Reviewer's report

Title: Fibroblast-Derived MT1-MMP Promotes Tumor Progression In Vitro and In Vivo

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Reviewer: Nor Eddine SOUNNI

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General

This report seeks to delineate the role of fibroblast-derived MT1-MMP, MMP-2 or MMP-9 on head and neck squamous cell carcinoma invasion and tumor growth phenotypes. By using fibroblast null MMPs, recombinant TIMPs and proteases inhibitors, in an in vitro invasion assays of 2D-collagen Type I model by culturing fibroblast alone or in coculture with HNSCCs cells, the authors observe that the invasion of tumor cell is stimulated by WT fibroblast, reduced by MMP-2 null fibroblasts and abrogated by MT1-MMP null fibroblasts. MMP-9 null fibroblasts have no effect on in vitro cancer cell invasion. The in vivo tumor studies by co-injection of tumor cells with fibroblast in an orthotopic tumor growth model, allow the authors to conclude that MT1-MMP derived fibroblasts significantly stimulate tumor growth compared to cancer cell alone or co-injected with MMP-2 or MMP-9 null fibroblasts. Identifying fibroblast derived MMPs in tumor progression has been evidenced by several reports. This work demonstrates for the first time, a direct role of MT1-MMP derived fibroblast in tumor invasion and growth.

This report is technically sound and represents a good starting point for understanding the mechanism by which stroma membrane tethered MMP (MT1-MMP) regulates epithelial tumor invasion and growth. At this juncture however the authors cannot exclude the role of MT1-MMP produced by HNSCCs. To check this point, gene silencing of MT1-MMP in HNSCCs cell can be performed with the in vitro invasion test in coculture with fibroblast MT1-MMP-/- or WT.

The authors are able to show that fibroblast null MMP-9 invade Type I collagen gel like wild-type fibroblast, but not MT1-MMP or MMP-2 null fibroblast, this data is consistent with other reports, but how can the authors explain the fibroblast or cancer cells invading the collagen without using any chemo-attractant (for instance: PGDF-BB for fibroblast or HGF for cancer cells) in the lower compartment of the Transwell Chamber of the invasion assays?

The authors should show a profile of MT1-MMP production by western blot on WT fibroblast or MMP-2 and MMP-9 null fibroblast. Active MT1-MMP is produced at 60 KDa form after intracellular processing of the inactive 63 KDa form by furin, by using an antibody directed against hemopexin domain, the authors can prove the functionality of fibroblast derived MT1-MMP and support the data of invasion inhibition by furin inhibitor.

The in vivo tumor growth with WT or MMP null fibroblast represents the most original section of this report. The absence of MT1-MMP in fibroblast fails to induce tumor growth, and that MMP-2 or MMP-9 null fibroblast had respectively 48 % and 49 % reduced in vivo FaDu tumor growth. The authors did not observe any histological difference on invasion, grade or angiogenesis; this may be, due to time limitation of this model. Although the authors report that the mechanism by which fibroblast derived MT1-MMP promotes tumor growth is under investigation, this point needs more discussion by citing reports indicating the multifunctional role of MT1-MMP.

Their functions have been extended from pericellular proteolysis and control of cell migration to cell signaling, control of cell proliferation, apoptosis and angiogenesis.
Minor remark:
Page 14, line 3: It is unlikely that this signaling…Please delete the repeated “That”

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
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Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after discretionary revisions
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No
Declaration of competing interests:
I declare that I have no competing interests