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Human somatic mutations originate in mutator/hypermutable metakaryotic stem cells during the fetal/juvenile period.

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The origins of the somatic mutations required for carcinogenesis have long been sought in terms of both the identity of cells and their mutational mechanisms. John Cairns (1976) put forward the proposition on arithmetical grounds that they must arise primarily in the stem cell lineage of either organogenesis, maintenance turnover or both. We have offered evidence that the mutations that lead to clusters of mutant cells in adult tissue (lung, colon) arise in the stem cells of organogenesis but not from maintenance stem cells in adult life. In particular, we have shown that the stem cells of human organogenesis are not eukaryotic cells but "metakaryotic" cells that divide by amitosis. During nuclear segregation by amitosis they create a pan-genomic dsRNA/DNA replicative intermediate that is reconverted to dsDNA in two sister cells nuclei. Dividing metakaryotic stem cells nuclei express large quantities of DNA polymerases beta and zeta that are associated with high "by-pass" error rates in human eukaryotic cells. These findings are consistent with clinical measurements of mutant clusters of five point mutations in micro-anatomical lung epithelia permitting calculation of gene inactivation mutation rates of 2-4 x 10^-4 per gene copy doubling during organogenesis. This rate is a thousand fold higher than that found in human eukaryotic cells in vitro. We conclude that human organogenic stem cells are mutator/hypermutable metakaryotic cells that accumulate mutations only in the fetal/juvenile period. Such mutations in the form of inactivation of tumor suppressor gene copies would constitute tumor initiation. Tumor initiation would simply permit continued growth of an initiated colony at the juvenile growth rate with a doubling interval of 5-6 yrs. Initiation does not thus confer genomic instability; it is a constitutive quality of metakaryotic stem cells. We find that a mathematical model incorporating these biological observations and calculated mutation rates for stem cells in colon organogenesis accurately predicts the age-specific colorectal cancer mortality rates for human adults in the age interval 15-104 yrs.

Biography

Elena Gostjeva completed her PhD from Vavilov's Institute of Genetics, Moscow, Russia in 1986. Then she immediately was enrolled into studies of genetic risk assessment at Chernobyl Radiobiological Expedition headed by Institute of Evolutionary Morphology and Ecology of Animals at USSR Academy of Sciences. In 1994, after collapse of Soviet Union she was appointed as the Head of the group 'Genetic Risk Assessment of Chernobyl Fallout' at Kiev Polytechnical Institute, Ukraine. She conducted her research in Ukraine in collaboration with Prof. Lars Ehrenberg at the University of Stockholm and Swedish Radiation Protection Institute. In 1997, she joined MIT, USA working on mutational spectrometry applied in measuring mutations in human tissues. In 2003, after discovery of metakaryotic stem cells and up to date she continues to work at MIT under sponsorship of 'United Therapeutics' Inc. She has published 7 original papers in stem cells and cancer research and has 7 patents, 2 granted in the areas of stem cells in development, cancer, wound healing, atherosclerosis, organ transplant restenosis, veterinary as well as patents in drugs and regiments to target cancer stem cells.

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