Analysis of Hierarchy in Gene Expression Reveals Principles Underlying Metastatic Aggressiveness of Inflammatory Breast Cancer

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Short Abstract — We quantified the hierarchical organization in the networks of collective dissemination-associated and inflammatory breast cancer (IBC)-associated genes in multiple cell lines and tumor samples. CCC, a measure of hierarchical organization, was found to be higher in epithelial versus mesenchymal cell lines and in IBC versus non-IBC breast tumor samples, for both sets of genes. Our results suggest a role for retention of some epithelial traits by disseminating tumor cells in the metastatic aggressiveness of IBC and a correlation of hierarchy in expression of collective dissemination-associated genes with high rates of metastatic relapse. Our analysis indicates that the CCC encodes additional information regarding the complexity of gene expression in cancer cells and can be a prognostic factor for IBC and other aggressive cancer sub-types.

Keywords — collective dissemination, inflammatory breast cancer, EMT, hierarchy, E/M hybrid, CCC.

I. INTRODUCTION

Clusters of circulating tumor cells (CTCs), despite being rare, may account for more than 95% of metastases [1, 2]. Cells in these clusters do not undergo a complete epithelial-to-mesenchymal transition (EMT) but retain some epithelial traits as compared to individually disseminating tumor cells [3]. Determinants of single cell dissemination versus collective dissemination remain elusive. Inflammatory breast cancer (IBC), a highly aggressive breast cancer subtype that chiefly metastasizes via CTC clusters, is a promising model for studying mechanisms of collective tumor cell dissemination [4]. Previous studies on breast cancer and adult acute myeloid leukemia, motivated by a theory that suggests physical systems with hierarchical organization tend to be more adaptable, have found that the expression of metastasis associated genes is more hierarchically organized in cases of successful metastases [5, 6].

II. METHODS

We used the cophenetic correlation coefficient (CCC) to quantify the hierarchical organization in the expression networks of two distinct gene sets, collective dissemination associated genes and IBC associated genes, in cancer cell lines and in tumor samples from breast cancer patients. Hypothesizing that a higher CCC for collective dissemination associated genes and for IBC associated genes would be associated with a more evident epithelial phenotype and with worse outcomes in breast cancer patients, we evaluated the correlation of CCC with different phenotypic groups.

III. RESULTS

The CCC of both gene networks, the collective dissemination associated gene network and the IBC associated gene network, was higher in (a) epithelial cell lines as compared to mesenchymal cell lines and (b) tumor samples from IBC patients, as compared to samples from non-IBC breast cancer patients. A higher CCC of both networks was also correlated with a higher rate of metastatic relapse in breast cancer patients. Neither the levels of CDH1 gene expression, nor gene set enrichment analysis could provide similar insights.

IV. CONCLUSIONS

These results suggest that retention of some epithelial traits in disseminating tumor cells as IBC progresses promotes successful breast cancer metastasis to distant organs. The CCC provides additional information regarding the organizational complexity of gene expression in comparison to differential gene expression analyses. We have shown that the CCC may be a useful metric for investigating the collective dissemination phenotype and a prognostic factor for IBC.

REFERENCES


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