

## The correlation between PLC- $\beta$ 2 and miR-146a in breast ductal carcinoma in situ (DCIS) defines its malignant potential

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Ductal carcinoma in situ (DCIS), which represents the most frequently diagnosed tumor in women in industrialized countries, may be a crucial step in the progression of breast lesions to invasive ductal carcinoma (IDC) (1). Among the signaling molecules deregulated in breast tumors, the beta2 isoform of the phosphoinositide-dependent phospholipase C (PLC- $\beta$ 2) strongly correlates with malignancy of invasive tumors and breast tumor-derived cells (2, 3). In breast tumor-derived cell lines cultured under hypoxia, PLC- $\beta$ 2 regulates the levels of cancer stem cell and epithelial-to-mesenchymal transition (EMT) markers (4), suggesting its involvement in breast cancer progression. By using archival FFPE breast tumor samples, we demonstrated that PLC- $\beta$ 2 is up-regulated in DCIS, in which it inversely correlates to the levels of miR-146a, known to act as a tumor suppressor in breast cancer (5). By using the MCF10DCIS cell line, a well-established model of DCIS-derived cells, we demonstrated that the de-regulation of miR-146a is sufficient to modulate the expression of PLC- $\beta$ 2, in turn able to affect the epithelial-to-mesenchymal shift as well as the number of cells expressing CD133. These data indicate that miR-146a and PLC- $\beta$ 2 are members of an intracellular network able to ensure the maintenance of the non-invasive phenotype of DCIS and suggest that alterations in their levels can determine the appearance of an invasive phenotype. The potential prognostic relevance of PLC- $\beta$ 2/miR-146a relationship was investigated in primary DCIS from patients who developed an invasive ductal carcinoma in the contralateral breast. The PLC- $\beta$ 2/miR-146a correlation was found negative in primary DCIS from patients who did not recur and strongly positive in DCIS from patients who developed a contralateral IDC. We propose that the assessment of the correlation between the levels of PLC- $\beta$ 2 and miR-146a in primary DCIS at diagnosis could be beneficial to identify patients with either low or high propensity to develop invasive recurrence. Since a major problem in the management of patients with DCIS is the lack of reliable prognostic markers, our results might be of value in selecting the most appropriate therapies for individual women with non-invasive breast neoplasia.

### References

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### Keywords

Ductal carcinoma in situ (DCIS); PLC- $\beta$ 2; miR-146a.