The good, the bad, and the uncertain: Can matrix metalloproteinase 12 simultaneously be protumorigenic and antitumorigenic?

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Central Message

Matrix metalloproteinase 12 promotes the malignant phenotype in non-small cell lung cancer cells, and higher expression is correlated with worse overall survival.

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In this issue of the *Journal*, Ella and colleagues¹ study the role of matrix metalloproteinase 12 (MMP-12) in lung cancer. Although MMP-12's relationship to chronic obstructive pulmonary disease and asthma is well documented,²⁻⁴ its role in non-small cell lung cancer (NSCLC) is contradictory. The relationship between MMP-12 overexpression in both chronic obstructive pulmonary disease and other malignancies has prompted several reports of MMP-12 and NSCLC.^{2,3,5-8} These studies have yielded remarkably conflicting results. On the one hand, higher MMP-12 expression has been shown to correlate with increased tumor growth, invasion, metastases, recurrence, and suppression of immune responses.⁹⁻¹¹ On the other hand, other studies have demonstrated that MMP-12 may exert a protective effect by suppressing growth and metastases while modulating apoptosis.¹²⁻¹⁴ Both macrophages and tumor cells produce MMP-12, which may contribute to the opposing functions.^{10,14} Efforts to demonstrate the role of MMP-12 in NSCLC have fallen short.

Ella and colleagues¹ demonstrate the tumorigenic effect of tumor-derived MMP-12 with insightful and original findings. First, they performed univariable and multivariate analyses of 3 lung cancer microarray data sets, cancer Biomedical Informatics Grid (caBIG), Gene Expression Omnibus (GEO), and The Cancer Genome Atlas (TCGA) and demonstrated that higher MMP-12 levels were associated with lower median overall survivals. As Ella and colleagues¹ note, these conclusions merit caution given the retrospective findings and the inability to perform a comprehensive multivariate analysis. Importantly, a survival analysis per stage is not reported. With an immunohistochemical staining of a lung cancer tissue array, they observed higher expression of MMP-12 in nearly all NSCLC lung histologic types when compared with normal lung tissue. They stress that MMP-12 expression in all histologic types represents important additional knowledge on

this topic; however, the array included only a small number of small cell, large cell, neuroendocrine, carcinoid tumors, and bronchoalveolar carcinoma.

Another particularly notable finding is that exposing tumor cells to lung microenvironment both in vitro and in vivo drives higher expression of tumor cell-derived MMP-12. These findings are consistent with previous experiments demonstrating that MMP-12 in tumors is primarily induced from stromal cells rather than macrophages.⁹⁻¹¹ They also observe that knocking down MMP-12 both in vitro and in vivo decreased the malignant phenotype of the cells, as noted by a marked reduction in colony formation. In their in vivo model, they directly inject the lung to recapitulate early-stage lung cancer. Ideally, they would report whether MMP-12 was associated with different survivals among patients with stage I NSCLC, rather than grouping all stages, to be consistent with this model. In addition, tail vein injections to model metastatic colonization could strengthen the conclusions of MMP-12 in all stages of NSCLC, especially because they noted reports of no difference in recurrence according to MMP-12 expression. One final note is that most of the experiments were performed in a murine cell line (LLC) as well as one human-derived line from a large cell carcinoma (H460). Ideally, these experiments would be confirmed in adenocarcinoma or squamous cell carcinoma. Regardless of these limitations, Ella and colleagues¹ are to be commended for

reporting original and compelling evidence for the tumorigenic properties of MMP-12 in NSCLC. They have both used interesting models to study the endlessly complex tumor microenvironment and correlated these models with patient-derived data.

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