studies identified on TIMP-4, one of these demonstrating an increased expression in PrCa [20] and the other one indicating a negative correlation with the grade [115].

2.4. A Disintegrin and Metalloproteinases (ADAMs)

Twenty-two studies investigated members of the ADAM subgroup in the context of PrCa (Table 4). A number of these provided strong evidence of positive involvement in various aspects of the disease progression. Thus, ADAM-15 expression in PrCa positively correlated with the stage, grade, metastasis and recurrence, with its ablation decreasing both the migration and metastasis [190,199,200]. ADAM-17 expression was also shown to be significantly increased in PrCa and correlated with invasiveness, with ablation decreasing the proliferation and invasiveness [201,202]. ADAM-28 expression was similarly demonstrated to be higher in PrCa, with enforced expression enhancing the proliferation and migration [203].
| Authors                  | Year  | ADAM   | PrCa Platform                                      | Role                                                                 |
|-------------------------|-------|--------|---------------------------------------------------|----------------------------------------------------------------------|
| Arima et al. [204]      | 2007  | ADAM-10| Yes—Prostate cell lines and prostate samples      | ADAM-10 nuclear localization significantly increased in PrCa compared to benign and correlated with Gleason score. Ablation of ADAM-10 decreased cell proliferation. Serum and urine ADAM-12 levels significantly higher in PrCa patients compared to healthy controls, but no correlation with stage. ADAM-15 expression correlated to stage, Gleason grade, lymph node metastasis and PSA recurrence. |
| Bilgin Doğru et al. [205]| 2014  | ADAM-12| Yes—Prostate samples/urine                        | ADAM-8 expression correlated with higher Gleason score, but not PSA relapse-free survival. ADAM-9 expression significantly higher in PrCa compared to normal tissue, and associated with shortened PSA relapse-free survival, especially in androgen-ablated patients. ADAM-19 expression decreased in PrCa compared to normal tissue, and positively correlated with lower grade and reduced relapse. Over-expression of ADAM-19 reduced proliferation and migration, but increased cell death. Ablation of ADAM-9 increased apoptosis, increased sensitivity to radiation and chemotherapy, and induced epithelial phenotype. |
| Burdelski et al. [199]  | 2017  | ADAM-15| Yes—Prostate samples                              | Expression of ADAM-17 (but not ADAM-9 or ADAM-10) increased in PrCa compared to benign samples. Expression of ADAM-15 significantly higher in PrCa and associated with increased Gleason score and angioinvasion. Enforced ADAM-17 expression increased cell proliferation. ADAM-9 expression reduced in castrate-resistant PrCa compared to hormone-sensitive PrCa, with low expression in castrate-resistant PrCa associated with shorter overall survival. |
| Fritzsche et al. [206]  | 2006  | ADAM-8 | Yes—Prostate samples                              | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Fritzsche et al. [207]  | 2008  | ADAM-9 | Yes—Prostate samples                              | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Hoyne et al. [208]      | 2016  | ADAM-19| Yes—Prostate samples and prostate cell lines      | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Josson et al. [209]     | 2011  | ADAM-9 | Yes—cells                                         | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Karan et al. [189]      | 2003  | ADAM-9, 10 and 17 * | Yes—cells and patients                           | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Kuefer et al. [190]     | 2006  | ADAM-15 *| Yes—Prostate samples and prostate cell lines     | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Lin et al. [201]        | 2012  | ADAM-17| Yes—Prostate cell lines                           | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Lin et al. [210]        | 2012  | ADAM-9 | Yes—Prostate samples                              | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Liu et al. [211]        | 2013  | ADAM-9 | Yes—Prostate cell lines and mice                  | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| McCulloch et al. [212]  | 2000  | ADAM-9, 10, 11, 15 and 17 | Yes—Prostate cell lines                          | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| McCulloch et al. [213]  | 2004  | ADAM-10| Yes—Prostate samples and prostate cell lines      | Expression of ADAM-9 increased proliferation in vivo and tumor growth in mice. ADAM-9, 10, 11, 15 and 17 expressed in PrCa cell lines, with androgens increasing expression of ADAM-9 and 10 while ADAM-17 was downregulated. |
| Najy et al. [200]       | 2008  | ADAM-15| Yes—Cells                                        | Ablation of ADAM-15 reduced secretion in PrCa with additional basal cell in benign glands. Ablation of ADAM-15 reduced migration and adhesion in vitro and decreased bone metastasis in mice. ADAM-12 expressed in stromal cells adjacent to epithelial cells in PrCa. ADAM12 knock-out mice showed delayed tumor progression. |
| Peduto et al. [214]     | 2006  | ADAM-12| Yes—Mice                                         | ADAM-12 expressed in stromal cells adjacent to epithelial cells in PrCa. ADAM12 knock-out mice showed delayed tumor progression. |
The results regarding ADAM-9 were more complex, with one study showing no change in expression in PrCa [189] and others showing an increased expression that correlates with malignancy and reduced survival [207,216] but another reporting a decrease in expression in castrate-resistant compared to androgen-sensitive PrCa [210]. However, the ablation of ADAM-9 reduced the proliferation and tumor growth and increased the differentiation, decreasing the metastatic ability while increasing the sensitivity to chemotherapeutic drugs [209]. For ADAM-10, the nuclear localization rather than expression was increased in PrCa, with ablation decreasing the growth [204]. For ADAM-12, the serum levels have been demonstrated to be increased in PrCa, with expression found in stromal tissue, and progression delayed in knockout mice [205,214].

The clear exception in this family was ADAM-19, which was found to be more highly expressed in normal tissue compared to PrCa and negatively correlated to the grade and relapse, with the enforced expression leading to decreased proliferation, metastatic ability and survival [208].

2.5. A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTSs)

Eight studies were identified that related to the ADAMTS subgroup in PrCa progression (Table 5). The majority focused on ADAMTS-1, providing evidence of a tumor-suppressing function. ADAMTS-1 expression was typically decreased in PrCa samples, patients with metastatic disease, and a PrCa cell line variant with higher metastatic potential but elevated in slower-growing PrCa tumors in mice [65,179,219,220]. This was supported by functional data from the cells in which ADAMTS-1 expression had been modulated, which suggested a role in growth, although this appeared to depend on the cell line used [219]. ADAMTS-15 was also shown to be able to suppress tumor growth and migration, although it augmented survival [221]. Other members of the ADAMTS subgroup have also been shown to be expressed in PrCa cell lines, but their role in PrCa progression remains elusive [222].

| Authors             | Year | ADAM | PrCa Platform                                                                 | Role                                                                                     |
|---------------------|------|------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Peduto et al. [215] | 2005 | ADAM-9| Yes—Mice                                                                     | ADAM-9 expression elevated in mouse PrCa model. ADAM-9 knock-out resulted in well differentiated tumors. Overexpression of ADAM-9 led to epithelial hyperplasia and intraepithelial neoplasia. ADAM-9 nuclear expression observed in hormone refractory PrCa and in relapse patients, with levels correlated with the risk of relapse. ADAM-28 expression increased in PrCa samples compared to normal tissue and in PrCa cell lines. Over-expression of ADAM-28 stimulated proliferation and migration, whereas ablation of expression or activity reduced these phenotypes. |
| Pen et al. [216]    | 2012 | ADAM-9| Yes—Prostate samples, prostate cell lines and mice                           | ADAM-9 nuclear expression observed in hormone refractory PrCa and in relapse patients, with levels correlated with the risk of relapse. |
| Rudnicka et al. [203]| 2016 | ADAM-28| Yes—Prostate samples and prostate cell lines                               | ADAM-9 expression increased in PrCa samples compared to normal tissue and in PrCa cell lines. Over-expression of ADAM-28 stimulated proliferation and migration, whereas ablation of expression or activity reduced these phenotypes. |
| Shigemura et al. [217]| 2007 | ADAM-9| Yes—Prostate cell lines                                                       | ADAM-9 expressed in AR-positive PrCa cells. ADAM-9 expression elevated in in malignant compared to benign prostate tissue. ADAM-9 expression correlated to transition to androgen-independence and cellular stress. |
| Sung et al. [218]   | 2006 | ADAM-9| Yes—Prostate samples and prostate cell lines                               | ADAM-9 expression correlated to transition to androgen-independence and cellular stress. |
| Xiao et al. [202]   | 2012 | ADAM-17| Yes—Prostate cell lines                                                       | ADAM-17 expression correlated with invasiveness. Enforced expression of ADAM-17 increased invasiveness, whereas ablation decreased invasiveness. |

* Included in at least one other table.
**Table 5.** Studies on A Disintegrin and Metalloproteinase with Thrombospondin Motifs (ADAMTSs) in PrCa.

| Authors          | Year | ADAMTS | PrCa Platform                                                                 | Role                                                                 |
|------------------|------|--------|-------------------------------------------------------------------------------|----------------------------------------------------------------------|
| Binder et al. [221] | 2020 | ADAMTS-15 | Yes—Prostate samples, prostate cell lines and mice                          | ADAMTS-15 expressed and active in PrCa samples. Enforced ADAMTS-15 expression decreased migration and proliferation but increased survival in vitro and suppressed tumor growth in mice. |
| Cross et al. [222] | 2005 | ADAMTS-1, 4, 5, 9 and 15 | Yes—Prostate cell lines                                                   | ADAMTS-1, ADAMTS-4, ADAMTS-5, ADAMTS-9 and ADAMTS-15 expressed in PrCa. |
| Gustavsson et al. [185] | 2008 | ADAMTS-1 * | Yes—Prostate cell lines and mice                                            | ADAMTS-1 expression decreased in PrCa cell line with enhanced angiogenic and tumorigenic properties, compared to parent. |
| Gustavsson et al. [220] | 2009 | ADAMTS-1 | Yes—Prostate samples                                                        | ADAMTS-1 expression decreased in prostate cancer cells compared to benign prostate glands. No correlation with Gleason score, but expression lower in patients with metastatic disease. |
| Gustavsson et al. [219] | 2010 | ADAMTS-1 | Yes—Prostate cell lines and mice                                            | ADAMTS-1 ablation decreased tumor growth, but in other PrCa cells enforced expression inhibited tumor growth. |
| Jennbacken et al. [65] | 2009 | ADAMTS-1 | Yes—Prostate cell lines and mice                                            | ADAMTS-1 expression increased in slow growing tumors in mice. |
| Kim et al. [179] | 2012 | ADAMTS-1 * | Yes—Prostate samples                                                        | ADAMTS-1 mRNA overexpressed in PrCa samples. |
| Molokwu et al. [223] | 2010 | ADAMTS-1 and 15 | Yes—Prostate cell lines                                                     | ADAMTS-15 (but not ADAMTS-1) expressed in PrCa. |

* Included in at least one other table.

3. Discussion

3.1. Overview

This study used a systematic-like review strategy to identify publications examining the role of metzincins in PrCa progression. While limited to articles in PUBMED and MEDLINE and those written in English, this approach was likely to yield the vast majority of relevant research publications. It is evident from a close examination of the 205 articles identified that the contributions made by members of the metzincin superfamily to PrCa disease progression are complex. For many individual members and, indeed, the entire Astracin family, there is currently no evidence of involvement. However, a significant number of metzincins are positively associated with PrCa, supported by functional evidence in a number of cases, while others were negatively associated with this disease. The positive associations were particularly strong with specific members of the MMP, MT-MMP and ADAM subgroups, while those within the ADAMTS subgroup or the important TIMP family of regulators were more likely to show negative associations.

3.2. Positive Associations

The clearest evidence for positive contributions to PrCa and its progression was for MMP-2, MMP-7, MMP-9, MT1-MMP, ADAM-15, ADAM-17 and ADAM-28, with supporting evidence for MMP-1, MT3-MMP, MT6-MMP and ADAM-9 (Tables 1, 2 and 4). This is underpinned by studies that have identified associations between the expression and PrCa, which, in the case of MMP-7 expression [60,63,73,88,99,104,106,110,135,147] and ADAM-15 expression [190,199,200], correlated with the pathological stage and poorer outcomes for patients. This was supported by functional analyses that consistently identified enhancements in the proliferation, invasion/spread and metastasis/migration facilitated...
by them [56,106,110,200] (Figure 2). This identified these specific metzincins as likely tumor-promoting factors and so represented the obvious candidates as disease biomarkers or as potential targets for therapeutic agents.

Figure 2. Metzincins and their regulators in prostate cancer. Schematic representation of prostate cancer progression highlighting the key cellular functions that are modulated by the indicated metzincin superfamily members, along with the regulatory Tissue Inhibitor of Metalloproteinase (TIMP) proteins (green: Lumen, orange: Luminal cells, purple: Basal cells, and blue: Basement membrane).

3.3. Negative Associations

The strongest evidence for negative contribution to PrCa is for TIMP-2 and TIMP-3, as well as ADAM-19, ADAMTS-1 and ADAMTS-15 (Tables 3–5). Such a role for the ADAMTS proteins is somewhat counterintuitive, since these enzymes cleave ECM components like other metzincins [224], including those involved in PrCa disease progression [220,221]. However, the functional evidence points to these enzymes inhibiting key phenotypes, including proliferation and metastasis/migration, although not survival (Figure 2), presumably due to the different specificities for ECM components compared to other metzincins [220,221]. ADAM-19 was also implicated in the proliferation, metastasis/migration and survival (Figure 2), although this could relate to the known nonenzymatic functions for these enzymes. A negative role for the TIMP family was less surprising, given their primary role in the inhibition of MMP enzymes [225], with this impact extending across the entire gamut of relevant cell functions (Figure 2). These molecules can also be considered biomarker candidates to aid in prognosis. Therapeutic approaches targeting these proteins would likely be more limited, however, since they would need to augment, rather than inhibit, their function.

3.4. Mixed Associations

For other metzincins, the evidence for their involvement in PrCa was even more variable and contradictory, such as for MMP-11. Indeed, even those metzincins or regulators with consistent positive or negative correlations with PrCa were often reported in some studies to have no correlation or, indeed, the opposite correlation. This suggests a complex interplay between metzincins and PrCa.
3.5. Understanding the Complexity

In interpreting the variable and, at times, conflicting data, there are a number of factors that need to be considered. Firstly, different studies have utilized alternate approaches, such as analyzing the expression at the gene versus protein levels, that do not always correlate \[24,68,82,83,91,101,140,189\] or examining the enzymatic activity, which is not always reflective of metzincin expression \[119,226\], or, instead, considering the cellular localization \[140\]. Moreover, different samples have been analyzed in the literature, including plasma/serum, urine and tumor biopsies from PrCa patients, with several studies highlighting the differences between tissues \[119\], while the exact PrCa stage is also critical \[117\]. Other studies have employed PrCa cell lines and xenotransplanted tumors in mice, the relevance of which to human disease is assumed but not guaranteed. Secondly, it is clear that the factors controlling the expression of these enzymes and their regulators are complex. Thus, many metzincins have been demonstrated to be regulated by androgens \[107,213,217,223,227,228\], which can clearly be a complicating factor given the environment in which these cancers develop. In addition, expression is also impacted by oncogenes \[85,147\], inflammation and inflammatory cytokines \[99,229\], as well as angiogenic factors such as vascular endothelial factor \[216\], which are intrinsic features of any cancer. The cellular environment can further influence both expression \[127\] and activation \[143\]. Therefore, discerning the direction of causality between the expression and PrCa is not always straightforward.

In most cases, the effects of the metzincin superfamily member (or inhibitor) have been presumed to relate to the primary role for metzincins in regulating components of the ECM, which is known to be a particularly key element of metastasis \[9,13\]. However, which substrates are important? The cleavage of laminin \[159,176\], perlecan \[56\] and beta-4 integrin \[230\] have all been shown to correlate with the effects of protumorigenic metzincins, particularly on metastasis, whereas versican has been identified as a target of the antitumorigenic ADAMTS-15 \[221\]. Clearly, more research is required to understand this important aspect of metzincin pathobiology. Moreover, other roles should also be considered, especially given reports suggesting that nuclear localization may be important in some situations \[204,213,216\], with both ADAMs and ADAMTSs known to have nonenzymatic roles.

There also remains a lack of depth in our understanding of how metzincins are regulated at the protein level, including by other metzincins. TIMPs are clearly important for the negative regulation of MMPs \[114\]. TIMPs are typically downregulated as cancer progresses and can act as independent correlates of PrCa progression \[25,32,95,112,114,116,177–179\], especially when combined with MMP expression \[83,105,116\]. TIMP-2 and TIMP-3 have also been shown to inhibit ADAMTS-1 \[185\]. Are there equivalents for ADAM and other ADAMTS enzymes? In addition, MT1-MMP has been shown to exert its role at least in part through the direct activation of MMP-2 \[140,159\]. Is this crosstalk common across metzincins? More research is needed to gain further insight in this area.

4. Materials and Methods

This study represents a systematic-like review of the role of the metzincin superfamily of proteases in PrCa progression. The search terms were identified through a PCC (population, context and concept) format by the research team with keywords, Boolean operators, truncations and Medical Subject Headings (MeSH) used to develop a database search strategy in collaboration with a specialist health librarian. In reporting the review, the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) was utilized.

4.1. Search Strategy

A preliminary search was undertaken using MEDLINE and then a full search run through both the PUBMED and MEDLINE databases.
4.2. Inclusion and Exclusion Criteria

All studies were considered based on the inclusion and exclusion criteria shown in Table 6. Search terms for inclusion were “metzinzin”, “metalloproteases”, “metalloproteinase”, “MMP”, “TIMP”, “ADAM”, “ADAMTS”, “BMP1” or “meprin” and “neoplasm”, “neoplasia”, “cancer”, “tumor” or “cysts”. Reasons for exclusion after the full-text review are detailed in Figure 3. No restrictions were put on the date that articles were published.

| Table 6. Search terms and inclusion/exclusion criteria used in this systematic-like review. |
|-------------------------------------------------------------|
| **Population** | Men, mice/rats or cells. | Involved other animal species or cells not related to PrCa progression. |
| **Concept** | All human metzincin superfamily members, including members of the MMP, MT-MMP, ADAM, ADAMTS, BMP1/TLL and Meprin subgroups, as well as the TIMP family of regulators. | Examining proteins other than metzincin superfamily members or TIMPs, or in different cancer types, other diseases, or normal biology. |
| **Context** | Studies that investigated the role of the metzincin superfamily in PrCa progression. | Did not specially look at the role of metzincin superfamily members in PrCa cancer progression. |

Figure 3. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) overview of the systematic-like review. Flow chart of the systematic-like review process undertaken, including the details of identification, screening and assessment for eligibility.
4.3. Study Selection and Data Extraction

Searches of the published literature were conducted by M.J.B. in collaboration with a specialist health librarian. Titles and abstracts were retrieved from the search and screened. Full-text article review and data extraction was then conducted, with the reasons for exclusion documented. The reference lists of the included articles were also reviewed to identify further potential articles for inclusion in the review.

4.4. Data Analysis

Database searching identified 10,443 publications. After duplicate removal, the titles and abstracts from 8327 were reviewed against the inclusion criteria. Full-text versions of 1248 articles were then further reviewed, identifying 205 articles for inclusion (Figure 2). The reasons for exclusion were a lack of focus on PrCa (n = 603) or the metzincin superfamily (n = 50) or the role of the metzincin superfamily family in PrCa progression (n = 98) or on the biology of the metzincin superfamily (n = 108) or not peer reviewed (n = 18) or being review articles (n = 173) or articles unable to be accessed or retracted (n = 11) or not in English (n = 3). The 205 included articles covered members of the Matrixin family subgroups MMP and MT-MMPs, the TIMPs and the Adamalysin family subgroups ADAMs and ADAMTSs, but there were none regarding the Astracin family subgroups BMP/TLL or Meprin.

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