

EPITHELIAL CELL ADHESION MOLECULE UP-REGULATES C-MYC AND INDUCES CELL PROLIFERATION

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Epithelial cell adhesion molecule (EpCAM) is a membrane glycoprotein expressed on adenomatous and simple epithelia, where it is involved in homophilic adhesion at the basolateral membrane. Carcinomas strongly over-express EpCAM through an, as yet, unknown mechanism. Interestingly, otherwise EpCAM-negative squamous epithelia are seen to express EpCAM concomitant with their transformation and de-differentiation. The amount of EpCAM and the number of expressing cells both increase with the grade of dysplasia. Despite an important amount of data correlating the expression of EpCAM with cellular proliferation and de-differentiation, such as the co-expression with Ki-67, a marker for proliferation, it is unknown whether EpCAM may directly contribute to carcinogenesis. Here, we show that EpCAM has a direct impact on cell cycle and proliferation, and the ability to rapidly upregulate the proto-oncogene c-myc and cyclin A/E. Human epithelial 293 cells as well as murine NIH3T3 fibroblasts expressing EpCAM had a decreased requirement for growth factors, enhanced metabolic activity and colony formation capacity. Importantly, the inhibition of EpCAM expression with antisense mRNA led to a strong decrease in proliferation and metabolism in human carcinoma cells. Moreover, domain swapping experiments demonstrated that the intracellular part of EpCAM is necessary and sufficient to transduce the effects described. Thus, the data presented here highlight the role of EpCAM demonstrating for the first time a direct link to cell cycle and proliferation.