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

Gadd45a knockout mice resemble p53 knockouts

ArticleInfo		
ArticleID	:	3535
ArticleDOI	:	10.1186/gb-2000-1-1-reports002
ArticleCitationID	:	reports002
ArticleSequenceNumber	:	26
ArticleCategory	:	Paper report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 1999–10–20 Received : 1999–10–20 OnlineDate : 2000–3–17
ArticleCopyright	:	BioMed Central Ltd2000
ArticleGrants	:	
ArticleContext	:	130591111

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Abstract

Mice with a disrupted Gadd45a gene share several phenotypic characteristics with p53 knockout mice, including genomic instability, increased carcinogenesis and exencephaly.

Significance and context

The tumor suppressor gene *p53* has been referred to as the 'guardian of the genome'. Mutations in the *p53* gene are found in many human tumours, and *p53* loss is associated with diverse consequences including genomic instability, loss of cell-cycle checkpoint controls, increased carcinogenesis, decreased apoptosis, reduced DNA repair and a low frequency of exencephaly (a developmental brain defect). Many functions of p53 protein are related to its ability to regulate gene expression. Identified p53-regulated genes account for some of the p53 functions; for example, the *p21/Cip1/Waf1* inhibitor of cyclin-dependent kinases regulates cell-cycle checkpoint control in G1 phase and *bax* regulates apoptosis (see Figure 1). The p53 effector genes involved in genomic instability are unknown, however. This is the first report to use a genetic approach to define a role for *Gadd45a*, an established p53-regulated gene, in genomic stability and growth control.

Figure 1 Examples of known *p53* effector genes that have distinct cellular effects.

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Key results

The authors generated mice with a disrupted *Gadd45a* gene using a standard homologous recombination approach. Most of the *Gadd45a*$^{-/-}$ mice were viable and fertile. The authors note a low frequency of exencephaly (8%), similar to that reported for p53$^{-/-}$ mice. Embryonic fibroblasts isolated from these mice exhibited features of cells lacking p53: they grew faster than wild-type cells, escaped senescence, and could be transformed with a single activated oncogene. Furthermore, these *Gadd45a*-deficient fibroblasts showed increased aneuploidy, chromosomal aberrations, centromere fusions, aberrant cytokinesis and centrosome amplifications. The *Gadd45a*-deficient mice were hypersensitive to γ-irradiation-induced carcinogenesis, whereas heterozygote mice were intermediate in sensitivity between deficient and wild-type animals. The knockout mice also displayed increased numbers of cells

in the thymus without evidence of decreased apoptosis. Finally, the authors report reduced G2 checkpoint control following treatment with DNA-damaging agents (ultraviolet radiation and methyl methane sulphonate).

Links

For information about p53, visit the p53 database at the Institut Curie, the Weizmann Institute, and Prostatepointers.

Conclusions

The authors note that other tumour suppressor genes, such as *Brca1* and *Brca2*, also regulate *Gadd45a* expression, supporting the notion that *Gadd45a* has a broad role in surveillance of genome stability. They refer to Gadd45a as an 'alarm factor', alerting the cell to stress and cellular injury. They suggest that in the absence of *Gadd45a* defective cytokinesis, centromeric fusions and amplifications are likely to contribute to unbalanced chromosome segregation and subsequent aneuploidy.

Reporter's comments

Convincing evidence is provided here that distinct downstream effectors may account for different aspects of the pleiotropic phenotypes observed upon *p53* mutation. Clearly, much work is now needed to investigate the mechanism by which the Gadd45 protein maintains genomic stability. Gadd45 has been reported to interact with PCNA, p21 and Cdc2 proteins, suggesting that it plays diverse roles in regulating genome stability and cell cycle control. The similarities between *Gadd45a* and *p53* null mutation phenotypes will encourage researchers to investigate Gadd45a status in human tumours and to focus on this *p53* effector in future anti-cancer drug intervention strategies.

Table of links

Nature Genetics

p53 database

Weizmann Institute

References

1. Hollander MC, Sheikh MS, Bulavin DV, Lundgren K, Augeri-Henmueller L, Shehee R, Molinara TA, Kim KE, Tolosa E, Ashwell JD: Genomic instability in Gadd45a-deficient mice. Nat Genet. 1999, 23: 176-184. 1061-4036

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