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CDH3/P-cadherin overexpression in breast carcinomas: its regulatory mechanisms, the role in cell invasion, and the association with cancer stem cell properties

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One of the most basic characteristics of cancer cells is the loss of cell-cell adhesion and acquirement of invasive properties. During cancer progression, the regulation and expression of cell-cell adhesion molecules (like cadherins) play a pivotal role. In most invasive tumors, E-cadherin is downregulated and N-cadherin is *de novo* expressed (known as epithelial-to-mesenchymal transition). However, in some invasive carcinomas, E-cadherin expression is maintained, with the concomitant *de novo* expression of another cadherin – P-cadherin. Their co-expression occurs frequently in breast carcinomas, which show a worst patient prognosis when compared with patients harboring tumors with loss of E-cadherin as single event. In the last ten years, our group has been mainly interested in understanding the role of P-cadherin overexpression in cancer cells, as well as the gene regulatory mechanisms behind its aberrant expression.

P-cadherin has been extensively studied concerning its function and prognostic value in breast cancer. Its overexpression has been identified in 30% of invasive carcinomas, being highly associated with proliferative lesions of high histological grade and decreased patient survival. Recently, we showed that P-cadherin overexpression confers an invasive capacity to breast cancer cells, inducing the secretion of MMPs, which are responsible by the cleavage of its extracellular domain, giving rise to a P-cadherin soluble form. We proved that this fragment is a pro-invasive factor, which needs to be inhibited to render cancer cells non-invasive.

Still, we identified the intracellular signaling pathway that regulates and activates the P-cadherin (*CDH3*) gene promoter, inducing P-cadherin overexpression in breast cancer cells. We found that an antiestrogen is able to increase *CDH3* promoter activity, as well as to induce activating histone epigenetic modifications at putative C/EBPβ binding sites in the *CDH3* gene promoter. We showed, for the first time, that C/EBPβ is able to regulate P-cadherin overexpression.

Furthermore, our recent data supports the idea that P-cadherin has a role in cancer stem cell biology. We found that breast cancer cell lines, presenting the highest levels of P-cadherin, show the highest expression of the stem cell markers CD49f, CD44 and CD24, as well as ALDH1 activity. Importantly, we reproduced these results in primary tumors, where we found that P-cadherin overexpression occurs in breast carcinomas with a cancer stem cell phenotype ($CD44^{+}CD24^{-/low}$) and ALDH1 expression. These results are now being experimentally addressed by mammosphere, 2D and 3D culture *in vitro* assays, to be then confirmed *in vivo*.

In conclusion, our results open new avenues in breast cancer treatment, since P-cadherin is likely to be a good therapeutic target for invasive carcinomas overexpressing this protein. Scientifically, our studies will help to understand better the pathogenesis of breast cancer and other cancer models involving cadherin's alterations.

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