

How an imprint can lead to cancer

Mutations in DNA may not be the sole mechanism that leads to cancer. New research suggests that variations in the imprint left on a genome by a parent can influence tumour development. The mechanism, which appears to be linked to how cells differentiate, takes us another step closer to understanding the factors that predispose some people to cancer.

Epigenetics and cancer

Parental imprinting is an area in the field of epigenetics. Whereas genetics is concerned with DNA, epigenetics is the study of chemical modifications of the DNA-protein complexes that form chromosomes (i.e., chromatin). In the dominant modern view, the etiology of cancer centres on genetic changes, usually in the form of mutations to oncogenes or tumour suppressor genes, that result in unchecked cellular growth. Lately, however, it is becoming clear that epigenetic changes also play a role.¹

The effect of methyl groups on DNA is one example: adding methyl groups turns tumour suppressor genes off, whereas removal of methyl groups activates normally silent oncogenes. Genomic imprinting is another: imprinting occurs when both

maternal and paternal alleles are present, but 1 allele is preferentially expressed. This parentally based difference is thought to be involved in viability, growth and behaviour. Abnormal imprinting is thought to contribute, for example, to the development of Beckwith-Wiedemann syndrome (BWS).^{1,2} This disorder results in a predisposition to tumour growth early in life, often manifested as Wilms' tumours. Although BWS is associated with genetic changes, it has also been linked to the loss of imprinting of *IGF2*, the human insulin-like growth factor II gene.³ This gene is normally expressed from the paternal chromosome only, with the maternal copy "silent" owing to imprinting. This imprint loss, and the increases in *IGF2* protein levels that follow, contribute to the pathogenesis of BWS, likely because of the protein's role as a growth factor.

Increases in *IGF2* protein concentrations are also found in various human cancers (e.g., colorectal cancer), which raises the question of whether epigenetic mechanisms generally influence our risk of cancer.

Although BWS is rare, work in Feinberg's laboratory^{3,4} suggests that loss of imprinting may be a more general phenomenon.³ In 2003, loss of imprinting of the *IGF2* gene was detected in normal lymphocytes and the colonic mucosa of 10% of healthy adults.³ The risk of colorectal adenomas among those with loss of imprinting was 3.5–5 times that of healthy adult subjects with normal imprinting.⁵

In their latest work,⁴ Feinberg's team confirmed that association in an experiment in which female mice that would pass on either an imprinted or a nonimprinted copy of *IGF2* were crossed with male mice possessing a mutation (*Apc*) in the adenomatous polyposis coli gene that predisposes mice (and

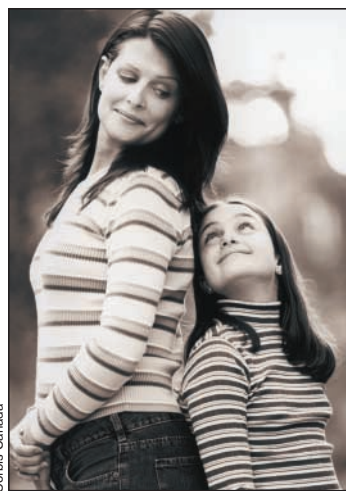
humans) to familial colonic polyposis. Although the offspring of these parents were all predisposed to cancer, only half were affected by a loss of imprinting of *IGF2*. The mice with abnormal imprinting acquired twice as many intestinal adenomas as those whose imprinting was normal. The intestinal crypts (spaces between villi) in abnormally imprinted mice were found to be longer, and also associated with increased numbers of undifferentiated epithelial cells. In addition, Feinberg's group⁴ found that some human patients who have a loss of imprinting also appear to have more undifferentiated cells in their colons, which suggests that the cells may be precancerous.

These observations suggest that mutations in parental imprinting can influence cell differentiation and may as a consequence increase cancer risk. Such links provide a first peek at one of the mechanisms by which epigenetics may contribute to cancer development. The work also raises questions: Does abnormal imprinting of genes unrelated to cancer create environments that predispose people to disease?⁴ Is epithelial differentiation linked to the development of cancer? Future study should bring more about imprinting to light. — David Secko, Vancouver

References

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DOI:10.1503/cmaj.050423



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