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APOPTOSIS

Cancer cells come to a sticky end

Warning — matrix adhesion can seriously damage your health. Instead of providing support and protection, a close relationship between cells and the underlying extracellular matrix (ECM) can increase their susceptibility to death following DNA damage.

Loss of adhesion from the ECM is sufficient to trigger apoptosis in some normal cells, but what about in cancer cells, in which detachment is an essential step on the path to malignancy? Jean Lewis *et al.*, reporting in the 19 March issue of *Proceedings of the National Academy of Sciences*, showed that ligation to integrins — receptors that mediate the attachment of cells to the ECM — increased the level of apoptosis in fibrosarcoma cells that had been treated with the DNA-damaging drug araC. Although not universal among transformed cells, several other cell types — including human M21L melanoma cells and rhabdomyosarcoma cells, as well as mouse embryo fibroblasts (MEFs) — exhibited this differential behaviour in response to DNA damage, depending on whether their integrins were engaged.

To confirm that integrins were responsible for apoptotic susceptibility, the ability of agonistic anti-integrin antibodies to restore the apoptotic response in the detached fibrosarcoma cells was examined. Treatment of detached cells with antibodies that bind either the $\beta 1$ or $\alpha v \beta 3$ integrins was, indeed, sufficient to restore araC-induced cell death, using caspase activity as an assay of apoptosis.

So how do integrins mediate these effects? The checkpoint protein CHEK1 was activated in both adherent and suspended cells, so the defect must occur further downstream. p53 is a crucial mediator of apoptosis, and is degraded by MDM2, which, in turn, can be sequestered by ARF, so could one of these components be responsible for the apoptotic resistance that occurs in suspended cells? Following detachment of MEFs from the ECM, Arf protein levels rapidly declined, whereas Mdm2 levels remained high. Mdm2-mediated degradation of p53 therefore increased; p53 protein levels decreased with slower kinetics than those for Arf, and this correlated with the onset of apoptotic resistance.

But p53 has a broader role as ‘guardian of the genome’, so could treatment of detached cells with cytotoxic agents increase genomic instability? Following irradiation, MEFs that were grown in suspension displayed a significantly increased

number of chromosomal rearrangements compared with those that retained their integrin-mediated ECM attachments.

So do we need to re-think our approach to cancer therapy, given these results? Not only do detached cells escape chemotherapy-induced apoptosis, but the treatment might also accelerate tumour progression by promoting genomic instability. Activating integrins before conventional treatment — in the subset of cancer types that exhibit this behaviour — might be one solution to this problem.

Emma Greenwood

References and links

ORIGINAL RESEARCH PAPER Lewis, J. M. *et al.* Integrins regulate the apoptotic response to DNA damage through modulation of p53. *Proc. Natl Acad. Sci. USA* **99**, 3627–3632 (2002)

WEB SITES

Encyclopedia of Life Sciences:

<http://www.els.net>

apoptosis: molecular mechanisms | integrins: signalling and disease

Martin Schwartz's lab:

<http://www.scripps.edu/vb/schwartz/>