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Letter to the Editor

Orders of magnitude change in phenotype rate caused by mutation

To the Editor,

In a letter entitled, "Orders of magnitude change in phenotype rate caused by mutation" Ping Ao points out that "there is no cancer theory without major difficulties, including the prevailing gene-based cancer theories" [1]. In the light of this argument Ao has also reviewed our article, 'The chromosomal basis of cancer', which holds that cancer is caused by specific chromosomal alterations [2]. Our theory proposes that the high rates at which cancer cells generate cancer-specific phenotypes – such as invasiveness, drug resistance, new morphologies, new metabolisms and metastasis – are due to high rates of chromosomal alterations, which are catalyzed by cancer-specific aneuploidy. In other words our theory holds that changing karyotypes, rather than mutating genes, generate neoplastic and preneoplastic phenotypes at high rates. An editorial accompanying our article has lent general support to this theory [6].

Ao kindly acknowledges that our "chromosomal cancer theory appears strong". But in line with his argument – that all cancer theories have difficulties – Ao points out that our "wholesale criticism of [the] mutation cancer theory is premature". To illustrate his point Ao asserts that he can answer the question posted in our article: "(4) What kind of mutation would be able to alter phenotypes at rates that exceed conventional gene mutations 4–11 orders of magnitude?" Ao advances known mutants of the repressor of lysogenic lambda phage as examples for such mutator genes. Depending on specific mutations of the lambda repressor, de-repressions or inductions of lysogenic phage can vary over 9 "orders of magnitude".

The main point at issue, however, in the item, (4), under debate is the rate at which mutations arise and back-mutate, not the relative degrees by which specific mutations affect the functions of the respective gene. But none of the lambda mutations described by Ao alter the rates of mutation of any genes. Thus Ao confuses the phenotypic variations arising from different mutations of a given gene with the rates at which mutations occur.

In contrast to the phenotypes of mutations of the lambda repressor, the phenotypes of most eukaryotic genes are buffered against mutations by a second un-mutated allele [8] and by metabolic controls exerted by products of un-mutated genes from within a common biochemical assembly line [3,5,7]. Since lambda genes are not buffered in the bacterial host, the wide ranges of phenotypic expressions of the un-buffered mutations of the lambda repressor in *E. coli* are now used as sensitive indicators to measure gene mutation rates in cancer cells. For this purpose lambda phages are introduced into the germline of mice and the transgenic lambda repressor genes of normal and cancer cells are then analyzed in bacteria to detect putative mutator genes. But despite the high sensitivity of this system, no mutator genes were found in various preneoplastic and neoplastic cells of tumors in mice [4].

It would appear then that the chromosomal cancer theory might be an exception to Ao's argument that "there is no cancer theory without major difficulties".

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References

[1] P. Ao, Orders of magnitude change in phenotype rate caused by mutation, *Cell. Oncol.* (2007), in press.

[2] P. Duesberg, R. Li, A. Fabarius and R. Hehlmann, The chromosomal basis of cancer, *Cell. Oncol.* **27** (2005), 293–318.

[3] J.L. Hartman, B. Garvik and L. Hartwell, Principles for the buffering of genetic variation, *Science* **291** (2001), 1001–1004.

[4] J.L. Jakubczak, G. Merlino, J.E. French, W.J. Muller, B. Paul, S. Adhya et al., Analysis of genetic instability during mammary tumor progression using a novel selection-based assay for in vivo mutations in a bacteriophage lambda transgene target, *Proc. Natl. Acad. Sci. USA* **93** (1996), 9073–9078.

[5] H. Kacser and J.A. Burns, The molecular basis of dominance, *Genetics* **97** (1981), 639–666.

[6] G.A. Meijer, Chromosomes and cancer, Boveri revisited, *Cell. Oncol.* **27** (2005), 273–275.

[7] D. Rasnick and P. Duesberg, How aneuploidy affects metabolic control and causes cancer, *Biochem. J.* **340** (1999), 621–630.

[8] F. Vogel and A.G. Motulsky, *Human Genetics: Problems and Approaches*, Springer Verlag, Berlin, Heidelberg, New York, Tokyo, 1986.