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Abstract

Interleukin (IL)-11 Is Involved in the Functional Liaison between Breast Tumor Cells and the Surrounding Stroma †

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Abstract: Current advances in molecular profiling methodologies and the accessibility of multi-omics datasets are paving the way toward a better understanding of heterogeneous diseases, including breast cancer (BC). In this regard, we sought to uncover the transcriptional changes triggered by estrogen and insulin in a primary BC cell line (BCAHC-1), which expresses the 46kDa isoform of the estrogen receptor (ER)α and the insulin receptor, as we have previously ascertained. Raw data from RNA sequencing of BCAHC-1 cells were processed by the Bcl2Fastq 2.20 version of the Illumina pipeline, while in silico analyses were performed in R Studio using the TCGA dataset. Real-time PCR, immunoblotting, ELISA and chromatin immunoprecipitation experiments were used to identify the molecular events triggered by estrogen and insulin in BCAHC-1 cells and cancer-associated fibroblasts (CAFs). Furthermore, migration and invasion assays allowed us to ascertain the mechanisms triggering these biological responses in the presence of the aforementioned hormone treatments. First, we determined that 17β-estradiol (E2) and insulin stimulate a peculiar IL-11 expression and IL-11 secretion in BCAHC-1 cells. Thereafter, bioinformatics analyses confirmed the up-regulation of IL-11 in ER-positive BCs, with respect to adjacent normal tissues, and its association with worse survival. Next, the involvement of IL-11 in pro-metastatic transduction signaling was established via pathway enrichment analyses. Notably, we found that the secretion of IL-11 by BCAHC-1 cells prompts an invasive phenotype of CAFs through the up-regulation of genes belonging to the extracellular matrix organization pathway, namely, the intercellular adhesion molecule 1 and integrin alpha 5. Overall, our findings indicate that IL-11 secretion by BC cells may elicit a paracrine action on the surrounding stroma and introduce invasive properties, suggesting that IL-11 could be considered a valuable target in comprehensive treatments of ER-positive BC patients.

Keywords: breast cancer; tumor microenvironment; IL-11; bioinformatics

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