CELL POLARITY

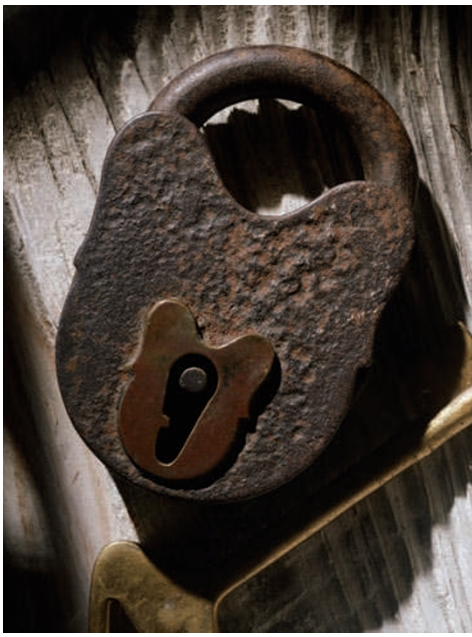
Morphogenesis is the key

Polarization of luminal mammary epithelial cells is crucial for normal function and there is accumulating evidence that regulators of polarity, such as scribble (SCRIB), are lost or deregulated in the early stages of carcinoma development. Senthil Muthuswamy and colleagues have now elucidated a mechanism for the transforming effect of SCRIB loss that may be applicable to the loss of other polarity regulators.

Mammary glands are composed of smaller acinus structures that are formed by proliferation of mammary epithelial cells to produce a lobe; apoptosis of the cells in the middle contributes to the creation of an empty lumen. This morphogenesis can be generated *in vitro* by three-dimensional culture of MCF-10A cells. Zhan and colleagues showed that loss of SCRIB expression in these cells (through stable RNA interference) partially deregulated the apical–basal polarity of luminal epithelial cells and significantly affected the organization of epithelia within the acinus: only ~20% of the acini had empty lumen. Moreover, pluripotent mouse mammary epithelial cells in which SCRIB was knocked down failed to reconstitute glandular structures in the mammary fat pad of mice and instead produced multi-layered epithelia. Of these mice, 10% developed tumours, indicating that SCRIB is a tumour suppressor in mammary epithelia.

Hyperactivation of oncogenes, such as *MYC*, is known to induce both proliferation and apoptosis. Zhan and colleagues showed that apoptosis is the dominant response in MCF-10A cells after MYC hyperactivation. They found that SCRIB is required for MYC-induced expression of the pro-apoptotic protein BIM (also known as BCL2L11) through activating the Rac-GTP–JNK–phospho-JUN pathway. Interestingly, loss of SCRIB reduced levels of apoptosis — but did not affect proliferation — by suppression of the MYC-induced apoptosis pathway in mammary epithelial cells. The authors showed that loss of SCRIB resulted in tumours ~10-fold larger than those produced by MYC alone in an orthotopic mouse model of breast cancer. Analyses of these tumours revealed that apoptosis was significantly reduced on loss of SCRIB, and this corresponded with reduced activation of the Rac–JNK–JUN–BIM pathway. Therefore, loss of SCRIB appears to cooperate with MYC to drive the transformation of mammary epithelial cells.

Is this relevant to human tumours? SCRIB was downregulated in 17 of 32 human breast tumour samples and mislocalized from cell–cell junctions to the cytoplasm in numerous breast cancer cell lines and in 10 of 20 samples of ductal carcinoma *in situ*. Forced mislocalization of SCRIB is sufficient to prevent MYC-induced apoptosis and mimics *SCRIB* RNA interference phenotypes, indicating that SCRIB can be inactivated by downregulation or mislocalization and that it is a tumour suppressor that functions to promote apoptosis when morphogenesis is deregulated by oncogene hyperactivation.



Therefore, the authors suggest that hyperproliferation alone is too simplistic when considering tumour initiation and, instead, that deregulated morphogenesis needs to accompany hyperproliferation for transformation to occur.

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ORIGINAL RESEARCH PAPER Zhan, L. *et al.* Deregulation of scribble promotes mammary tumorigenesis and reveals a role for cell polarity in carcinoma. *Cell* **135**, 865–878 (2008)