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TGF-βRI contributes to tamoxifen response in luminal B breast cancer with HER2 negative phenotype

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Background

Luminal B-like breast cancer with different HER2 phenotype is highly heterogeneous tumors harboring distinct prognosis and showing different treatment response [Testa et al., 2020]. Despite the positive ER expression, luminal B-like tumors can use alternative growth signaling pathways leading to progression and resistance to therapy [Creighton et al., 2012].

Among them, TGF signaling cascade, that induces pleiotropic effects determined by the cellular context. However, the value of TGF-β signaling components as potential resistance-related markers is not fully understood, especially in breast cancer molecular subtypes.

The aim of this study was to examine the contribution of TGF-β family proteins to tamoxifen response in luminal breast cancer patients with different HER2 phenotype.

Material and methods

A total of 60 specimens from patients with luminal B HER2 negative and luminal HER2 positive breast cancer who had received tamoxifen therapy at a dose of 20 mg/day for at least 5 years were included in the present study.

The level of TGF-β, TGF-βRI, TGF-βRII and ERα mRNA expression was assessed using a quantitative real-time RT-PCR assay. The expression level of the corresponding proteins was detected by immunohistochemistry.
Survival analyses were performed using the Kaplan-Meier method with log-rank test. Tamoxifen resistance was defined as clinical progression during of disease treatment or relapse.

The study was approved by the Ethics Committee of the Cancer Research Institute, Tomsk National Research Medical Center; every patient provided written informed consent.

Results

We evaluated TGF-β, TGF-βRI, TGF-βRII and ERα protein expression by IHC, and also their mRNA levels in tumor tissue of patients according to the tamoxifen response.
High expression level of TGF-βR1 was associated with greater degree of benefit from tamoxifen only in luminal B HER2 negative breast cancer patients (p = 0.021; Fig.1-2).

We have recently reported that TGF-βRI is linked with the distribution pattern of ERα expression in the hormone-receptor positive breast cancer [Babyshkina et al., 2021].
In this study, the homogeneous ERα expression was significantly related to effectiveness of tamoxifen in luminal B breast cancer patients with HER2 negative phenotype (p = 0.011).
In addition, luminal B HER2 negative tumors with TGF-βRI-positive expression tended to be closely associated with the homogeneous ERα expression (p = 0.180).

Kaplan-Meier estimates of tamoxifen-treated patients according to TGF-βRI expression showed increased benefit of tamoxifen treatment with increasing levels of TGF-βRI expression in luminal B HER2 negative breast cancer patients (log-rank p = 0.010; Fig.3-4).

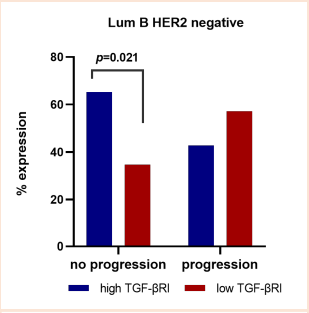

Fig.1 TGF-βRI expression in luminal B HER2 negative patient groups according to the tamoxifen response.

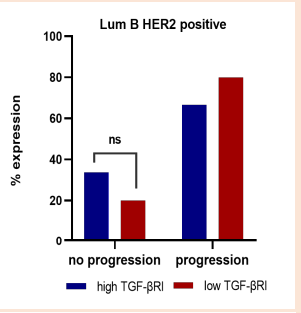

Fig.2 TGF-βRI expression in luminal HER2 positive patient groups according to the tamoxifen response.

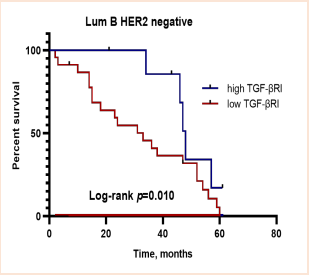

Fig.3 Progression-free survival stratified by TGF-βRI expression for luminal B HER2 negative patients group.

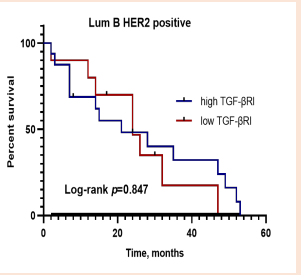

Fig.4 Progression-free survival stratified by TGF-βRI expression for luminal HER2 positive patients group.

Conclusion

The findings of the present study suggest that TGF-βRI may be used as a potential target for the tamoxifen treatment of luminal B breast cancer patients with HER2 negative phenotype.
Further study is required to assess the possible relationship between the TGF-β family proteins and tamoxifen responsiveness in luminal HER2 positive breast cancer.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

Acknowledgments

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