To the Editor:

Thank you for giving us the opportunity to revise and resubmit our manuscript. We agree with all of the criticisms and recommendations made by the reviewers and have re-written our paper to incorporate substantial new data and to respond to the suggestions made by the reviewers.

The following is a point-by-point response to the comments of the individual reviewers:

Reviewer #1: No specific points to address. We are in general agreement with this review of our paper.

Reviewer #2:
1. We have added substantial new data quantifying and comparing mast cells in breast cancer, other cancers, and normal tissues. Statistical analysis was performed.
2. We have provided additional documentation about the presence of FGF-7 in our cultured fibroblasts, including data from gene expression microarrays and Western blotting.
3. We have added new data regarding the effects of a lysate of a human mast cell line, HMC-1.
4. We now have incorporated new data from ten breast cancer tissues.
5. The experimental protocol used for immunostaining has been described in much more detail, including how the staining was quantified and the origins of the positive and negative controls.
6. We have provided more details about the culture medium, tryptase, and heparin used in our experiments.
7. The publication by Forsberg et al was added and cited in the discussion. We also provide a more detailed discussion about the NDST-2 mice.
8. We have added the Smorenburg reference and a new reference #21 regarding the direct effects of heparin on the proliferation of normal epithelial and tumor cells. This issue is now extensively considered in the revised Discussion.

Reviewer #3:
1. We have extensively rewritten the paper to make the two parts of the work more integrated and harmonious. In specific, we now emphasize that tryptase is also a surrogate marker for heparin in tissues because heparin is closely bound to tryptase. In addition, we now cite two new references [18, 19] to document that stromal fibroblasts in cancer express FGF-7. Finally, paragraph 5 of the revised Discussion now specifically attempts to link the two major parts of our work.
2. The sixth paragraph of the revised discussion now considers the possible role of other mediators from mast cells and fibroblasts.
3. We have included new data regarding the effects of a lysate of a human mast cell line (HMC-1) on the clonogenic growth of our co-culture system.
4. We have provided additional information about the origin of the allegedly normal fibroblasts used in this study.
5. We have added new data regarding the dose-response effect of multiple doses of heparin on the clonogenic growth of tumor cells in the co-culture system.
6. In paragraph 3 of the revised Discussion, we have added new information about the direct effects of heparin on tumor cells and epithelial cells.

In summary, we believe that we have responded in a substantive manner to the constructive comments made by the reviewers, and we feel that our paper has now been significantly improved by these revisions.
We thank you again for your review of our work, and we hope that it will now be considered suitable for publication.

Sincerely,
Michael Samoszuk, M.D.
Associate Professor of Pathology
University of California, Irvine