A prognostic signature based on two-miRNA and pathological data in early-stage HER2+ Breast Cancer patients

A. Adam-Artigues[1], M.Á. Beltrán[2], J.A. Carbonell-Asins[2], S. Zúñiga[3], S. Moragón[1], M.T. Martínez[1], C. Hernando[1], O. Burgués[1], F. Rojo[4], J. Albanell[5], >. Lluch[1], B. Bermejo[1], P. Eroles[1], Juan Miguel Cejalvo[1]

[1]Oncology Department, INCLIVA Biomedical Research Institute, Valencia, Spain, [2]Biostatistics Unit, INCLIVA Biomedical Research Institute, Valencia, Spain, [3]Precision Medicine Unit, INCLIVA Biomedical Research Institute and CIBERONC, Valencia, Spain, [4]Pathological Anatomy, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain, [5]Cancer Research Program, Hospital del Mar, Barcelona, Spain

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BACKGROUND

In early-stage HER2+ breast cancer (BC), de-escalation of systemic treatment remains a challenge. New biomarkers into risk scoring will help improvement in this field. We aim to develope a prognostic signature based on 2 miRNAs (A, B), quantitative and qualitative clinical variables in HER2+ BC patients.

METHODS

A retrospective patients' cohort (n= 45) who received standard treatment for localized disease was selected. We calculated a prognostic signature for disease-free survival (DFS) by principal components analysis combining pathological data (Ki67 and axillary lymph node status) and expression of miRNAs. Multiple DFS prognostic signatures were calculated and goodness of fit was evaluated by Akaike's Information Criterion to perform Cox model selection. Signature was dichotomized into high risk and low risk using maximally selected Log-Rank statistics by Hothorn and Lausen, as method for optimal cut-off. Target genes were predicted and functional enrichment analysis was performed with KEGG and validated by western blot after miRNA mimics transfection.

RESULTS

MiR-A and B were strongly correlated (r=0.84) **(Fig 1C)** and their expression was higher in primary tumor of patients who relapsed (miR-A p= 0.004 miR-B p= 0.018) **(Fig 1A and 1B)**.

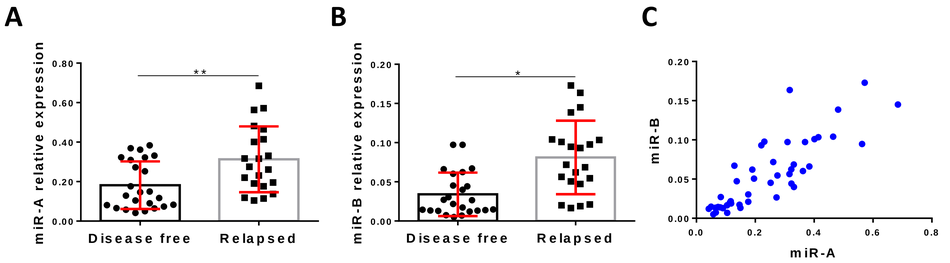

Fig. 1. MiR-A (A) and miR-B (B) relative expression of disease free versus relapsed patients. Correlation between miR-A and miR-B in HER2+ BC samples (C). Red lines represent median with interquartile range. * p<0.05 ** p<0.01

Our signature was significantly associated with relapse (HR 1.72; CI 95%: 1.24–2.38; p<0.01, AIC=114). Median DFS of high risk was 44 months while it was not reached in low risk after 67 months of median follow-up (HR 8.39; p=0.005, AIC=111). Significant differences in survival between groups were found (p<0.001) **(Fig. 2)**. This signature was not applicable in other BC subtypes.

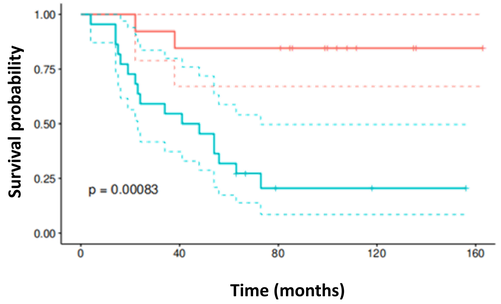

Fig. 2. DFS Kaplan-Meier curve in HER2+ BC patients stratified in high and low risk group based on signature score.

Functional enrichment analysis returned 55 significant pathways. Interestingly, P53, apoptosis and DNA damage were in the top 5 enriched pathways **(Fig. 3A)**. Protein expression of predicted targets from these pathways was decreased after miRNA overexpression **(Fig. 3B and 3C)**.

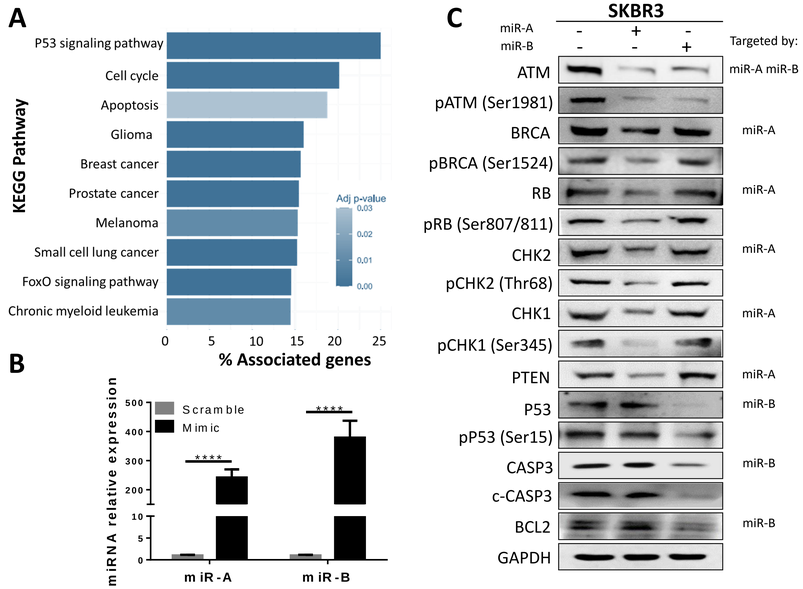

Fig. 3. KEGG pathway enrichment analysis for miR-A and miR-B (A). Relative expression of miR-A and miR-B after 72 hours of miRNA mimic transfection. Protein expression of predicted targets after overexpression of miR-A and miR-B in BT474 cell line assed by western blot analysis (C).

CONCLUSIONS

Both miRNA are related to main biological pathways associated to BC. Our prognostic signature identifies patients with early-stage HER2+ BC who might be candidates for de-escalated systemic treatment. This signature was able to classify patients for DFS in high or low risk groups at the moment of BC diagnosis. Further investigations to validate the value of this signature are on-going.

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aadam@incliva.es