PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Carcinogen selection

ArticleInfo		
ArticleID	:	4080
ArticleDOI	:	10.1186/gb-spotlight-20010510-02
ArticleCitationID	:	spotlight-20010510-02
ArticleSequenceNumber	:	151
ArticleCategory	:	Research news
ArticleFirstPage	:	1
ArticleLastPage	:	2
ArticleHistory	:	RegistrationDate : 2001–05–10 OnlineDate : 2001–05–10
ArticleCopyright	:	BioMed Central Ltd2001
ArticleGrants	:	
ArticleContext	:	130592211

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A recent hypothesis suggests that the type of genetic instability in cancers is the result of Darwinian selection pressures exerted by specific carcinogens. In the May 8 Proceedings of the National Academy of Sciences, Bardelli *et al*. describe experiments to test whether chromosomal instability (CIN) is induced by bulky-adduct-forming agents, whereas microsatellite instability is selected by methylating agents (*Proc Natl Acad Sci USA* 2001, **98:**5770-5775). They used a variant colorectal cell line, HCT116-H3, with no genomic instability. When Bardelli *et al*. treated the cells with 2-amino-1-methyl-6-phenylimidazol[4,5-b]pyridine (PhIP), a bulky-adduct-forming carcinogen found in well-cooked beef, they isolated resistant clones that displayed a CIN phenotype. In contrast, exposure to the alkylating agent N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) lead to the isolation of characteristic MIN cell lines. Conversely, controlled induction of the CIN phenotype (by expression of a dominant-negative *hBUB1* allele) was associated with PhIP resistance. These results prove that the nature of the carcinogen can select for different forms of genetic instability. They provide insights into the link between diet and colorectal cancer and have implications for the choice of compounds used to treat different cancer types.

References

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