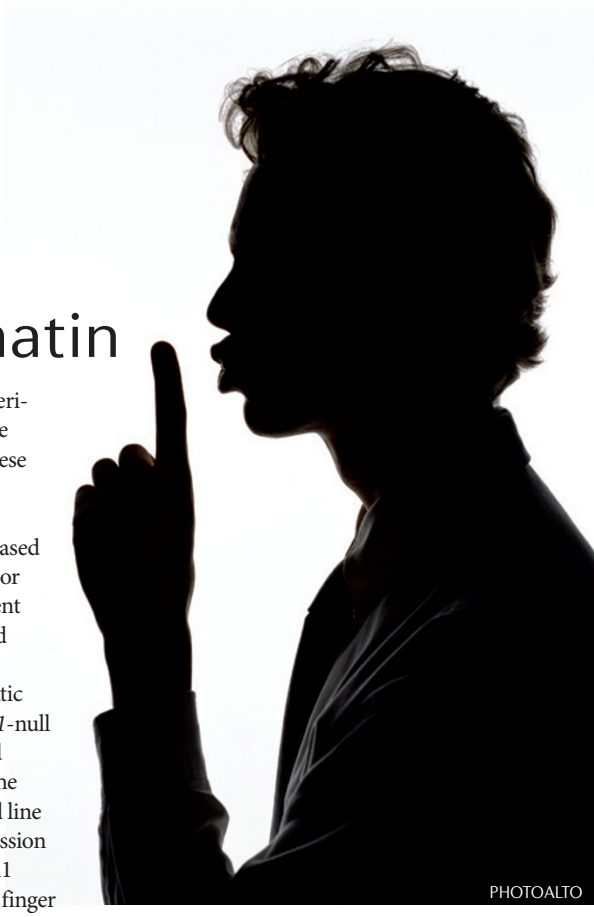
Nature Reviews Cancer | AOP, published online 29 September 2011; doi:10.1038/nrc3152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TUMOUR SUPPRESSORS

Silencing heterochromatin

Germline mutation of *BRCA1* generates a significant lifetime risk of developing breast and ovarian cancer. Why this mutation is almost certain to produce such tumours is not clear, despite our knowledge of the involvement of BRCA1 in DNA repair and genomic stability. A recent paper now suggests that the ability of BRCA1 to silence heterochromatic regions of the genome is another important piece of this puzzle.

Quan Zhu, Gerald Pao and colleagues at the Salk Institute were investigating the function of BRCA1 in neural stem cells. Having conditionally knocked out *Brca1* in the brains of adult mice, the authors observed changes in the expression levels of imprinted genes, including *Igf2* and *H19*. Examination of heterochromatic regions of DNA using DAPI staining and immunofluorescence with antibodies against the heterochromatin-binding protein HP1 indicated a reduction of pericentric heterochromatic foci in *Brca1*-null neurons. Having previously shown that BRCA1, by virtue of its RING finger domain, can monoubiquitylate histone 2A (H2A), the authors analysed the localization of monoubiquitylated H2A and found that it bound heterochromatin in *Brca1* wild-type cells and that this was disrupted in *Brca1*-null cells. Moreover, chromatin immunoprecipitation experiments indicated that BRCA1 and monoubiquitylated H2A co-localize at these regions.

> “a primary function of BRCA1 is to monoubiquitylate H2A to ensure its interaction with pericentric heterochromatin and the silencing of satellite transcripts”

Does this disruption of pericentric heterochromatin have biological consequences? These regions of heterochromatin contain repetitive DNA and satellite sequences, and increased expression of major and minor satellite transcripts was evident in *Brca1*-null brain tissue and neurons. Moreover, similar disruptions to heterochromatic regions were evident in *Brca1*-null mouse mammary tissue, and re-expression of BRCA1 in the human BRCA1-deficient cell line HCC1937 reduced the expression of satellite transcripts. BRCA1 mutants with inactive RING finger domains, or that are unable to bind the BRCA1 partner protein BARD1, which is required for the E3 ubiquitin ligase function of BRCA1, were unable to rescue the silencing of satellite DNA in HCC1937 cells. Further investigations showed that expression of monoubiquitylated H2A reduces expression of the major and minor satellite transcripts in BRCA1-deficient cells and also corrects other established defects associated with BRCA1 loss, such as increased p53-induced apoptosis, indicating that H2A is an important target of BRCA1.

Both mouse and human BRCA1-deficient breast cancers overexpressed satellite transcripts, and, importantly, overexpression of satellite RNA in normal human mammary epithelial cells induced changes that are associated with BRCA1 loss, such as amplified centrosomes, expression of γH2AX foci, which are found at regions of DNA damage, and defective homologous recombination DNA repair.

These findings indicate that a primary function of BRCA1 is to monoubiquitylate H2A to ensure its interaction with pericentric heterochromatin and the silencing of satellite transcripts. Expression of satellite transcripts seems to contribute to genomic instability that is associated with BRCA1 inactivation. However, why a deficiency in BRCA1 is tumorigenic predominately in breast and ovarian cells remains unknown.

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ORIGINAL RESEARCH PAPER Zhu, Q. *et al.* BRCA1 tumour suppression occurs via heterochromatin-mediated silencing. *Nature* **477**, 179–185 (2011)

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