

**New Doctorial Cancer Research**

**Role of Slug in Gastric Carcinoma—From  
Tissue Expression to Functional Analysis  
Using an In Vitro Model**

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**PhD Dissertation date:** July 24, 2008

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The aim of this work was to evaluate a putative role of the transcription factor and epithelial-mesenchymal transition (EMT) regulator Slug in gastric carcinoma progression, and in the modulation of adhesion molecules in gastric cell lines. Slug overexpression in tumors seems to be associated with aggressive features and patient short survival, and in some cases, with downregulation of E-cadherin.<sup>1</sup>

The analysis of a series of gastric primary carcinomas showed that Slug was upregulated in these tumors, which correlated inversely with the downregulation of E-cadherin. Furthermore, Slug upregulation significantly correlated with more advanced tumors and the presence of distant metastases.<sup>2</sup>

To better understand the specific effects of Slug in gastric carcinoma cells, an in vitro model stably expressing Slug was established. Slug transduction led to marked alterations in the cell phenotype and to the downregulation of E-cadherin. Moreover, Slug expression also affected the expression of other adhesion molecules as it led to a decrease in the protein expression of the tight-junction components Occludin, Claudin-4, and Claudin-5, as well as to the acquisition of invasive and motility properties and the loss of cell–cell adhesion. Significantly, the effects of Slug in these tight-junction proteins was not specific to the cell line as endogenous Slug silencing in a different gastric carcinoma-derived cell line resulted in increased Occludin, Claudin-4, and Claudin-5 protein expression. Furthermore, de novo expression of N-cadherin, a member of the cadherin family typically associated with invasion and metastatic properties of carcinoma cells, was also observed in Slug-transduced cells, which seemed to be essential for the acquisition of cell motility (Castro Alves, submitted for publication).

On the basis of the results obtained in this study, a model is proposed to explain the plasticity of the expression of components of junctional complexes, suggesting that transient changes, rather than complete silencing of adhesion molecules,

may be more advantageous for carcinoma cells along the processes of invasion and metastization.

Taken together, the results strongly suggest that Slug, a transcription factor involved in EMT regulation, plays a role in gastric carcinoma progression by downregulating the expression of key adhesion proteins, inducing the expression of N-cadherin, and conferring migratory and invasive behavior to cells. Slug upregulation may be considered a marker of poor prognosis in gastric carcinoma, which may have potential therapeutic implications.

### **Comment by Professor Jose Palacios**

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Dr. Catarina Castro Alves investigated the role of the Slug gene in gastric carcinoma using both in vivo and in vitro approaches providing important clues about the participation of Slug in this frequent tumor. The study is original because it is the first one that clearly demonstrates the in vivo participation of this E-cadherin repressor in the progression and metastatic ability of gastric cancer. One of the major contributions of this study is the identification of several target genes, whose expression is modulated directly or indirectly by Slug. Because at present we do not have effective treatments for gastric cancer, one of the most lethal human tumors, this work presents new ways to develop new therapeutic approaches. In addition, this study pointed out the importance of the epithelial mesenchymal transition (EMT) process in the progression of human tumors.

### **REFERENCES**

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2. Castro Alves C, Rosivatz E, Schott C, Hollweck R, Becker I, Sarbia M, Carneiro F, Becker KF. Slug is overexpressed in gastric carcinomas and may act synergistically with SIP1 and Snail in the down-regulation of E-cadherin. *J Pathol.* 2007;211(5):507–15.