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The evolution of mutation rates in human cancerous cells in vivo
-- Testing the hypothesis of snowball mutation effect

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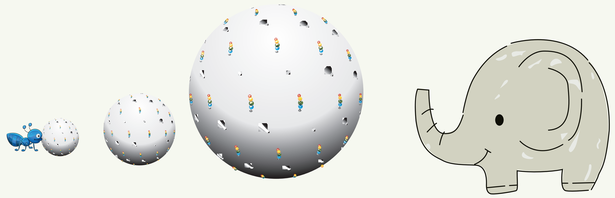
ABSTRACT

Mutation rate is a combined evolutionary effect and varies with different factors. Deciphering the evolution of mutation rate in cancerous cells not only help understanding the basic of tumorigenesis, but also expanding classical evolutionary theory to cellular level. However, with universal factors and t model, it is hard to explain large variations in tumor cases. A snowball effect about the mutation rate in cancerous cells is proposed to clarify the source of mutation variations. In this model, tiny effect of most mutatios from feedback between intracellular environment and somatic mutations will dramatically increase the mutation rate. Our model provides a new insight about the evolution of somatic mutation rate and help understanding the basic of cancer.

CONCLUSION



Snowball Effect: little ants produce huge effect

- Mutator cannot explain large variations for cancer cells;
- Many genes have tiny effect on mutation rate;
- Snowball effect comes from feedback between endogenous enviroment and somatic variations.

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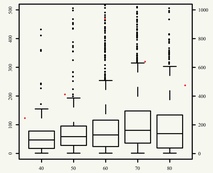
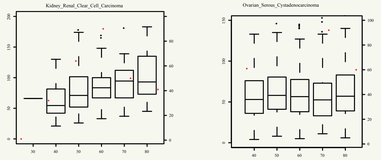
I.High Mutation Rate in Cancer Cells

Widespread distribution of cancer cds mutations



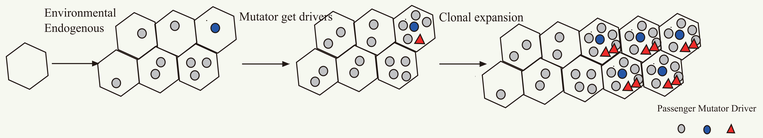
cancer mutations have a widespread distribution, for same age group, 3rd quartile were mainly 3~5 fold of that of 1st quartile

Age effect cannot account for large variations



varations within same age group indicate a variable mutation rate

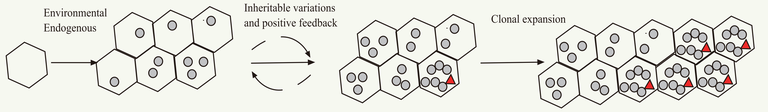
What was the real cause for these variations : Mutator ?



Only about 1/200 sites have mutator effect . The accumulation pattern of mutator gene is different with driver genes, but quite similar with random genes. Taken together, mutator genes are not key factors for most cases.

II.Snowball Effect of Mutation Accumulation

Snowball Model: Most genes have tiny effect on mutation rate



Tiny effect may come from positive feedback between endogenous factors and somatic mutation rate. Evidence include:

- many non repair genes are responsible for high mutation rate;
- metabolite can be inherited transgeneration.

Model Simulation: