GENETIC INSTABILITY

Genomic instability links diet to cancer

DOI:
10.1038/nrg2213

A genetic screen in yeast has found a surprising link between vitamin B6 deficiency and increased genome instability, a hallmark of cancerous cells. This study gives new insights into the causes of genetic aberrations, and provides a possible mechanistic explanation for epidemiological evidence that suggests a link between micronutrient deficiencies and cancer risk.

When faithful DNA replication is disrupted, genetic lesions are created. If the DNA-repair pathways that correct these lesions are faulty, illegitimate repair can result in gross chromosomal rearrangements (GCRs) such as translocations, amplifications, inversions and deletions. In particular, break-induced replication (BIR), a type of homologous recombination repair, is thought to be a major mechanism by which GCRs occur.

Kanellis and colleagues engineered a *Saccharomyces cerevisiae* strain that includes a GCR reporter located at a chromosomal position at which rearrangements take place by BIR. In a genome-wide screen, the authors picked out *BUD16* as a potent suppressor of GCR, and alignment studies revealed that this gene encodes a putative pyridoxal kinase (Pdxk), an enzyme that is crucial for the metabolism of vitamin B6 to produce pyridoxal 5′ phosphate (PLP), the biologically active form. Strikingly, *bud16*Δ mutant cells have a 124-fold increased GCR rate compared with wild-type cells, coinciding with a reduction in PLP levels to 1.8%.

Rad52 is essential for homologous recombination and hence DNA repair. *bud16*Δ *rad52*Δ double mutants showed synthetic sickness and poor viability, suggesting that *bud16*Δ cells have high levels of DNA disruption during replication, and rely on Rad52-mediated repair for survival. Furthermore, fluorescence microscopy showed that, after budding, Rad52 foci (or 'repair centres') were present in 57–75% of *bud16*Δ cells, compared with 2–21% in wild-type cells.

But do these symptoms of replication stress necessarily result from PLP depletion? By interfering with components of the PLP pathway, the authors generated a similar GCR phenotype to that of *bud16*Δ cells. Similar results were seen in mammalian cells: addition of a vitamin B6 analogue that inhibits PDXK in human cells (thereby reducing PLP levels) resulted in the induction of DNA lesions and activation of the DNA-damage response.

PLP is an essential cofactor in dTMP synthesis pathways; might this be the mechanism by which it prevents DNA lesions? *bud16*Δ cells have significantly higher uracil levels in their DNA compared with wild-type cells. It seems likely that the *bud16*Δ mutation, by disrupting Pdxk's role in nucleotide synthesis, causes an increase in dUMP pools, promoting incorporation of dUTP into DNA during replication. Uracil-excision processes might then promote the occurrence of lesions, leading to chromosomal instability.

Interestingly, the authors go on to propose that the cellular response to low PLP could actually represent a defense mechanism against cancer — depletion of metabolites resulting from overproliferation of cancerous cells might be sensed by the cells as replication stress, activating damage-response pathways to bring about senescence.

Carrie Patis

ORIGINAL RESEARCH PAPER Kanellis, P. *et al.* A screen for suppressors of gross chromosomal rearrangements identifies a conserved role for PLP in preventing DNA lesions. *PLoS Genet.* **3**, e134 (2007)