Dissecting the pro-tumorigenic role of interleukin (IL)-11 by both transcriptomic analysis of primary breast cancer cells and large-scale in silico investigations

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Introduction. The advent of high-throughput methodologies and the availability of multi-omics datasets are crucial to define heterogeneous diseases at the molecular level[1-3]. Indeed, the analysis of biological data represents a powerful tool toward the identification of new targets and the accomplishment of innovative therapeutic approaches in diverse diseases, including cancer[4,5]. Here, we aimed to dissect the transcriptional changes induced by estrogen and insulin in a primary breast cancer (BC) cell line, namely BCAHC-1, which is characterized by a peculiar expression of the 46 kDa isoform of estrogen receptor (ER)α and the insulin receptor (IR). As interleukin (IL)-11 appeared as the strongest up-regulated gene by both estrogen and insulin, we therefore explored its biological role by performing large-scale in silico investigations.

Results

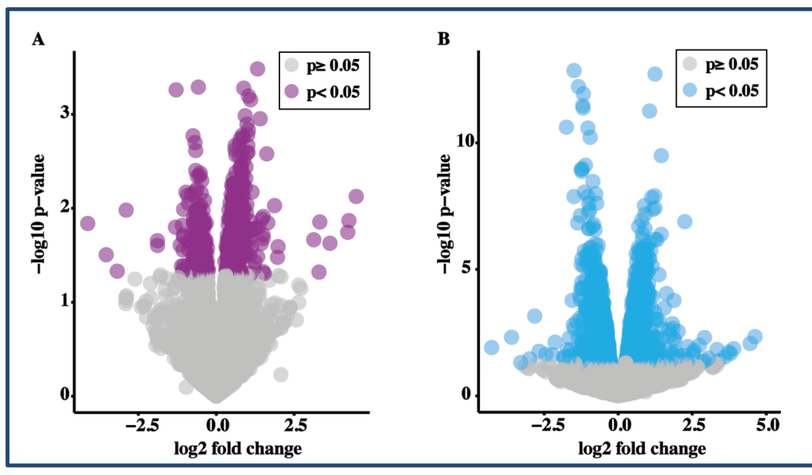

Figure 1. Volcano plots depicting the mRNA expression changes in BCAHC-1 cells treated for 12 h with 17β -estradiol (E2) (A) or insulin (B), as found by RNA-seq analysis.

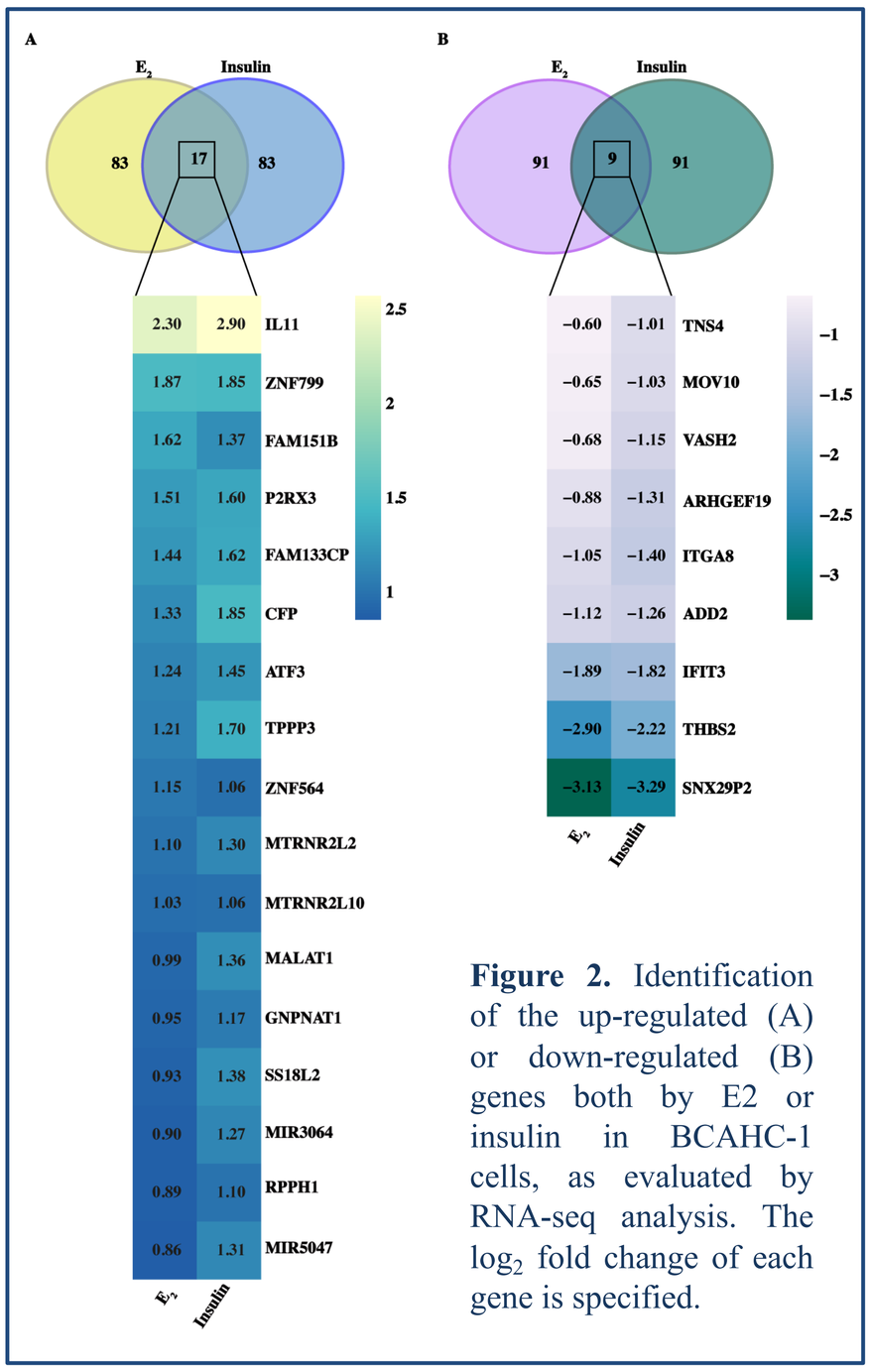

Figure 2. Identification of the up-regulated (A) or down-regulated (B) genes both by E2 or insulin in BCAHC-1 cells, as evaluated by RNA-seq analysis. The log_2 fold change of each gene is specified.

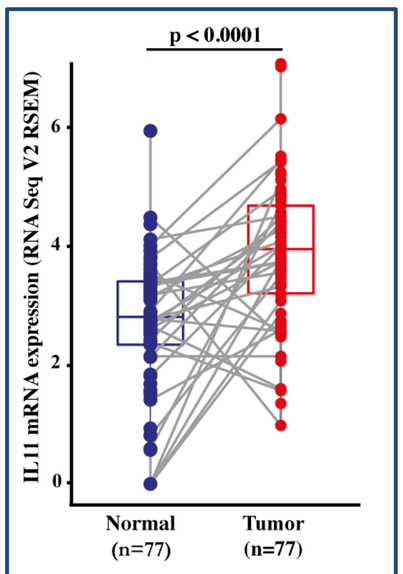

Figure 3. Pairwise comparison of IL-11 expression levels in ER-positive BC samples and the adjacent normal tissues, as found by querying the TCGA dataset.

References

1. Xiang Y et al., Trends in Cancer 2018, 4:823 – 837
2. Gray GK et al., Developmental Cell 2022, 57:1400- 1420.
3. Cao Y et al., Nat Rev Cancer 2:500-508.
4. Jiang P et al., Nat Rev Cancer 2022, 1-15.
5. Hassan M et al., Int J Mol Sci. 2022, 23(9):4645.

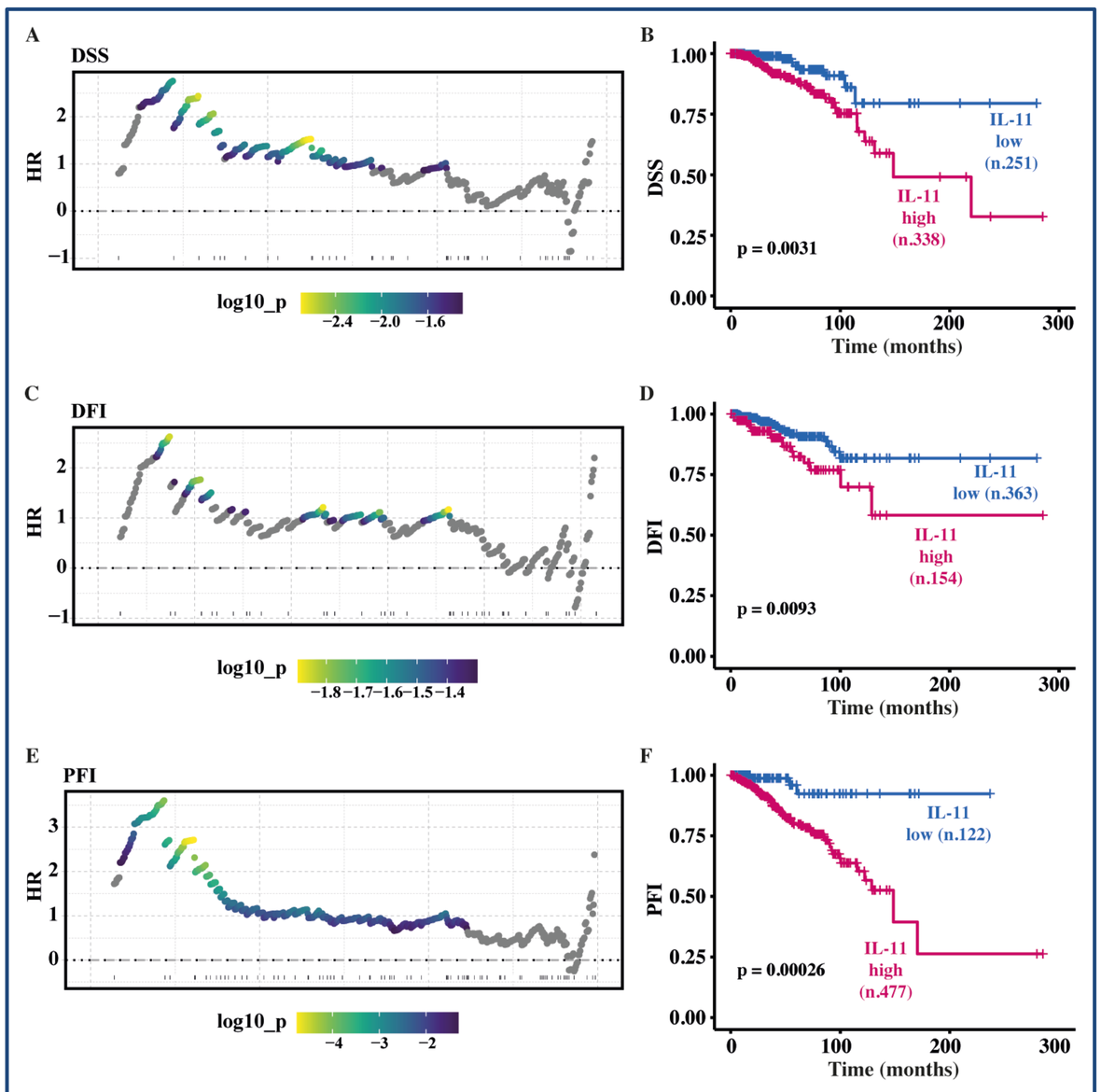

Figure 4. High IL-11 expression is associated with worse clinical outcomes in ER-positive BC samples of the TCGA database. (A, C, E) Patients were divided into high and low expression of IL-11 on the basis of the established cut-point, which was calculated considering IL-11 expression and disease-specific interval (DSS) (A), disease-free interval (DFI) (C) or progression free interval (PFI) (E) of each patient. (B, D, F) Kaplan-Meier plots depicting the correlation of IL-11 expression and DSS (B), DFI (D) and PFI (F) according to the cut-points shown in panels A, C and E.

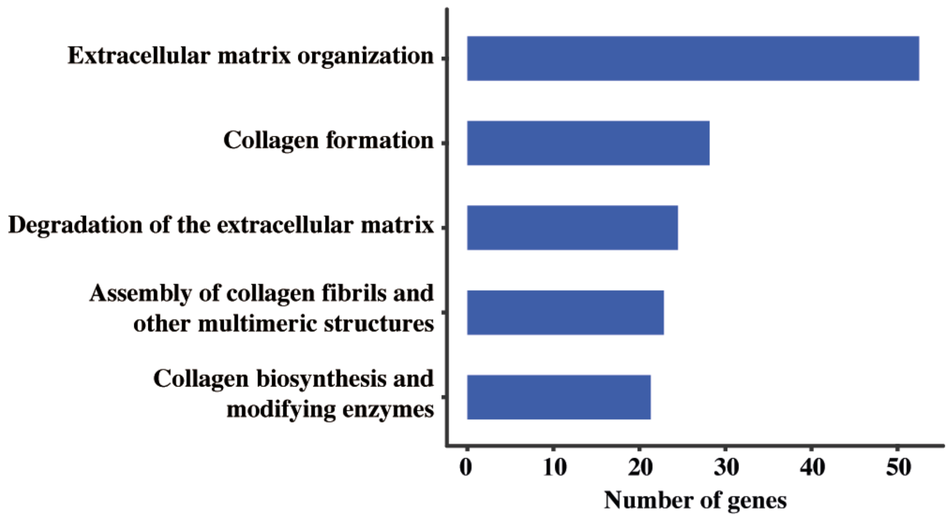

Figure 5. Reactome pathway analysis reveals the association of IL-11 with pro-tumorigenic pathways. The number of genes clustered in each pathway is indicated along the x-axis of the bar plot, whereas the different Reactome pathways are shown along the y-axis. $p < 0.0001$.

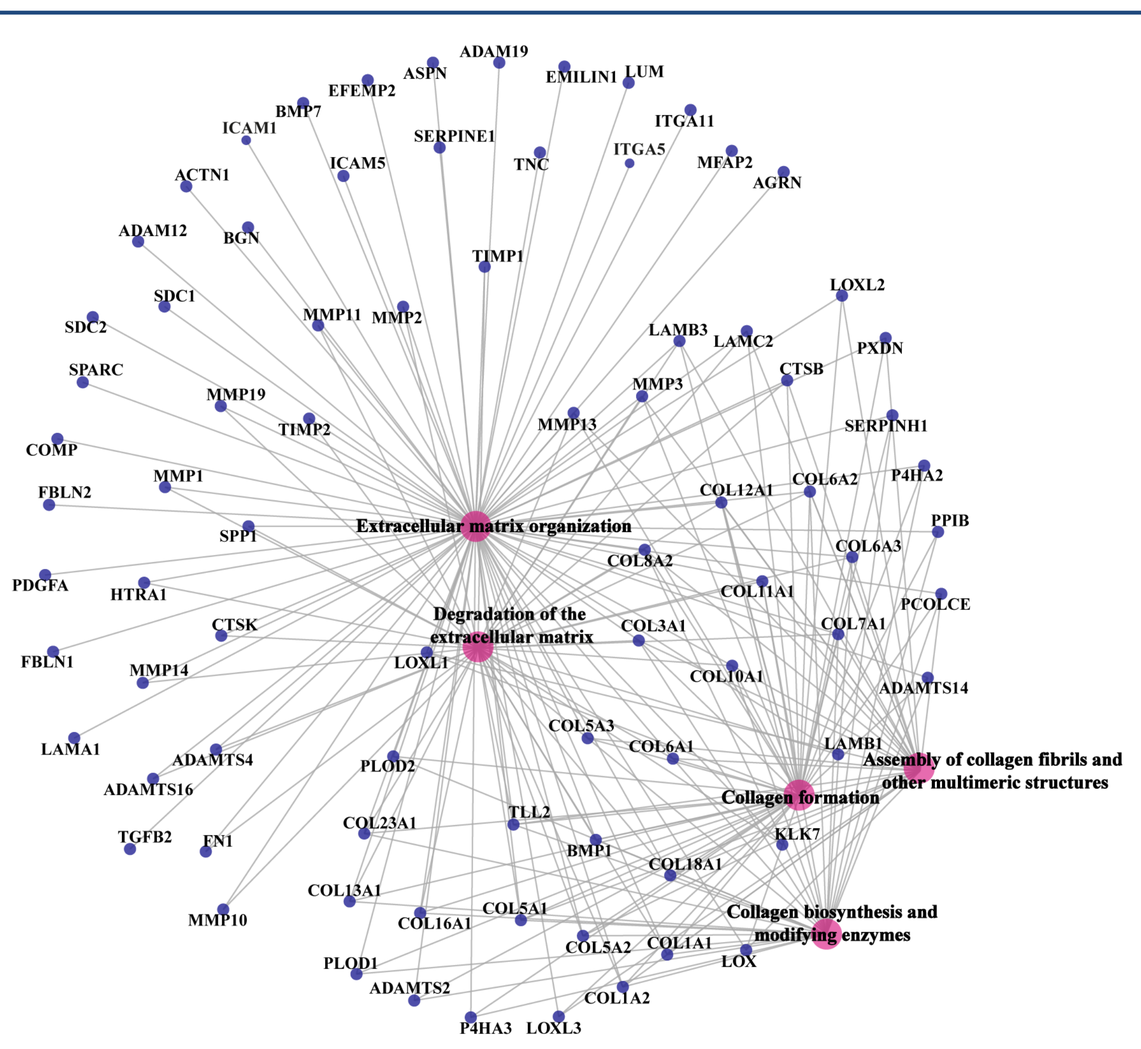

Figure 6. Gene network analysis displaying the connection among the IL-11 correlated genes belonging to the transduction pathways shown in figure 5.

Conclusions. Our findings indicate that E2 and insulin up-regulate the expression levels of IL-11 in BCHAC-1 cells. Moreover, our analyses suggest that high IL-11 expression levels may contribute to a more aggressive phenotype of ER-positive BCs. Additional in vitro and in vivo investigations are warranted in order to assess the usefulness of therapeutic strategies targeting IL-11 in BC.