



In particular, attention should be directed at identifying genes downstream of DAF-2 signaling that coordinately affect the rate of aging in all of the cells in the body. □

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Mitochondria: integrators in tumorigenesis?

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The mitochondrial genomes of tumor cells accumulate mutations during transformation. A new study raises questions regarding the way in which mutations accumulate and has implications for the potential role of mitochondrial function in tumor phenotype.

In the ancient history of tumor cell biology and biochemistry (that is, pre-1995), it was established that mitochondrial DNA accumulates more damage from genotoxic agents than does the nuclear genome, probably because the mitochondria have less efficient DNA repair systems than the nucleus^{1–3}. This is consistent with more recent observations that mutations appear in mitochondrial DNA of tumor cells, and can be homoplasmic – that is, present in each of the hundreds of mitochondrial genomes in a cell and in virtually all of the cells of a tumor⁴. Further, following the fusion of two tumor cell lines, the mitochondrial genome of one quickly replaced that of the other, leading to the conclusion that once a particular mitochondrial sequence becomes homoplasmic in a cell, selective growth advantage conferred by mutations in either that mitochondrial genome, or in the nuclear genome of the cell, can result in the mitochondrial alteration becoming homoplasmic in the tumor⁴.

On page 147 of this issue, a study by Hilary Collier and colleagues⁵ indicates otherwise. The authors present a mathematical model that shows the presence of a homoplasmic mitochondrial mutation in a tumor can result from random segregation of mutant genomes in the many cell generations that occur during tumor development⁵. The predictions of the model agree with experimental data documenting the incidence and nature of tumor mitochondrial mutations. It would therefore seem that there is no need to

invoke a selective advantage for a mutation in the mitochondrial genome to explain its presence. The model also predicts, in agreement with more limited data, that homoplasmic mitochondrial variations should arise with significant frequency in normal tissues derived from stem cells that have undergone a high number of cell divisions.

Models of mitochondrial mutations

The report should stimulate extensive debate regarding the validity of the model. At this point, a reasonable, if broad, speculation is that, among a high background of random mutations that provide no selective advantage, there are a smaller number of mutations that alter mitochondrial function and cell physiology in a manner that has significant effects on tumor development, or phenotype in one of several tumor-associated environments (for example, hypoxia, angiogenic insufficiency or stimulation, or shift of metabolic phenotype). This is a scenario similar to that of tumors with defects in DNA repair: thousands of mutations accumulate in the nuclear genome, the vast majority of which are functionally and physiologically silent and overlaying the few that have an impact on tumorigenesis. Unfortunately, there is still no way to identify the functionally important mutations⁶.

It is even harder to identify relevant mutations in the mitochondrial genome because we do not know how mutations in the many genomes of individual mitochondria, and among the hundreds of mitochondria per

cell, interact genetically in terms of dominant and recessive effects. Even if consideration is focused only on mutations that become essentially homoplasmic, the problem will be difficult to solve.

First, mitochondrial function is intimately linked to the expression of nuclear genes, both directly, as some mitochondrial proteins and subunits of mitochondrial complexes involved in electron transport and oxidative phosphorylation are encoded by nuclear genes, and indirectly, as mitochondrial oxidative phosphorylation is linked to many pathways of intermediary metabolism. Therefore, the extensive mutations in nuclear genes coupled with altered profiles of gene expression that characterize tumors, will potentially interact with mitochondrial mutations. It is possible that only rare combinations of coincident changes in the two genomes may be of functional significance, and indeed there is evidence that nuclear–mitochondrial gene interaction provides a selective advantage for a particular mitochondrial genome^{7,8}.

Second, given the large number of cell divisions necessary for tumor development—estimated at 600 by Collier *et al.*⁵—an alteration in mitochondrial function that is exceedingly subtle in terms of its biochemical or physiological manifestation may be all that is necessary to significantly alter the probability of tumor formation or the final clinical phenotype, including the malignant potential, of the tumor. Cell and molecular biologists are generally not comfortable working with such small phenotypic effects.



The potential of potentials

What are some of the effects of mitochondrial mutations that one should look for? Our personal bias would place the effects on the mitochondrial membrane potential ($\Delta\Psi_m$) at the top the list. The $\Delta\Psi_m$ is established and maintained by electron transport coupled to the pumping of protons from the mitochondrial matrix to the intermembranous space. This creates a gradient composed of two parts: a pH gradient and the $\Delta\Psi_m$ (ref. 9). Anything that affects the efficiency of electron transport can therefore affect the $\Delta\Psi_m$.

The mitochondrial membrane potential is important in both the translation and stability of proteins encoded by mitochondrial DNA and synthesized within the organelle¹⁰, as well as in the translocation across the mitochondrial membrane of nuclear encoded proteins that are synthesized in the cytoplasm, but destined for the mitochondria due to encoded targeting sequences¹¹. But perhaps of greatest interest regarding tumor formation is the fact that dissipation of the $\Delta\Psi_m$ is often linked to the release of cytochrome c (and possibly other factors) from the mitochondrion, which initiates apoptotic cascades (ref. 12).

The presence of a $\Delta\Psi_m$ is necessary for the stimulation of an apoptotic cascade in colon carcinoma cells, and is also necessary for the cell cycle arrest that precedes initiation of apoptosis¹³. Thus, the mitochondrial membrane potential may coordinate pathways of cell maturation that are necessary for tissue homeostasis and that become uncoupled in tumor development. In fact, recent evidence from our laboratory has demonstrated that isogenic cell lines selected

for stable differences in the $\Delta\Psi_m$ have different growth properties and responses to inducers of maturation pathways.

The way in which $\Delta\Psi_m$ mediates coordination of maturation pathways may involve the interaction of pro- and anti-apoptotic and growth factors with the membrane. The transcription factor TR3, which resides in the nucleus during cell growth, translocates to the mitochondrial membrane following an apoptotic stimulus¹⁴. At its mitochondrial location, TR3 causes the release of cytochrome c to initiate an apoptotic cascade. In this case, the stimulation of the apoptotic pathway may be directly tied to the removal of the transcription factor from the nucleus, thereby down-regulating the growth pathway. A number of other proteins involved in apoptosis, some of which are also involved in cell cycle regulation, localize to the mitochondrion in response to apoptotic stimuli¹⁵. We need to understand how alterations in mitochondrial function, especially the $\Delta\Psi_m$, influence efficiency of sequestration of such factors at this organelle, as well as their interactions and effects.

Studies of the presence and mechanisms of mitochondrial DNA mutations focus attention on the role of mitochondrial genetics in tumor formation. However, mitochondrial function and potential downstream effects, such as alterations in the $\Delta\Psi_m$, can be influenced by the metabolic state of the cell. For example, there is a direct relationship between the cholesterol content of the mitochondrial membrane and proton permeability¹⁶. Nutritional factors may therefore influence the probability of tumor formation and phenotype

through such mechanisms. Moreover, the number of metabolic pathways that could have an impact on mitochondrial functions is very large. Therefore, it has been suggested that the mitochondrion could be the 'integrator' of many signals that have a potential impact on tumor related processes^{13,15}. Such epigenetic interactions between nutrients and mitochondrial genetic alterations, polymorphisms or function have not been considered when addressing the epidemiology of dietary links to cancer, or in cellular or molecular investigations in this area. This may contribute to the sometimes confusing and conflicting data in this field. Therefore, the mitochondrion may not only integrate critical biochemical and signaling pathways in the cell, but also our thoughts on seemingly disparate mechanisms that influence tumor formation and phenotype. □

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To be or not to BMP

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Three years after *MADH4* (also known as *SMAD4*) was identified as a gene critical to juvenile polyposis, *BMPR1A*, encoding a receptor in the same pathway, has been identified as another susceptibility gene. The TGF β /BMP superfamily of molecules has not only been shown to be defective in neoplasia but also in the non-cancer developmental syndromes primary pulmonary hypertension and hereditary hemorrhagic telangiectasia.

Juvenile polyposis syndrome (JPS) is a diagnosis of exclusion among the so-called hamartoma polyposis syndromes. A hamartoma is a benign growth comprised of at least two of the elements of the gastrointestinal tissue but in a developmentally

disorganized fashion. JPS is an autosomal dominant disorder characterized by gastrointestinal hamartomatous polyps and a risk for colorectal and other gastrointestinal cancers. Its diagnosis can only be made when the other hamartomatous polyposes,

which carry different neoplastic risks, have been ruled out. So, identifying genes that underlie susceptibility to JPS would help clinical practice enormously. James Howe and colleagues² identified germline mutations in *MADH4*, in a subset of people with