TUMOUR SUPPRESSORS

The trials of separation

The tumour suppressor BRCA2 has been shown to participate in DNA repair and recombination reactions during S phase. These functions do not, however, account for the array of cellular abnormalities that occur when BRCA2 is defective. Ashok Venkitaraman and colleagues investigated the function of BRCA2 throughout mitosis, and found that it also has a role during cell separation.

The authors monitored cell division by serial time-lapse imaging of murine embryonic fibroblasts (MEFs) that possessed a mutation that truncates and inactivates the gene — $Brca2^{Tr/Tr}$. These cells took significantly longer to progress from anaphase onset to cell separation than the wild-type controls. There was also a higher frequency of binucleate cells, which is indicative of incomplete cytokinesis. These abnormalities were also observed *in vivo*, when $Brca2^{Tr/Tr}$ cells were isolated from mouse embryos.

But is this phenotype unique to the truncation genotype? The authors depleted *BRCA2* in HeLa cells using RNA interference (RNAi) and confirmed that *BRCA2* deficiency resulted in an extension in the time from anaphase onset to the completion of cell division.

To investigate which part of the process was defective, the authors observed key events in cytokinesis in cells depleted for *BRCA2* by RNAi. Cytokinesis is initiated by the actomyosin contractile ring, but in over 50% of RNAi-treated cells, myosin II was not concentrated correctly at the forming cleavage furrow. Nor did it accumulate as it should at each cell edge during the abscission of cells in telophase, when the cells actually break apart. Consistent with this, $Brca2^{Tr/Tr}$ MEFs frequently accumulate at abscission.

So are these defects also found in naturally occurring BRCA2-deficient cancer cells? Importantly, the Capan-1 cell line — isolated from a patient carrying the non-functional *BRCA2* 6174delT mutation — also has many binucleate cells, and cells with abnormal myosin II localization in abscission.

To further support the role of BRCA2 in cytokinesis, BRCA2 was found to have a similar localization to another cytokinetic protein, aurora-B. Both localize in central structures during the elongation phase of cytokinesis and then move to the midbody during late cleavage and abscission.

So, BRCA2 seems to have a non-essential role in regulating the fidelity of cell separation, and this can account for several previously unexplained phenotypes of BRCA2-deficient cancer cells, such as polyploidy and aneuploidy. This type of chromosomal instability could certainly contribute to the cancer predisposition observed in individuals who inherit *BRCA2* mutations.

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References and links

ORIGINAL RESEARCH PAPER Daniels, M. J., Wang, Y., Lee, M. & Venkitaraman, A. R. Abnormal cytokinesis in cells deficient in the breast cancer susceptibility protein BRCA2. *Science* 16 Sep 2004 (doi: 10.1126/science.1102574)

FURTHER READING Venkitaraman, A. R. V. Tracing the network connecting BRCA and Fanconi anaemia proteins. *Nature Rev. Cancer* **4**, 267–276 (2004)

WEB SITE

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http://www.hutchison-mrc.cam.ac.uk/groups/venkitaraman/About_lab.html