

PLC- β 2 plays a phenotype dependent role in the malignant potential induced by hypoxia in breast cancer cells

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Hypoxia plays a crucial role in malignant progression of solid tumors, including breast cancer, since neoplastic cells adapt to low oxygen availability by modulating the expression of genes involved in survival, proliferation, metabolic reprogramming, stem cell maintenance, EMT, angiogenesis, invasion and metastasis (1). Among the signaling molecules deregulated in breast tumors, the beta2 isoform of the phosphoinositide-dependent phospholipase C (PLC- β 2) is expressed in the large majority of primary invasive tumors from all histological subtypes in which it strongly correlates with malignancy and with a poor prognosis (2). PLC- β 2 is also expressed in breast tumor-derived cells, in which it improves proliferation and motility and sustains invasion capability (3). A decreased PLC- β 2 expression is induced by hypoxia in the BT-474 and MCF7 cell lines, that is correlated with the hypoxia-induced modulation of the EMT markers E-cadherin and Vimentin, as well as of the stem cell marker CD133. In contrast, hypoxia induced the increase of PLC- β 2 levels in MDA-MB-231 cells, in which it supports the hypoxia-related reorganization of actin cytoskeleton. In all examined cell lines, the prevention of the effects of hypoxia on PLC- β 2 also reduced the recovery of HIF-1 α , in turn able to exert a phenotype-related role in modulating EMT and expression of CD133 during the cell response to low oxygen. Our data highlighted a peculiar effect of low oxygen availability on PLC- β 2 expression in breast tumor cells with different phenotypes and allocate PLC- β 2 in the complex and interconnected transcriptional activity induced by hypoxia. Our results also suggest that the forced modulation of PLC- β 2 programmed on the basis of the tumor phenotype may prevent malignant progression of breast neoplasia as a consequence of intra-tumoral hypoxia.

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References

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Keywords

Breast cancer; hypoxia; PLC- β 2; EMT; CD133.