

*Abstract*

E-cadherin is a calcium-dependent glycoprotein that mediates cell-cell adhesion and is important in differentiation, cell growth and maintenance of cell polarity.

The involvement of E-cadherin in tumour development has been extensively demonstrated, with many human carcinomas exhibiting reduced E-cadherin expression. In gastric cancer, the protein is abnormally expressed in more than half of the cases of the sporadic diffuse subset. Furthermore, germline loss-of-function mutations in the CDH1 gene were shown to represent the genetic cause of approximately 1/3 of HDGC cases.

During tumourigenesis, loss of E-cadherin expression and/or function can lead to increased cell motility, cell-cell detachment and, ultimately, to invasion. Moreover, recent evidences point for the possible involvement of the protein in modulating intracellular signalling and thus have a contribution during initial stages of tumour development.

To investigate the hypothesis that E-cadherin modulates intracellular signalling and to understand to what extent two germline mutations localized in different domains of E-cadherin and identified in HDGC cases maintain normal function, we transduced Wild-type, extracellular-mutated and intracellular-mutated forms of E-cadherin to a cell that does not express the protein. We analyzed expression and putative activity changes to key proteins of four signalling pathways implicated in cell survival, proliferation, cell-matrix adhesion and invasion.

We demonstrate that expression of Wild-type E-cadherin inhibits PI3K and RTKs signalling, a capacity most likely dependent on the extracellular domain. We show that MMPs activity and FAK-dependent intracellular signalling is decreased with the expression of normal E-cadherin. Finally, and despite similar outcomes in terms of invasion, motility and overall malignancy, missense mutations localized in different domains of E-cadherin render opposite effects in intracellular signalling. Results obtained for the extracellular mutation were comparable to the lack of protein situation. In contrast, cells with the intracellular mutation behaved more similarly to Wild-type cells.

Taken together, our results show that E-cadherin modulates intracellular signalling. These novel properties may contribute to tumour development by influencing cell

proliferation and survival, cell adhesion, motility and invasion. Although these are preliminary findings, the possibility that causes for malignancy associated with mutations localized at the extracellular domain of E-cadherin may have been identified is very promising, in particular for gastric neoplasias treatment.