RISK AND PREVENTION

An aspirin a day...

...keeps colorectal cancer away. Regular use of aspirin prevents or inhibits the development of colorectal cancer. However, Martinez and colleagues now show that the degree of risk reduction that results from taking aspirin depends on the variation of the ornithine decarboxylase (*ODC*) gene between individuals.

ODC is a key enzyme in the synthesis of polyamines — compounds that are essential for cell proliferation. Increased levels of polyamines are implicated in hereditary colorectal cancers that have mutations in the adenomatous polyposis coli (*APC*) gene. *APC* influences the expression of *c-MYC* (and its antagonist *MAD1*), which transcriptionally regulates *ODC* — mutant *APC* leads to an increase in *ODC*. Expression of *ODC* is also increased in patients with colorectal cancer who have no genetic risk.

A polymorphic site (A316G) has been identified between two binding sites for *c-MYC* in the *ODC* promoter that affects *ODC*-promoter activity. The authors genotyped 688 participants in an adenoma recurrence trial for *ODC* and found that 56% were homozygous for the G allele, 6% were homozygous for the A allele and the remaining 38% were heterozygous at this locus. Participants homozygous for A had a 0.48 odds of recurrence compared with homozygous G individuals. In addition, 30% of the study participants took aspirin regularly, and these people were 0.32 times less likely to have adenoma recurrence. If these aspirin users were also homozygous for the *ODC* A allele, their odds of recurrence were significantly reduced to 0.10.

So, does the A316G polymorphism affect the activity of *ODC*? When wild-type *APC* was expressed in HT29 colon-tumour cells — mimicking normal colon epithelia — *c-MYC* was suppressed and *MAD1* was induced. If the

HT29-*APC* cells were transfected with *ODC/A*, activity of the *ODC* promoter was significantly reduced. Transfection of *ODC/G* had no such effect. If *MAD1* was constitutively expressed in the HT29-*APC* cells, a 78% A-allele specific inhibition of *ODC*-promoter activity was observed, indicating that *MAD1* directly affects the *ODC* promoter.

To investigate the role of aspirin the authors treated the *ODC/G*- and *ODC/A*-transfected HT29-*APC* cell lines with therapeutic concentrations of aspirin — the drug had no effect on *ODC* promoter activity, or on *ODC* enzyme activity. However, aspirin induced the activity of spermidine/spermine *N*-1-acetyltransferase (*SSAT*), which is involved in polyamine catabolism and export. Expression of *SSAT* is also induced by another non-steroidal anti-inflammatory drug (NSAID), indomethacin.

So, *ODC* polymorphism and aspirin work via unique mechanisms to influence a common metabolic pathway — that of polyamine synthesis. Studies are underway to assess the benefit of combining NSAIDs with *ODC* inhibitors in individuals with a high risk of developing colorectal cancer.

Ezzie Hutchinson

References and links

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WEB SITE

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THERAPEUTICS

How degrading!

The proteasome is a ubiquitous regulator of many cellular functions, and therefore would not seem to be a good cancer-specific target. Several reagents have nonetheless been developed to block its function, and have had surprising results. Anderson and colleagues report that bortezomib — the first small-molecule inhibitor of proteasome activity to be tested in clinical trials — is effective in treating patients with refractory myeloma.

Unlike other proteases, the proteasome contains an active site amino-terminal threonine residue that is accessible to small molecules. Bortezomib — a boronic acid dipeptide — inhibits the catalytic activity of the proteasome and induces apoptosis in cancer-cell lines without affecting normal cells. The drug also has considerable efficacy as a single agent against human tumour xenografts, and enhances the apoptotic effects

of chemotherapeutic agents and radiation.

Bortezomib induces apoptosis in cultured myeloma cells isolated from patients whose disease is resistant to conventional therapy, and a previous Phase I trial indicated that the drug was safe in patients with myeloma. They therefore tested it in a Phase II study of 202 patients with highly refractory disease.

Amazingly, the treatment had a 35% overall response rate, including a 10% rate of complete response. The median duration of response was 12 months, and treatment led to a 2–4-fold increase in time to progression. Toxic effects included thrombocytopenia, peripheral neuropathy and neutropenia, but severe side effects were uncommon.

So, how does bortezomib work? Bortezomib inhibits proteasomal degradation of I κ B, allowing NF- κ B to remain sequestered in the cytoplasm. This blocks NF- κ B's ability to translocate to the nucleus, where it would normally induce expression of anti-apoptotic target genes, sensitizing tumour cells to chemotherapeutic agents and radiation. Furthermore, bortezomib downregulates

expression of adhesion molecules by myeloma cells, and decreases bone-marrow-cell expression of cytokines that mediate myeloma cell growth, survival and migration. Inhibition of the proteasome has also been shown to decrease MAPK signalling, as well as to upregulate activity of p53 and the cell-cycle inhibitor p27.

Complete responses are rare in patients with advanced refractory myeloma, and based on these results, the Food and Drug Administration recently approved bortezomib for treatment of patients with refractory multiple myeloma. The drug is also being tested in Phase I and II trials for other haematological cancers and solid tumours. A Phase III trial is also underway to compare bortezomib with dexamethasone for the treatment of myeloma.

Kristine Novak

References and links

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WEB SITE

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