Matrix Metalloproteases in PDAC

Subjects: Biology

Contributor: C. Arnold Spek

Pancreatic cancer is a dismal disorder that is histologically characterized by a dense fibrotic stroma around the tumor cells. As the extracellular matrix comprises the bulk of the stroma, matrix degrading proteases may play an important role in pancreatic cancer. It has been suggested that matrix metalloproteases are key drivers of both tumor growth and metastasis during pancreatic cancer progression. Based upon this notion, changes in matrix metalloprotease expression levels are often considered surrogate markers for pancreatic cancer progression and/or treatment response. Indeed, reduced matrix metalloprotease levels upon treatment (either pharmacological or due to genetic ablation) are considered as proof of the anti-tumorigenic potential of the mediator under study.

Keywords: MMP ; MMP2 ; MMP9 ; MMP7 ; MMP14 ; matrix metalloproteases ; PDAC ; pancreatic cancer

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a devastating disease with the worst survival outcome of any cancer [1]. Its incidence, which is around 10 per 100,000 individuals, is rising in developed countries [2][3], with 458 thousand new cases and 432 thousand deaths in 2018 worldwide [4]. The 5-year survival rate is around 9%, and the 10-year mortality is approaching 99% [5]. Progress towards improving survival has been slow, and current treatment options are inadequate. The only significant progress that has been made is in the form of lower mortality rates for patients eligible for resections, and a slight prolongation and improved quality of life in patients with inoperable disease with the use of chemotherapeutic agents. Single-agent gemcitabine treatment has been the standard of care for inoperable PDAC for many years, although the observed benefits are small in daily practice [6][7][8][9] and seem restricted to patients with a good performance status [10]. More recently, nanoparticle albumin-bound paclitaxel was shown to exert superior antitumor activity compared to gemcitabine monotherapy, thereby establishing nab-paclitaxel and gemcitabine combination therapy as first-line chemotherapy regimens in PDAC [11]. In patients with a good performance status, combination therapy with folinic acid, fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) is superior over other treatments [12] and FOLFIRINOX is consequently emerging as the new standard of care for relatively fit patients [13]. Importantly however, even in the specific group of patients eligible for FOLFIRINOX treatment, the survival benefit is limited [14].

1.1. Tumor Microenvironment of PDAC

PDAC is characterized by a strong desmoplastic reaction, which results in an archetypal tumor microenvironment, consisting of a dense stroma surrounding the tumor cells [15][16]. The stroma forms the bulk of the tumor, taking up to 90% of the total tumor mass and consists of many cellular and acellular components like (myo)fibroblasts, macrophages, blood vessels and extracellular matrix components such as, among others, collagen I, collagen IV, laminin and fibronectin. In the stroma, the extracellular matrix has traditionally been considered to be a stable structure that mainly plays a supportive role in maintaining tissue morphology. Nowadays, however, it is evident that the extracellular matrix forms a dynamic and versatile milieu that affects the fundamental processes of the surrounding cells [17][18]. Accordingly, the loss of extracellular matrix homeostasis and integrity is considered one of the hallmarks of cancer and typically defines transitional events, resulting in cancer progression and metastasis [19]. Moreover, the loss of extracellular matrix homeostasis due to stromal depletion aggravates pancreatic cancer progression in preclinical animal models [20][21][22].

1.2. Matrix Metalloproteases in the Tumor Microenvironment

The desmoplastic PDAC stroma contains many different proteases that play a key role in the crosstalk between tumor and stromal cells. An intriguing group of proteases in the tumor microenvironment consist of matrix metalloproteases (MMPs), which are primarily known for their ability to degrade extracellular matrix components. Altered expression and/or activity of MMPs in the tumor microenvironment is likely to lead to the loss of homeostasis of the extracellular matrix, thereby driving PDAC progression. Based upon this notion, MMPs are considered important contributors to PDAC progression and experimental PDAC studies frequently use MMPs as surrogate markers for treatment responses. Decreased MMP levels

are, nowadays, considered as important signs of the anti-tumorigenic potential of the gene/compound/miRNA under study. In the current review, we address whether the literature supports the concept that MMPs drive PDAC progression and if decreased MMP levels under experimental settings are indicative of the treatment response. To this end, we performed a systematic review of patient and experimental animal studies, focusing on MMPs in PDAC.

1.3. Overview of Matrix Metalloproteases

MMPs are calcium-dependent zinc-containing endopeptidases of the metzincin protease superfamily. They typically contain an N-terminal propeptide of approximately 80–90 amino acids, with a conserved PRCGXPD motif that is responsible for maintaining latency via the binding of the cysteine residue to the zinc atom in the active site [23]. After the proteolytic removal of the propeptide, the active form of MMP contains a calcium-dependent catalytic domain of around 200 amino acids, which contains a hydrophobic S1′-pocket that determines substrate specificity, proceeded by a linker region of variable length, and the C-terminal hemopexin-like domain, which spans approximately 200 amino acids. The hemopexin-like domain, which is absent in some MMP family members, plays a functional role in substrate binding and/or in interactions with tissue inhibitors of metalloproteases (TIMPs), a family of specific MMP protein inhibitors [24].

Since the identification of a diffusible collagenolytic factor in living amphibian tissue that is capable of degrading undenatured calf skin collagen [25], a total of 24 MMPs have been identified in humans [26]. According to their substrate specificity, MMPs are classified into subfamilies: (1) collagenases, (2) gelatinases, (3) stromelysins, (4) matrilysins, (5) membrane-type MMPs and (6) others. Despite the general acceptance of the classification system based on extracellular matrix substrates, MMPs are rather promiscuous in substrate recognition and also proteolytically cleave substrates beyond extracellular matrix proteins.

2. Conclusions

The potential clinical relevance of MMPs in PDAC has largely been addressed using patient-derived tumor material. These studies show a rather consistent picture with respect to MMP overexpression in tumors compared to control sections, although almost 25% of the studies do not show significant differences between patients and controls. However, the association of MMP overexpression with clinical characteristics is not as convincing as suggested in the literature. Half of the studies show that high MMP levels are associated with (lymph node) metastasis and reduced survival, whereas the other half of the studies do not show any correlation with clinical characteristics. Patient-derived data do not, therefore, seem to allow firm conclusions that MMP expression levels (in general) are associated with PDAC progression and poor prognosis to be drawn, especially when considering that publication bias may have resulted in negative studies not being published.

Initial preclinical experimental animal models using broad spectrum MMP inhibitors are more in line with the general role of MMPs in PDAC progression, as different inhibitors limit tumor growth and metastasis in subcutaneous, orthotopic and spontaneous PDAC models. The contribution of individual MMPs in PDAC progression is, however, not very well established. Only MMP2, MMP7 and MMP14 are shown to potentiate tumor growth and/or metastasis in multiple independent papers. For others, the literature is conflicting or missing and no clear conclusions can be drawn. Importantly, however, conflicting results do not indicate that the individual MMPs have no effect in PDAC. The biology of PDAC and MMP is complex and MMPs may act in a context-dependent manner, with both tumor-promoting and tumor-inhibiting effects. The conflicting role of MMP9 serves as an excellent example for this notion. The data rather convincingly show that tumor MMP9 expression drives PDAC progression, but systemic MMP9 ablation triggers invasive growth and metastasis by blocking MMP9-dependent tumor-inhibiting effects in the bone marrow.

Despite the presence of a large range of MMP-deficient animals and the relative ease of generating MMP deficient cells with CRISPR technology, the majority of MMPs have not been studied in preclinical PDAC animal models. To fully appreciate the importance of individual MMPs in PDAC progression and to assess their potential clinical relevance, we have to await studies that combine (pharmacological inhibition in) genetic Kras-driven spontaneous models with subcutaneous and/or orthotopic models, in which MMPs are specifically depleted in stromal or tumor cells. In particular, experiments that address pharmacological treatment with specific MMP inhibitors after tumors could turn out to be invaluable for establishing the context-dependent role of individual MMPs in PDAC. Before such studies have been performed, we should be careful not to generalize the available literature.

Although broad spectrum MMP inhibitors limit PDAC progression in preclinical animal models [27][28][29][30][31][32][33][34][35][36], they seem to lack efficacy in a clinical setting [37][38]. This disparity between preclinical data and clinical trials can be attributed to several factors—for instance, differences in pharmacokinetics, pharmacodynamics and metabolism and the failure to accurately model the tumor microenvironment [39]. In particular, xenograft models, which lack a functional

immune system, show a reduced complexity and cellular diversity compared to human disease models. Moreover, the degree of aneuploidy in human tumors results in great variety within inter-tumoral gene modifications, in a different manner compared to how it occurs in mice [40][41]. All of these species-related differences limit the capacity of preclinical mouse models to accurately predict the response of MMP inhibitors in PDAC patients.

In conclusion, based on our systematic review on the role of matrix metalloproteases in PDAC, we conclude that the available literature is not as consistent as envisioned and that, although individual matrix metalloproteases seem to contribute to PDAC growth and metastasis, our review does not support the generalized notion that matrix metalloproteases drive PDAC progression.

References

1. Neoptolemos, J.P.; Urrutia, R.; Abbruzzese, J.L.; Büchler, M.W. (Eds.) Pancreatic Cancer; Springer: New York, NY, USA, 2018; Volume XXXIII, pp. 3–18.

2. Rawla, P.; Sunkara, T.; Gaduputi, V. Epidemiology of pancreatic cancer: Global Trends, Etiology and Risk Factors. World J. Oncol. 2019, 10, 10–27.

3. Simard, E.P.; Ward, E.M.; Siegel, R.; Jemal, A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J. Clin. 2012, 62, 118–128.

4. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424.

5. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics 2019. CA Cancer J. Clin. 2019, 69, 7–34.

6. Burris, H.A., III; Moore, M.J.; Andersen, J.; Green, M.R.; Rothenberg, M.L.; Modiano, M.R.; Cripps, M.C.; Portenoy, R.K.; Storniolo, A.M.; Tarassoff, P.; et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. J. Clin. Oncol. 1997, 15, 2403–2413.

7. Cunningham, D.; Chau, I.; Stocken, D.D.; Valle, J.W.; Smith, D.; Steward, W.; Harper, P.G.; Dunn, J.; Tudur-Smith, C. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J. Clin. Oncol. 2009, 27, 5513–5518.

8. Heinemann, V.; Quietzsch, D.; Gieseler, F.; Gonnermann, M.; Schönekäs, H.; Rost, A.; Neuhaus, H.; Haag, C.; Clemens, M.; Heinrich, B.; et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. J. Clin. Oncol. 2006, 24, 3946–3952.

9. Louvet, C.; Labianca, R.; Hammel, P.; Lledo, G.; Zampino, M.G.; André, T.; Zaniboni, A.; Ducreux, M.; Aitini, E.; Taïeb, J.; et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: Results of a GERCOR and GISCAD phase III trial. J. Clin. Oncol. 2005, 23, 3509–3516.

10. Reni, M.; Cordio, S.; Milandri, C.; Passoni, P.; Bonetto, E.; Oliani, C.; Luppi, G.; Nicoletti, R.; Galli, L.; Bordonaro, R.; et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: A randomised controlled multicentre phase III trial. Lancet Oncol. 2005, 6, 369–376.

11. Awasthi, N.; Zhang, C.; Schwarz, A.M.; Hinz, S.; Wang, C.; Williams, N.S.; Schwarz, M.A.; Schwarz, R.E. Comparative benefits of Nab-paclitaxel over gemcitabine or polysorbate-based docetaxel in experimental pancreatic cancer. Carcinogenesis 2013, 34, 2361–2369.

12. Heinemann, V.; Haas, M.; Boeck, S. Systemic treatment of advanced pancreatic cancer. Cancer Treat. Rev. 2012, 38, 843–853.

13. Rombouts, S.J.; Mungroop, T.H.; Heilmann, M.N.; van Laarhoven, H.W.; Busch, O.R.; Molenaar, I.Q.; Besselink, M.G.; Wilmink, J.W. FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer: A Single Centre Cohort Study. J. Cancer 2016, 7, 1861–1866.

14. Suker, M.; Beumer, B.R.; Sadot, E.; Marthey, L.; Faris, J.E.; Mellon, E.A.; El-Rayes, B.F.; Wang-Gillam, A.; Lacy, J.; Hosein, P.J.; et al. FOLFIRINOX for locally advanced pancreatic cancer: A systematic review and patient level meta-analysis. Lancet Oncol. 2016, 17, 801–810.

15. Hidalgo, M. Pancreatic cancer. N. Engl. J. Med. 2010, 362, 1605–1617.

16. Bijlsma, M.; van Laarhoven, H. The conflicting roles of tumor stroma in pancreatic cancer and their contribution to the failure of clinical trials: A systematic review and critical appraisal. Cancer Metastasis Rev. 2015, 34, 97–114.

17. Hynes, R.O. The extracellular matrix: Not just pretty fibrils. Science 2009, 326, 1216–1219.

18. Lu, P.; Weaver, V.M.; Werb, Z. The extracellular matrix: A dynamic niche in cancer progression. J. Cell Biol. 2012, 196, 395–406.

19. Filipe, E.C.; Chitty, J.L.; Cox, T.R. Charting the unexplored extracellular matrix in cancer. Int. J. Exp. Pathol. 2018, 99, 58–76.

20. Özdemir, B.C.; Pentcheva-Hoang, T.; Carstens, J.L.; Zheng, X.; Wu, C.; Simpson, T.R.; Laklai, H.; Sugimoto, H.; Kahlert, C.; Novitskiy, S.V.; et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell 2014, 25, 719–734.

21. Rhim, A.D.; Oberstein, P.E.; Thomas, D.H.; Mirek, E.T.; Palermo, C.F.; Sastra, S.A.; Dekleva, E.N.; Saunders, T.; Becerra, C.P.; Tattersall, I.W.; et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. Cancer Cell 2014, 25, 735–747.

22. Catenacci, D.V.; Junttila, M.R.; Karrison, T.; Bahary, N.; Horiba, M.N.; Nattam, S.R.; Marsh, R.; Wallace, J.; Kozloff, M.; Rajdevet, L.; et al. Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients With Metastatic pancreatic cancer. J. Clin. Oncol. 2015, 33, 4284–4292.

23. Massova, I.; Kotra, L.P.; Fridman, R.; Mobashery, S. Matrix metalloproteinases: Structures, evolution, and diversification. FASEB J. 1998, 12, 1075–1095.

24. Brew, K.; Dinakarpandian, D.; Nagase, H. Tissue inhibitors of metalloproteinases: Evolution, structure and function. Biochim. Biophys. Acta 2000, 1477, 267–283.

25. Gross, J.; Lapiere, C. Collagenolytic activity in amphibian tissues: A tissue culture assay. Proc. Natl. Acad. Sci. USA 1962, 48, 1014–1022.

26. Mittal, R.; Patel, A.P.; Debs, L.H.; Nguyen, D.; Patel, K.; Grati, M.; Mittal, J.; Yan, D.; Chapagain, P.; Liu, X.Z. Intricate Functions of Matrix Metalloproteinases in Physiological and Pathological Conditions. J. Cell Physiol. 2016, 231, 2599–2621.

27. Park, J.K.; Kim, M.A.; Ryu, J.K.; Yoon, Y.B.; Kim, S.W.; Han, H.S.; Kang, G.H.; Kim, H.; Hwang, J.H.; Kim, Y.T. Postoperative prognostic predictors of pancreatic ductal adenocarcinoma: Clinical analysis and immunoprofile on tissue microarrays. Ann. Surg. Oncol. 2012, 19, 2664–2672.

28. Haq, M.; Shafii, A.; Zervos, E.E.; Rosemurgy, A.S. Addition of matrix metalloproteinase inhibition to conventional cytotoxic therapy reduces tumor implantation and prolongs survival in a murine model of human pancreatic cancer. Cancer Res. 2000, 60, 3207–3211.

29. Zervos, E.E.; Norman, J.G.; Gower, W.R.; Franz, M.G.; Rosemurgy, A.S. Matrix metalloproteinase inhibition attenuates human pancreatic cancer growth in vitro and decreases mortality and tumorigenesis in vivo. J. Surg. Res. 1997, 69, 367–371.

30. Zervox, E.E.; Franz, M.G.; Salhab, K.F.; Shafii, A.E.; Menendez, J.; Gower, W.R.; Rosemurgy, A.S. Matrix metalloproteinase inhibition improves survival in an orthotopic model of human pancreatic cancer. J. Gastrointest. Surg. 2000, 4, 614–619.

31. Zervos, E.E.; Shafii, A.E.; Rosemurgy, A.S. Matrix metalloproteinase (MMP) inhibition selectively decreases type II MMP activity in a murine model of pancreatic cancer. J. Surg. Res. 1999, 81, 65–68.

32. Jimenez, R.E.; Hartwig, W.; Antoniu, B.A.; Compton, C.C.; Warshaw, A.L.; Fernández-Del Castillo, C. Effect of matrix metalloproteinase inhibition on pancreatic cancer invasion and metastasis: An additive strategy for cancer control. Ann. Surg. 2000, 231, 644–654.

33. Gao, C.C.; Gong, B.G.; Wu, J.B.; Cheng, P.G.; Xu, H.Y.; Song, D.K.; Li, F. MMI-166, a selective matrix metalloproteinase inhibitor, promotes apoptosis in human pancreatic cancer. Med. Oncol. 2015, 32, 418.

34. Matsushita, A.; Onda, M.; Uchida, E.; Maekawa, R.; Yoshioka, T. Antitumor effect of a new selective matrix metalloproteinase inhibitor, MMI-166, on experimental pancreatic cancer. Int. J. Cancer 2001, 92, 434–440.

35. Kilian, M.; Gregor, J.I.; Heukamp, I.; Hanel, M.; Ahlgrimm, M.; Schimke, I.; Kristiansen, G.; Ommer, A.; Walz, M.L.; Jacobi, C.A.; et al. Matrix metalloproteinase inhibitor RO 28-2653 decreases liver metastasis by reduction of MMP-2 and MMP-9 concentration in BOP-induced ductal pancreatic cancer in Syrian Hamsters: Inhibition of matrix metalloproteinases in pancreatic cancer. Prostaglandins Leukot. Essent. Fatty Acids 2006, 75, 429–434.

36. Iki, K.; Tsutsumi, M.; Kido, A.; Sakitani, H.; Takahama, M.; Yoshimoto, M.; Motoyama, M.; Tatsumi, K.; Tsunoda, T.; Konishi, Y. Expression of matrix metalloproteinase 2 (MMP-2), membrane-type 1 MMP and tissue inhibitor of metalloproteinase 2 and activation of proMMP-2 in pancreatic duct adenocarcinomas in hamsters treated with N-nitrosobis(2-oxopropyl)amine. Carcinogenesis 1999, 20, 1323–1329.

37. Moore, M.J.; Hamm, J.; Dancey, J.; Dagenais, M.; Fields, A.; Hagan, K.; Greenberg, B.; Colwell, B.; Zee, B.; Tuet, D.; et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J. Clin. Oncol. 2003, 21, 3296–3302.

38. Fields, G.B. The Rebirth of Matrix Metalloproteinase Inhibitors: Moving Beyond the Dogma. Cells 2019, 8, 984.

39. Gopinathan, A.; Morton, J.P.; Jodrell, D.; Sansom, O.J. GEMMs as preclinical models for testing pancreatic cancer therapies. Dis. Model. Mech. 2015, 8, 1185–1200.

40. Swayden, M.; Soubeyran, P.; Iovanna, J. Upcoming Revolutionary Paths in Preclinical Modeling of Pancreatic Adenocarcinoma. Front. Oncol. 2020, 9, 1443.

41. Biankin, A.V.; Waddell, N.; Kassahn, K.S.; Gingras, M.C.; Muthuswamy, L.B.; Johns, A.L.; Miller, D.K.; Wilson, P.J.; Patch, A.M.; Wu, J.; et al. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. Nature 2012, 491, 399–405.