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EDUCATIONAL SECTION

Mitochondrial DNA, human evolution and the cancer genotype

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Mitochondrial DNA is a small, well characterized chromosome which is transmitted across the generations in the maternal lineage, independently of nuclear DNA. mtDNA acts in effect as a robust, species specific biological clock and tracer which can be used to follow the evolution and spread by geographic migration of populations from their origins. Mutations in mtDNA cause specific maternally hereditable diseases, and can be used for forensic purposes. They are not specifically implicated in neoplasia, but they may provide clues as to the nature and origins of cancer susceptibility in various populations.

Key words: mitochondrial DNA; human evolution; cancer.

INTRODUCTION

The pattern and incidence of cancers is heterogenous, tissue, age and species specific within broad limits. Thus, for example, within the human body, primary adenocarcinomas of the gut are common in the stomach and colorectum, but virtually unknown in the proliferative epithelium of the several metres of small bowel. Even within the stomach and colorectum, there is considerable site to site variation in the incidence of tumours, as for example, between caecum and transverse colon. Tumours only become common in the later years of life, suggesting that there are powerful inherent defence, structural and regulatory mechanisms which protect against tumour development in the first five decades. Conversely, in other species, such as domestic mammals, the pattern of tumours is different and the incidence of onset years earlier. Such patterns may reflect subtle and complex genetic influences inherited over many generations whose mechanistic origins have been lost in the mists of time.

For the individual, cancer is a destructive disease with a substantial intrinsic and genotypic element conferring susceptibility and determining outcome. We recognize a significant genetic derangement to the aetiology and progress of all tumours, and we have sought for many decades the singular environmental insults and genetic disruptions which might explain the disease in individuals. However, it is possible that our search for simple, mechanistic explanations of cancer break down because we are underestimating the complexity of the cancer genotype and its origins in human evolution. Thus, just as the distribution of height in the human population is determined in the genotype, albeit modified by environmental and dietary influences, so may cancer susceptibility have arisen by accident or design in our evolutionary history.

We may also seek to understand why cancer has adopted particular patterns across particular human populations, and its relevance to human evolution.[1] Human population expansion must have progressed from a relatively small pool of individuals within the ancestral lineage which developed such critical human characteristics as bipedalism, the opposable thumb and the capacity for cerebral and intellectual expansion. Indeed, studies have suggested that all modern Europeans are descended from seven ancestral matriarchal groups as recently as between 8000 and 45 000 years ago; that native Americans are descended from Asianic colonization between 3000 and 30 000 years ago;[W3,W4] and that the core genetic variation across the entire *Homo sapiens* species is remarkably limited. Thus, any genotypic characteristics and tendencies to particular patterns of disease which were carried almost incidentally

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by a small number of individuals in our relatively recent past would have expanded and multiplied enormously in the modern human population. At a time when the mean life expectancy was perhaps 40 years, there would be no selection pressure against cancer. And thus, the modern pattern of human cancer susceptibilities and expression may well have emerged as by accident from an incidental genotypic pattern in our ancestors, or in consequence of characteristics which evolved for very different purposes.

This hypothesis might be untestable but for the role of genomic analytical sequencing of mitochondrial DNA (mtDNA). This has allowed us to study evolutionary migrations and population admixtures, and may in time allow us to track back and to predict patterns of susceptibility to cancer and other diseases in individuals and communities.

MITOCHONDRIAL DNA

Mitochondrial DNA is a curious phenomenon. It has been characterized and sequenced in humans and other species, and its genes and gene products are fully documented.[2,3] It replicates autonomously and is transmitted through the maternal germ line independently of nuclear and chromosomal DNA, without exposure to the DNA reordering and shuffling powers of meiotic cell division. It is thus a powerful marker of female inheritance. Each cell in the human body contains upwards of several hundred mitochondria. Each mitochondion contains up to 10 copies of mtDNA. mtDNA appears to be inherited exclusively from the maternal oocyte, as sperm do not transmit it. Oocytes contain up to 100 000 copies of mtDNA, and the number of mitochondria is increased 100-fold in oocytes. Amplification of mtDNA may occur from one or a very few copies in the oocyte, as new mutations can be expressed very rapidly across the mitochondrial population in one or a very few generations.[W1]

Mitochondria produce ATP for energetic processes in eukaryotic cells. They appear to have evolved from primitive energy producing bacteria in symbiosis with eukaryotic cells.[4] mtDNA was first fully sequenced in 1981.[2] mtDNA is a circular, double-stranded chromosome whose structure and function is understood in exquisite detail.[3] Human mtDNA is 16 569 base pairs long, or less than 1/300 000 of the total human genome. It codes for two mitochondrial ribosomal RNA and 22 transfer RNA genes, and 13 polypeptides associated with the electron transport system of the mitochondrion. There are now large data repositories of mtDNA sequences for detailed evaluations of the significance of mutations, and for comparative and forensic purposes.[W7,W8] The structure of the mitochondrion and another 50 or so of the energy production enzymes are encoded in the principal, nuclear genome of the cell, and can thus also be impaired by 'conventional' genetic defects in appropriate genes, such as in Friedreich's ataxia and Wilson's disease.

THE SIGNIFICANCE OF mtDNA MUTATIONS

Mutations in mtDNA accumulate linearly with time, so the base sequence of mtDNA can be used as a precise biological clock to study longitudinal changes in the human population with time, to study the evolution of geographically and genetically distinctive subpopulations from our ancestral origins, and to compare the human genotype with other species. The steady accumulation of random mutations in mtDNA down the generations is a tool for calculating the age of mankind, the geographic origins, and the size and location of the core population from which modern man has diverged. Analysis of the sequence variation in human mtDNA with time and geography makes it possible to follow the migrations of populations with related mtDNAs, or haplogroups, and to trace the patterns of various mtDNA derived pathologies. mtDNA also has a role in forensic science, such as in linking DNA from unidentified bodies to maternal relatives.[W5]

HUMAN DISEASES ATTRIBUTABLE TO mtDNA MUTATION

Mutations in mtDNA are responsible for a number of genetic diseases in man. Mutational defects in mtDNA cause a spectrum of rare hereditary diseases of energy metabolism and aging which are never expressed in men and which are variably expressed in women, depending upon the proportion of affected mitochondria in the oocyte.[5] This mixture of normal and mutant mtDNA is known as heteroplasmy. Tissues with high energy demands are particularly susceptible to these defects. These diseases include Leber's hereditary optic neuropathy, neonatal haemochromatosis, Kearns–Sayre syndrome (which includes retinitis pigmentosa) and Pearson's syndrome of fatal anaemia in infancy, and rare encephalopathies. Drugs of the asazidothymidine (AZT) family also deplete mtDNA. mtDNA defects may also contribute to uncommon forms of diabetes. A contribution of mtDNA defects has also been proposed in aging disorders such as Parkinson's and Alzheimer's diseases.[W9]

CONCLUSIONS

Human mtDNA studies demonstrate that small and mobile populations can over time achieve extraordinary expansion and complexity. Many unwanted accidents of our fate such as cancer susceptibility may have been determined by fortuitous events in the much smaller

gene pool of our immediate ancestors. mtDNA codes no recognized cancer genes nor is it directly implicated in the aetiology or progression of any known tumours. Nevertheless, at a deeper level, the study of mtDNA may offer profound insights into the nature of cancer, because it leads us back directly to the genetic strengths and susceptibilities of our ancestors. mtDNA will thus feature in our understanding of cancer and is relevant to the general education of the surgical oncologist.

Key Points

1. The human mitochondrial DNA chromosome has been fully sequenced and characterized.
2. mtDNA is a powerful tool for population based, geographical, evolutionary, forensic and disease orientated studies.
3. This is because mutations in mtDNA occur at a fairly constant rate over generations without rearrangement, and thus act as a biological and evolutionary clock.
4. mtDNA is transmitted exclusively in the maternal lineage and independently of the 23 much larger chromosomes of human nuclear DNA.
5. Although there are no specific cancer associated genes in mtDNA, study of variations in mtDNA across populations and generations may provide powerful clues as to the nature, pattern and inheritance of the cancer genotype.

REFERENCES

1. Rew DA. The evolutionary biology of aging, death and human malignancy. *Eur J Surg Oncol* 1998; **24**: 568–72.
2. Anderson S, Bankier AT, Barrell BG *et al*. Sequence and organisation of the human mitochondrial genome. *Nature* 1981; **290**: 457–65.
3. Wallace DC, Lott MT, Brown MD, Huoponen K, Torroni A. Report of the committee on human mitochondrial DNA. In: Cuticchia AJ (ed.) *Human Genome Mapping: A Compendium*. Baltimore: John Hopkins University Press, 1995, 910–54.
4. Perna NT, Kocher TD. Mitochondrial DNA: molecular fossils in the nucleus. *Current Biology* 1996; **6:** 128–9.
5. Chinnery PF, Turnbull DM. Mitochondrial DNA and disease. *Lancet* 1999; **354** (Suppl. 1): 17–21.

WEB REFERENCES (ALL CURRENT AS AT 21.04.2000)

W1. www.ich.ucl.ac.uk/cmgs/mt21nh99.htm
Mitochondrial inheritance.
W2. www.cs.unc.edu/~plaisted/ce/mitochondria.html
Plaisted DA. Mitochondrial DNA mutation rates.
W3. http://zetaserver.ivsla.unive.it/Istituto/Convegni/Origini/Torroni.htm
Torroni A. mtDNA variation in Europe: implications for the origin of Europeans and disease studies.
W4. http://abcnews.go.com/sections/science/DailyNews/daughters000420.html
Viegas J. Daughters of Eve: a report.
W5. http://biocrs.biomed.brown.edu/books/essays/mitochondrialDNA.htm
Miller KR. The fire within: the unfolding story of human mtDNA.
W6. www2.prf.or.jp/ssoel/vo242/nakamura.htm
Nakamura H. The origin and evolution of the mitochondrion.
W7. www.gen.emory.edu/mitomap.html
Mitomap: a human mitochondrial genome database.
W8. www.ebi.ac.uk/htbin/Mitbase
A specialised database of vertebrate mtDNA hosted by the European Bioinformatics Institute, Cambridge, UK.
W9. www.columbia.edu/cu/21stC/issue-1.3
Schon EA and Dimauro S. Research on mitochondrial diseases.