

Low oxygen availability and malignant evolution of non-invasive breast tumors: potential protective role of all-trans retinoic acid (ATRA)

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Reduced oxygen availability plays a crucial role in malignancy of solid tumors, including breast cancer. Even if the presence of hypoxic areas is common in all breast lesions, no data clearly correlate low oxygenation with the acquisition of malignant features by non-invasive cells, particularly by cells from ductal carcinoma *in situ* (DCIS), the most frequently diagnosed tumor in women in industrialized countries [1]. We demonstrated that 96 hours of culture under moderate hypoxia is sufficient to induce in DCIS-derived cells motility and epithelial-to-mesenchymal transition (EMT) and to enlarge the number of cells expressing the stem cell marker CD133, indicative of their increased malignant potential.

Administration of all-trans retinoic acid (ATRA), a well-known anti-leukemic drug with an anti-tumor role in invasive breast tumor cells [2], supports the epithelial phenotype of DCIS-derived cells cultured under hypoxia and reduces the number of CD133 positive cells, abrogating almost completely the effects of poor oxygenation. In DCIS-derived cells, as in leukemic cells, ATRA up-regulates the $\beta 2$ isoform of PI-PLC (PLC- $\beta 2$), ectopically expressed in invasive breast tumors in which counteracts the effects of hypoxia on both EMT and CD133 levels [3]. This suggests that the mechanisms triggered by ATRA in non-invasive breast tumor cells cultured under hypoxia may, at least in part, depend on PLC- $\beta 2$ activity.

Overall, we assigned to hypoxia a role in increasing the malignant potential of DCIS-derived cells and identified in ATRA, currently used in treating acute promyelocytic leukemia (APL), an agonist potentially useful in preventing malignant progression of non-invasive breast lesions with hypoxic areas.

References

- [1] Gilkes and Semenza (2013) Role of hypoxia-inducible factors in breast cancer metastasis. *Future oncology* (London, England) 9: 1623–36.
- [2] Centritto et al. (2015) Cellular and molecular determinants of all-trans retinoic acid sensitivity in breast cancer: Luminal phenotype and RAR expression. *EMBO Mol Med* 7: 950–972.
- [3] Brugnoli et al. (2016) PLC- $\beta 2$ is modulated by low oxygen availability in breast tumor cells and plays a phenotype dependent role in their hypoxia-related malignant potential. *Mol Carcinog* 55: 2210–2221.

Keywords

Ductal carcinoma in situ (DCIS), hypoxia, ATRA, PLC- $\beta 2$