High tissue inhibitor of matrix-metalloproteinase 2 expression correlates with poor prognosis in breast cancer

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Background & objectives

TIMP2, tissue inhibitor of matrix-metalloproteinase 2, inhibits the matrix-metalloproteinase, MMP2, but may activate pro-MMP2. Hence its correlation with prognosis in breast cancer (BC) is contradictory. This study investigated the correlations of TIMP2 expression in BC with clinicopathological variables.

Methods

Differential expression analysis of TIMP2 was assessed in the lymphovascular invasion (LVI) positive versus negative cohorts in the METABRIC BC dataset. Immunohistochemical analysis for TIMP2 (1:50 dilution) expression was conducted on BC tissue microarrays (n=1048) and clinicopathological correlations were assessed, including VI and expression of MMPs, 2, 14 and 15.

Results

TIMP2 was associated with positive LVI in the METABRIC cohort (p= 0.002). On immunohistochemistry, significant positive correlations were found between TIMP2 protein expression and higher grade (p=0.019), including its components nuclear pleomorphism (p=0.004), mitotic count (p=0.000087), LVI (p=0.014) and Nottingham prognostic Index (p=0.024). TIMP2 expression showed a significant correlation with negative ER status (0.014) and Triple negative status (p =0.008). TIMP2 expression also showed a positive correlation with cytoplasmic MMP2, MMP14 and MMP15 ($p<0.0001$) expression. A significant difference in 10-year BC specific survival (BCSS) was seen between high and low TIMP2 expression (p= 0.018).

Conclusion

Overall, the study indicates that higher TIMP2 expression correlates with poor prognostic factors in BC including high grade, negative ER status, poor NPI and LVI. These effects may be explained through its activation of pro-MMPs, reflected by positive associations with MMP expression. Further studies of the ratio between MMPs and TIMP2 may help delineate its functional role in BC.