ISSN: 2755-0176

Journal of Cancer Research Reviews & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

# Metastatic Associated Fibroblast (MAF): is it a Key Driver of Tumour Metastasis in Oral Cancer

**Rajalakshmi G[1], Subramania Iyer[2*], Mahija Janardhanan[3] and Krishna Kumar Thankappan[4]**

[1]DHR Fellow/Scientist Head and Neck Oncology, Amrita Vishwa Vidyapeetham, Amrita Institute of Medical Sciences Kochi, India

[2]Prof &Head of Dept, Head and Neck Oncology, Amrita Vishwa Vidyapeetham, Amrita Institute of Medical Sciences Kochi, India

[3]Professor, Dept of Oral Pathology Amrita Vishwa Vidyapeetham, Amrita School of Dentistry Kochi, India

[4]Professor, Head and Neck Oncology, Amrita Vishwa Vidyapeetham, Amrita Institute of Medical Sciences Kochi, India

**ABSTRACT**

Metastases of a tumour suggests poor prognosis and still treatment strategies against metastatic tumours are inadequate. Its resistance against existing therapeutic agents makes metastatic tumour treatment still challenging. Numerous research work has been done on cancer associated fibroblast (CAF), evidently suggesting of its contribution towards tumour metastasis. Recently a different stromal fibroblast seen in the metastatic sites, characteristically different from CAF known as metastatic associated fibroblast (MAF) has caught attention. Emergent preclinical studies propose that MAF targeting can ease therapeutic resistance and arrest progression of metastatic growth. This review discusses the current knowledge on this novel cell population that may bear on further understanding on the metastatic process.

***Corresponding author**

Subramania Iyer, Prof &Head of Dept, Head and Neck Oncology, Amrita Vishwa Vidyapeetham, Amrita Institute of Medical Sciences Kochi, India.

**Received:** September 12, 2024; **Accepted:** September 20, 2024; **Published:** November 30, 2024

**Keywords:** Metastatic Associated Fibroblast, Pre metastatic Niche, Cancer Associated Fibroblast

## Introduction

Cancer remains as one of the major threats to human life in contrast to many discoveries revealing the detailed mechanisms about primary tumour formation. Researches on the cellular and molecular mechanisms of metastasis development is still lagging. Tumour associated mortalities are an overwhelming problem and reducing the associated deaths may depend on our competence in arresting or preventing metastasis [1].

Tumour metastasis is an intricate process controlled by various signalling pathways and the surrounding extracellular matrix (ECM) [1]. Tumour cell themselves along with other components in tumour microenvironment like immune cells, stromal cells (CAF), chemokines, and cytokines are involved in a complex crosstalk with tumour cells initiating metastasis. CAF are stromal component of cancer, epitomizing a dominant component of primary tumour which facilitates extra cellular matrix remodelling, thus tumour progression, metastasis, and therapeutic resistance [2].

Metastasis cascades are now believed to be necessitated by premetastatic niche followed by metastasis niche formation [3]. Pre-metastatic niches (PMN) are now generally presumed to be a true biological process and a key prerequisite in the formation of distant metastasis [4]. Recent researches have revealed critical cellular events on various tumour paradigms and interestingly fibroblasts at the metastatic site have shown its role in the metastatic milieu formation to be called as metastasis-associated fibroblasts (MAF) [5].

## Discussion

### Characteristic Features of Premetastatic Niche Associated Fibroblasts

Though CAF and MAF share many functional characteristics, their effects on tumour progression is found to be varying [5]. CAF in primary tumour have extensively explored but researches are less compared to MAF in metastatic tumours [6-7].

CAF is one of major constituent of the tumour microenvironment (primary tumour) whereas MAF are stromal fibroblasts that contributes to the establishment of metastatic lesions augmenting tumour proliferation, angiogenesis, immunosuppression, and migration thus therapeutic resistance [8-9]. Similarly, the activated stellate cells at metastatic site initiate the angiogenic switch resulting in invasion of endothelial cells which leads to tumour cells dissemination [8].

According to seed and soil hypothesis, a favourable fertile soil is essential for the growth of tumour cells in distant organ forming PMN [10]. MAFs are found to be associated with this organ remodelling process induced by tumour derived factors much before the arrival of tumour cells in remote organs.

Kaplan et al suggested MAFs upregulate fibronectin expression and platelet-derived growth factor receptor (PDGFR) expressing cells in future metastatic organ, facilitating PMN modulation within specific target organs, even before the arrival of cancer stem cells [11].

MAFs induce extra cellular matrix remodelling of target metastatic organs and upregulates the expression of fibronectin, lysyl oxidase (LOX) and MMP -9, thus augmenting PMN formation. MAFs also secrete proinflammatory cytokines and augment the stem ness aiding the tumour cell survival [12].

Matsusue R et al established smooth muscle actin (SMA)-positive MAFs cells in hepatic stellate cells which maintain the characteristic feature of PMN that indorse liver metastasis of colon cancer cells [13]. Fibroblast around the premetastatic stroma in breast cancer can serve and support the metastatic colonization of disseminated carcinoma cells in distant organs.

**Basis of MAFs**

Activation of MAFs is yet to be well-defined but possibly originate from resident fibroblasts, hepatic stellate cells, mesenchymal stem cells, mesothelial cells or from stromal cells derived from primary tumours [14]. MAFs are heterogeneous which can differentiate into myofibroblasts, growth factor or inflammatory gene expressing MAF.

**Functions of MAFs**

CAF comprises of around 80% of fibroblast population in a tumour which phenotypically resemble myo fibroblasts [15]. This express fibroblast activation protein (FAP), integrate α smooth muscle actin(αSMA), and deposit profuse amounts of fibronectin [16]. MAF reported to be heterogeneous and can be divided into myofibroblastic MAF, growth factor and inflammatory gene expressing MAF and portal fibroblast/mesothelial MAF populations [17-18]. Precursor mesenchymal cells from metastatic niche differentiate is found to differentiate into MAF by releasing specific cytokines.

MAFs create a tumour-friendly microenvironment augmenting the malignant characteristics of metastatic tumour cells. These are capable of mediating therapeutic resistance to antiangiogenic, immunotherapy by ECM remodelling, modulation of immune cells in TME, persuading angiogenesis etc [19].

MAFs are present even before the metastatic tumour cell arrives and gets activated either by adjacent tumour cells or from cells in the metastatic TME. Extra cellular vesicles of tumour cells and stromal cells also activates MAF.MAFs tends to diminish CD4+ T cell proliferation which play a key role in PMN formation and creates a fertile environment for metastatic tumour seeding. CAF originating from primary tumour exhibit a clear T cell activation where in MAF dampen T cell response. MAF is associated with to contribute unidentified immunosuppression in metastatic colorectal cancer.

**MAF & PMNs**

MAFs are one of key drivers in PMN formation, which are microenvironment established in distant remote organ induced by primary tumour before the arrival of tumour cells, there by favouring metastasis [20]. MAFs upregulates fibronectin in distant organ thus facilitating vascular endothelial growth factor receptor adhesion which is strongly associated with PMN formation [20-21].

MAF induce ECM remodelling of metastatic organ by up regulating lysyl oxidase (LOX), MMP 9 thus promoting PMN formation12. These secrete proinflammatory cytokines after activation such as IL 6/8, thus increasing their stemness [22-23].

**MAF: Potential Targeting Strategies**

Underlying molecular and cellular mechanisms of metastasis may establish new paradigms that may likely to guide future in the development of novel diagnostic and therapeutic strategies. Presently targeting strategies on MAF progresses, either on directly targeting MAFs or on targeting its mediators which can upstream and downstream signals of MAFs [24]. Current strategies targeting MAFs are mostly limited to pre-clinical models. MAF exhibit both inhibiting as well as promoting properties in metastatic growth [25].

A very few clinical trials are targeting FAP (Fibroblast Activation Protein) but these are expressed by both MAFs and CAFs. Simlukafusp Alfa (FAP-IL2v) targeting is also ongoing in oesophageal, breast, advanced/metastatic head and neck, and cervical cancers.

IL-6/Stat3 signalling along with the IL-6 receptor inhibitor tocilizumab can reduce the expression of MAFs in prostrate tumour and restore the sensitivity to hormonal therapy. IL-6 targeting is being tried on metastatic breast and pancreatic cancers [26- 27]. LOX inhibitor, β-aminoproprionitrile (BAPN) markedly reverse LOX-mediated metastasis in liver [28]. Preclinical studies on metastatic breast cancer suggests that the inhibition of IL-33 is a promising approach [29]. IL-33 inhibition also significantly reduces the number and size of metastatic lesion in lung.

**MAF: Current Understanding in Oral Cancers**

Even though studies addressing role of MAF in oral cancer metastasis is not available indirect evidence of its involvement in the downstream pathways is emerging. Marilena Vered et al evaluated the expression of LOX, fibronectin, vascular-endothelial growth factor receptor (VEGFR)-1, matrix metalloproteinase (MMP)-9 in cervical LN0/N0 from patients with oral cancer, suggesting the increased lenient pathway remotely paved by the primary oral tumour for the incoming metastatic cells [20].

Wakisaka et al. in OSCC showed that premetastatic lymphovascular niche (sinusoidal hyperplasia) appeared before formation of actual metastasis in the lymph nodes [4].

Various tumour models showed that tumour-derived factors stimulate the bone marrow-derived cells to interact with the premetastatic niche stroma in distant organ/lymph nodes to form lymph vascular niche. This lymph vascular niche facilitates tumour cell transport to the lymph nodes and contributes to the migration, residence, and survival of metastatic cancer cells. It will be valuable to unravel the importance of premetastatic niche and its relationship with the fibroblasts of metastatic site. PMN has a crucial effect and budding evidences support its formation is obligatory even in oral cancers. It is important to distinguish the presence of MAFs from another cellular component in tumour microenvironment in OSCC [21] More experimental evidences are required to signify the role of MAFs in the formation of premetastatic niche in OSCC.

**Conclusion**

Prevailing evidence suggests that MAFs facilitate metastatic tumour growth and mediate therapeutic resistance. Array of

studies in different cancers showed that MAFs are accountable for metastasis and may secrete crucial molecular proteins associated with the formation and maintenance of metastasis.

Considerate knowledge on MAFs, as a component of metastatic tumour is of greater significance in increasing the therapeutic targeting of metastatic tumours.

Even though MAFs suggestive of a promising target in pre-clinical studies, there may be discrepancies in actual human trials. Compared to CAF, only few studies have been reported on MAF, hence more research may be needed for a better understanding of MAFs, to improve therapeutic efficacy along with identification of the type of tumour that is suitable for anti-MAF therapy. Its role in different cancers including oral cancers need to be given thrust in future studies.

**References**

1. Hu JL, Wang W, Lan XL, Zeng ZC, Liang YS. et al. (2019) CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial-mesenchymal transition in colorectal cancer. Mol Cancer 18: 91.
2. Quail DF, Joyce JA (2013) Microenvironmental regulation of tumour progression and metastasis. Nat Med 19: 1423-1437.
3. Chin AR, Wang SE (2016) Cancer tills the premetastatic field: mechanistic basis and clinical implications. Clin Cancer Res 22: 3725-3733.
4. Wakisaka N, Hasegawa Y, Yoshimoto S, Miura K, Shiotani AN. et al. (2015) Primary tumour-secreted lymphangiogenic factors induce pre-metastatic lymph vascular niche formation at sentinel lymph nodes in oral squamous cell carcinoma. PLoS ONE 10: e0144056.
5. Pein M, Insua-Rodríguez J, Hongu T, Riedel A, Meier J, et al. (2020) Metastasis-initiating cells induce and exploit a fibroblast niche to fuel malignant colonization of the lungs. Nat Commun 11: 1494.
6. Raz Y, Cohen N, Shani O, Bell RE, Novitskiy SV, et al. (2018) Bone marrow-derived fibroblasts are a functionally distinct stromal cell population in breast cancer. J Exp Med 215: 3075-93.
7. O'Connell JT, Sugimoto H, Cooke VG, MacDonald BA, Mehta AI, et al. (2011) VEGF-A and Tenascin-C produced by S100A4 + stromal cells are important for metastatic colonization. Proc Natl Acad Sci 108: 16002-16007.
8. WelsJ, Kaplan RN, Rafii S, Lyden D (2008) Migratory neighbors and distant invaders: Tumor-associated niche cells Genes Dev 2008 22: 559-574.
9. Weiss L, Gilbert HA, Ballon SC (1980) Lymphatic system metastasis GK Hall & Co Boston 3: 2-40.
10. Akhtar M, Haider A, Rashid S, Al-Nabet ADMH (2019) Paget's "Seed and Soil" Theory of Cancer Metastasis: An Idea Whose Time has Come Adv Anat Pathol 26: 69-74.
11. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, et al. (2005) VEGFR1-positive haematopoietic bone marrow progenitors initiate the premetastatic niche. Nature 438: 82.
12. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, et al. (2017) Pre-metastatic niches: organ-specific homes for metastases. Nat Rev Cancer 17: 302-317.
13. Matsusue R, Kubo H, Hisamori S, Okoshi K, Takagi H, et al. (2009) Hepatic stellate cells promote liver metastasis of colon cancer cells by the action of SDF-1/CXCR4 axis Ann Surg Oncol 16: 2645-2653.
14. Ji Q, Zhou L, Sui H, Yang L, Wu X, et al. (2020) Primary tumors release ITGBL1-rich extracellular vesicles to promote distal metastatic tumor growth through fibroblast-niche formation. Nat Commun 11: 1211.
15. Batlle E, Clevers H (2017) Cancer stem cells revisited Nat Med 23: 1124-1134.
16. Hanahan D, Weinberg RA. (2011) Hallmarks of cancer: the next generation. Cell 144: 646-674.
17. De Palma M, Biziato D, Petrova TV (2017) Microenvironmental regulation of tumour angiogenesis. Nat Rev Cancer 17: 457-474.
18. Kobayashi H, Gieniec KA, Wright JA, Wang T, Asai N, et al. (2021) The Balance of Stromal BMP Signaling Mediated by GREM1 and ISLR Drives. Colorectal Carcinogenesis. Gastroenterology 160: 1224-1239.
19. Pausch TM, Aue E, Wirsik NM, Valls AF, Shen Y et al. (2020) Metastasis-associated fibroblasts promote angiogenesis in metastasized pancreatic cancer via the CXCL8 and the CCL2 axes. Sci Rep 10: 5420.
20. Vered M, Shnaiderman-Shapiro A, Schiby G, Zlotogorski-Hurvitz A, Salo T, et al. (2019) Markers of the pre-metastatic niche "knock on the door" of metastasis free cervical lymph nodes in patients with oral cancer ActaHistoche 121: 151447.
21. Nguyen DX, Bos PD, Massague J (2009) Metastasis: from ´ dissemination to organ-specific colonization. Nature Reviews Cancer 4: 274-284.
22. Kong J, Tian H, Zhang F, Zhang Z, Li J, et al. (2019) Extracellular vesicles of carcinoma-associated fibroblasts create a pre-metastatic niche in the lung through activating fibroblasts. Mol Cancer 18: 175.
23. Su S, Chen J, Yao H, Liu J, Yu S, et al. (2018) CD10(+) GPR77(+) CancerAssociated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness. Cell 18: 172-841.
24. Dong G, Chen P, Youtao et al (2018) CancerAssociated Fibroblasts Promote Cancer Formation and Chemoresistance by Sustaining Cancer Stemness. Cell 566: 0304-3835.
25. Bhattacharjee S, Hamberger F, Ravichandra A, Miller M, Nair A, et al. (2021) Tumor restriction by type I collagen opposes tumor-promoting effects of cancer-associated fibroblasts. J Clin Invest 131: e146987.
26. Du YE, Tu G, Yang G, Li G, Yang D, et al. (2017) MiR-205/YAP1 in Activated Fibroblasts of Breast Tumor Promotes VEGF-independent Angiogenesis through STAT3 Signaling Theranostics 7: 3972-3988.
27. Sansone P, Berishaj M, Rajasekhar VK, Ceccarelli C, Chang Q, et al. (2017) Evolution of Cancer Stem-like Cells in Endocrine-Resistant Metastatic Breast Cancers Is Mediated by Stromal Microvesicles. Cancer Res 77: 1927-1940.
28. Li Q, Zhu CC, Ni B, Zhang ZZ, Jiang SH, et al. (2019) Lysyl oxidase promotes liver metastasis of gastric cancer via facilitating the reciprocal interactions between tumor cells and cancer associated fibroblasts. EBioMedicine 49: 157-171.
29. Wang Z, Liu J, Huang H, Ye M, Li X, et al. (2021) Metastasis-associated fibroblasts: an emerging target for metastatic cancer . Biomarker Research 9: 47.