Nature Reviews Cancer | AOP, published online 20 September 2007; doi:10.1038/nrc2238

ONCOGENES

Suppressive organization

DOI:
10.1038/nrc2238

The cells in epithelial tissues are structurally organized and have apicobasal polarity, and this epithelial architecture has been shown to control many cellular processes including cell proliferation and death. Although it is known that oncogenes can disrupt the initial formation of epithelial architecture, Juha Klefstrom and colleagues now show that, once established, this architecture can regulate proliferation and apoptosis by the oncogene MYC.

The human mammary epithelial cell line MCF-10A forms three-dimensional growth arrested acinus-like structures when cultured in the extracellular matrix extract Matrigel. Using MCF-10A cells expressing an activatable MYC construct (MYC-ER^{tm}), the authors showed that chronic activation of MYC-ER^{tm}, beginning a day after the cells are seeded in Matrigel, leads to increased proliferation and the formation of structures that are 1.4 times larger than normal. However, after about 15 days in culture the structures did not grow further, despite continued expression of MYC, and this was probably owing to increased apoptosis.

What happens if the acinar structures are allowed to form before MYC is activated? After 20 days in Matrigel culture (when the acini were growth arrested), activation of MYC-ER^{tm} had no effect on the morphology, size or proliferation of the acini. Moreover, when the authors grew MYC-ER^{tm}-expressing MCF-10A cells in collagen I cultures to form cysts without polarity or organization, they found that the activation of MYC-ER^{tm} promoted proliferation in these unorganized structures, indicating that intact epithelial architecture is required to block MYC-induced proliferation. Short hairpin RNA (shRNA) that silenced the tumour suppressor LKB1 (a member of the Par family of cell polarity proteins) caused the formation of MCF-10A cell structures in Matrigel that were unorganized but still retained some aspects of polarity and still underwent growth arrest after 20 days. When MYC-ER^{tm} was activated in these unorganized LKB1-deficient growth-arrested structures, the authors found that MYC was now able to induce proliferation.

As MYC also induces apoptosis, the authors asked how this was affected by epithelial architecture. Although MYC does not induce apoptosis on its own in established acini, it sensitizes the cells to tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. However, in cells expressing *LKB1* shRNA, activation of MYC-ER^{tm} alone was able to induce apoptosis, indicating that epithelial architecture can also protect cells from MYC-induced apoptosis.

Klefstrom and colleagues have shown that epithelial architecture can suppress oncogene-driven proliferation and apoptosis in this *in vitro* model, and it will be interesting to see whether LKB1 or other Par proteins cooperate with MYC to induce tumorigenesis *in vivo*.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Partanen, J. I., Nieminen, A. I., Makela, T. P. & Klefstrom, J. Suppression of oncogenic properties of c-Myc by LKB1-controlled epithelial organization. *Proc. Natl Acad. Sci. USA* 31 August 2007 (doi: 10.1073/pnas.0704,677,104)

FURTHER READING Debnath, J. & Brugge, J. S. Modelling glandular epithelial cancers in three-dimensional cultures. *Nature Rev. Cancer* **5**, 675–688 (2005)

PHOTODISC