

# TMED2 as a marker of prognosis in breast cancer [Letter]

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## Dear Editor

We thank Lin et al for their interesting study proposing TMED2 overexpression as a potential marker of poor prognosis in breast cancer.<sup>1</sup> While the results imply that TMED2 overexpression decreases survival rates, we are hesitant to agree with the authors' statement claiming its prognostic power until certain aspects of the study are clarified. We further propose recommendations for consideration in future investigations to maximize the potential of this study.

The authors identified and isolated two novel cell types arising from a murine breast cancer cell line, 4T1, termed sphere cells (SC) and non-sphere cells (NSCs), that differ in their morphological, differentiative, proliferative, and metastatic properties. Transcriptomic analysis showed an upregulation of 44 and 27 metastasis-promoting genes in SCs and NSCs, respectively. It is unclear why the authors chose to focus solely on TMED2, and this may represent a missed opportunity to explore a wider range of prognostic markers. Considering the restriction of all downstream experiments to TMED2, we were surprised at the lack of depth and strong causal evidence for its role in breast cancer in this paper. The authors claim that the decreased survival and increased metastatic properties associated with SCs, compared to NSCs, are a function of TMED2 overexpression. The published work does not comment on the possible influence of the other 43 pro-metastatic genes, which are also overexpressed in this cell type. Should the authors continue to examine TMED2's role in poorer survival outcomes and increased metastasis, we propose experiments that control for other factors contributing to cell phenotype; for example, knocking out or silencing TMED2 in SCs to confirm ablation or hindering of cell metastasis *in vivo*. Similarly, expression of TMED2 in NSCs and subsequent rescue of their ability to metastasize would provide strong evidence for the authors' hypothesis.<sup>2</sup> A recent study on TMED2 as a prognostic marker in ovarian cancer was successful in showing the causal link between its expression and function.<sup>3</sup>

Finally, we emphasize the importance of relating the authors' findings to human cancer. This study's data analysis showed that TMED2 overexpression in human samples corresponds to lower rates of survival, but only in ER-positive breast cancer. Lin et al reveal no correlations between TMED2 mRNA expression and cancer grades, lymph-node statuses, or TP3 status. Attempts at isolating SCs and NSCs from a variety of human breast cancer cells were unsuccessful. In order for the findings of this study to command stronger clinical relevance, TMED2

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expression, proliferative rates, or differentiation potential of human lines could be investigated.<sup>4</sup> The lack of bifurcated morphological phenotypes in these lines does not exclude them as a valuable resource in investigating TMED2 expression in human breast cancer. Another option could be to use patient-derived xenografts originating from tumors with either low or high TMED2 expression to show relevance to humans.<sup>5</sup>

In conclusion, the present study is an important starting point in exploring TMED2 as a potential prognostic marker in breast cancer and, with some additional considerations, could result in significant advancements in breast cancer prognosis.

## Disclosure

The authors report no conflicts of interest in this communication.

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