



Cancer and obesity Malignant flab

At last, an understanding of how overeating causes cancer

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OVERWEIGHT women are more likely to develop breast cancer than lean ones. Why has been a mystery. But it is now less mysterious thanks to the work of Kevin Gardner, a researcher at America's National Cancer Institute in Bethesda, Maryland. Dr Gardner and his colleagues have found that processing calories affects the activity of *BRCA1*, a gene that encodes a well-known tumour-suppression protein. Mutations of this gene are strong predictors of breast and ovarian cancer—so strong that the gene's DNA sequence is the subject of litigation in America about whether natural gene sequences can be patented, and thus the market in tests for these mutations cornered.

Dr Gardner's discovery is that a substance called C-terminal binding protein (CtBP) helps regulate *BRCA1*. Since the activity of CtBP is, itself, governed by the processing of calorie-rich molecules, the more of those molecules the body processes, the more at risk of cancer it becomes.

Previous work has shown that CtBP senses the amount of energy in a cell by binding to a small molecule called NADH. This chemical is a by-product of metabolism, and cells that are processing an excessive amount of energy for storage have a superabundance of it compared with the amount of a related molecule called NAD⁺. As the ratio of NAD⁺ to NADH falls, CtBP combines with NADH. This changes CtBP's shape and enables it to form complexes with several other proteins. These complexes control the activity of DNA by shutting off certain genes. Dr Gardner and his team report in the latest issue of *Nature Structural & Molecular Biology* that one of the genes so controlled is *BRCA1*.

The protein encoded by *BRCA1* is involved in DNA repair. Cells that lack a working version of it gradually accumulate genetic changes. Though most of these changes either have little impact or will lead to the cell's death, some may promote the formation or progression of tumours. A low NAD⁺/NADH ratio, according to Dr Gardner's work, has a similar effect to a *BRCA1* mutation. It leads to less DNA repair and more mutations.

That, unfortunately, combines with another effect of too much fat, which is that it stimulates the production of oestrogen by cells that are involved in the storage of fat. More oestrogen means more cell proliferation in hormone-sensitive tissues—a category that includes the breasts and the ovaries. Therefore, just when those cells are being told to undergo the error-prone process of replication and division and need their DNA-repair system most, CtBP slashes that system to ribbons.

Though this is the first clear link between calorie intake and cancer that has been seen at the molecular level, Dr Gardner says his result is consistent with numerous past experiments. For example, breast tumours are more aggressive and less genetically stable in heavily fed mice than in animals confined to a calorie-restricted diet. So, along with all the other reasons to keep trim, there is a new one: it may help to keep you free of cancer.

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