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Letter to Editor

## Cancer might be a failed response to renegade mitochondria

> Cancer is one of the most intensively studied phenomena in biology, yet mortality rates from the disease are little changed in decades. Perhaps that's because we are thinking about the problem in the wrong way.
> —Davies, 2014

> Mitochondria have a critical role to play in the successful conquest of cancer. Further and deeper investigations of this organelle assure profound insights into the missing molecular mechanisms of malignancy.
> —Verschoor (2013), p. 7

> Is mutation of mitochondria the cause of malignant degeneration?
> —Graffi, 1968, p. 945 (also Graffi, 1940a, 1940b)

### 1. Successful response to renegade mitochondria: Apoptosis

Given a hundred to a thousand mitochondria per cell, each with prokaryotic 'naked' DNA that is highly susceptible to mutation without repair (see Penta et al., 2001; Verschoor, 2013 for review), cells containing both wild type and mutant mitochondria (heteroplasmic cells, see Wallace and Chalkia, 2013 for review) may be generated every few minutes, if not every few seconds, in organisms that have more than a trillion cells.

Under that much stochastic pressure (Neubert et al., 1981; Aanen et al., 2014), natural selection would favor the evolution of wild type mitochondria that collude with nuclear DNA to generate enough BAX protein (Dejean et al., 2006; Scatena, 2012) to initiate apoptosis. This would be the ultimate reproductive success by kin selection (Hamilton, 1964) when self-sacrificing wild type mitochondria and their cell's nuclear genome are replaced by a genetically identical homoplasmic cell after an adjoining cell undergoes mitosis (Fig. 1)[2]. Perhaps this hypothesis could be falsified in an *in vitro* model of cancer that would enable comparison of malignancy generation rates in an apoptosis-permissive medium versus an apoptosis-restrictive medium.

### 2. Failed response to renegade mitochondria

If the apoptotic cascade is retarded by toxins and/or nuclear gene products, renegade mitochondria may reproduce rapidly enough to trigger sufficient anti-apoptotic Bcl-2 (Hanahan and Weinberg, 2011) to block apoptosis and thereby allow reproductive competition between wild type and renegade mitochondria (Fig. 2A and B).

Before undergoing mitosis, cells need at least twice the number of mitochondria required for each daughter to survive. If the mitotic causal arrow can work in both directions, such that mitotic signals can trigger a substantial increase in mitochondria, or a substantial increase in mitochondria can trigger mitosis (consider Gimenez-Cassina and Danial, 2015), reproductive competition between renegade and wild type mitochondria could drive mitosis (Hartung, 1982a, Fig. 2C).

Mitosis requires activation (de-methylation) of genes that generate mitosis. If competition between mitochondria stimulates mitosis in a line of heteroplasmic daughter cells, the continuous activation of genes that generate mitosis without undergoing re-methylation and de-methylation between generations would increase a cell line's reproductive rate and so be naturally selected (cf. Cosenza et al., 1991). That could lead to "Sequential mitoses at a radical rate, such that daughters do not have time to fully re-differentiate before dividing again" which could be accomplished by reactivating genes that were "coding when the organism was a blastocyst" (Hartung, 1982b) … perhaps the origin of cancer stem cells (Karsten and Goletz, 2013; Plaks et al., 2015).

Sequentially de-differentiating heteroplasmic cell lines would become malignant cancer (Fig. 2D), but spatial clumping of either renegade or wild type mitochondria, with or without asymmetrical mitosis (Hartung, 1982a), could also produce either type of de-differentiated homoplasmic daughters (Fig. 3)[3]. De-differentiated homoplasmic cells may be the basis of benign cancer, or the basis of slow growth when they form the majority cell type in tumors comprising both heteroplasmic and homoplasmic cells. In this scenario, cancer cells do not transform from benign to malignant, but start as malignant … with some mitotic divisions generating relatively benign cancer cell lines. Perhaps this hypothesis could be tested by making cytoplasmic hybrids (cybrids) that combine normal nuclei with malignant, heteroplasmic cytoplasm (Hartung, 1982b).

### 3. The upshot

If this view has merit, it may be the case that most malignant cells re-differentiate in response to endogenously generated cytokines and hormones in a manner that is analogous to processes that occur as blastocysts become embryos, such that the vast majority of tumors remain microscopic, resolve naturally, and are never diagnosed. If so, when spontaneous remission fails, judicious stimulation or titrated infusion of appropriate cytokines, tumor

[2] An ability to resolve reproductive competition between mitochondria may have been the primordial impetus for the evolution of the apoptotic cascade, and so an adaptation required for the evolution of metazoan multicellularity.

[3] A surround of benign cancer cells may protect malignant cells from the immune system.

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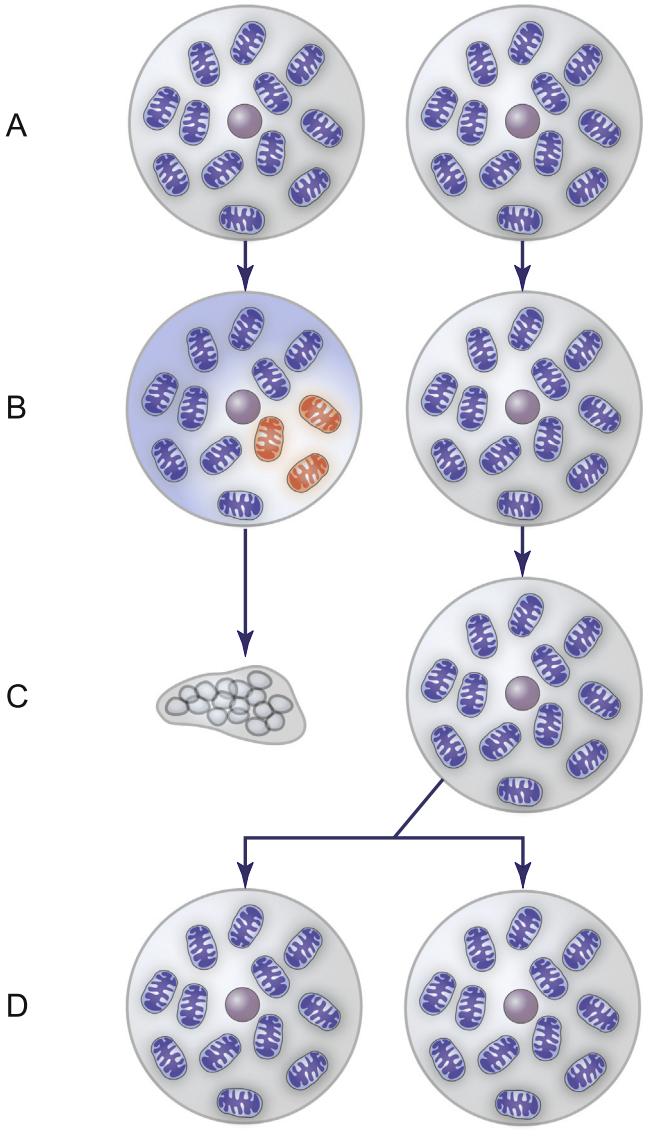


**Fig. 1.** Successful response to renegade mitochondria: Apoptosis. (A) Identical differentiated homoplasmic cells with only wild type mitochondria. (B) Same cells, but one with a small population of renegade mitochondria and pro-apoptotic BAX protein (blue shading). (C) Apoptosed cell with same adjoining cell. (D) Daughters of adjoining differentiated cell after undergoing mitosis… identical to cells in A above.

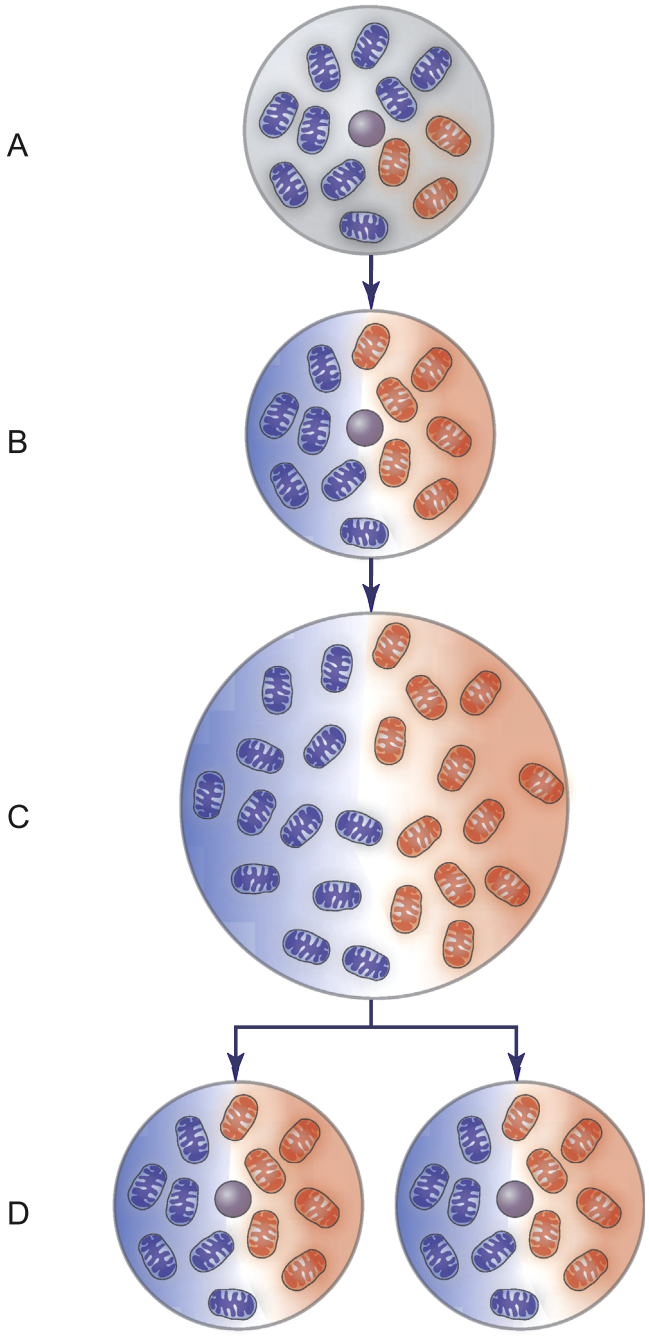


**Fig. 2.** Failed response to renegade mitochondria. (A) Cell with what would be sufficient renegade mitochondria to trigger apoptosis were it not for toxic impairment and/or nuclear gene products (transcripts, proteins) that retard the apoptotic cascade [toxins and genes thereby associated with cancer, and so thought of as first-cause carcinogens and oncogenes, but here considered minor impediments in cells where the alacrity of the apoptotic response is not critical, e.g., cells that do not contain renegade mitochondria (see Davies, 2014 on the futility of the *Somatic Mutation Theory of Cancer*)]. (B) Same cell with enough renegade mitochondria to trigger anti-apoptotic Bcl-2 (red shading) sufficient to prevent apoptosis and there by disinhibit reproductive competition between wild type and renegade mitochondria. (C) Same cell with enough mitochondria to trigger mitoses. (D) Heteroplasmic daughter cells that will generate successively de-differentiating daughters leading to malignant cell lines (A in Fig. 3).

differentiation factors (TDF's, Platica et al., 2004) and growth differentiation factors (GDF's, Herpin et al., 2004) may cause malignant cells to reacquire the capacity to apoptose (Li et al., 2012)[4].

[4] Re-differentiation by coarser means, most prominently all trans-retinoic acid (ATRA), have shown promise in vitro, but the equivocal performance of ATRA and other retinoids' in clinical trials is discouraging. The logic of using any substance to promote re-differentiation is encouraging, but retinoids' failure against solid tumors suggests that they would be most effective against a highly curable type of leukemia, acute promyelocytic leukemia. Unfortunately, a recent meta-analysis concluded that "ATRA based regimens compared to non-ATRA based regimens did not demonstrate a survival benefit" (Muchtar et al., 2013).

## 4. Suggestive correlates

Given chromosomal crossover and independent segregation during meiosis, identical replacement by mitosis of an adjoining cell (Fig. 1) would not be available to meiotic oocytes, such that

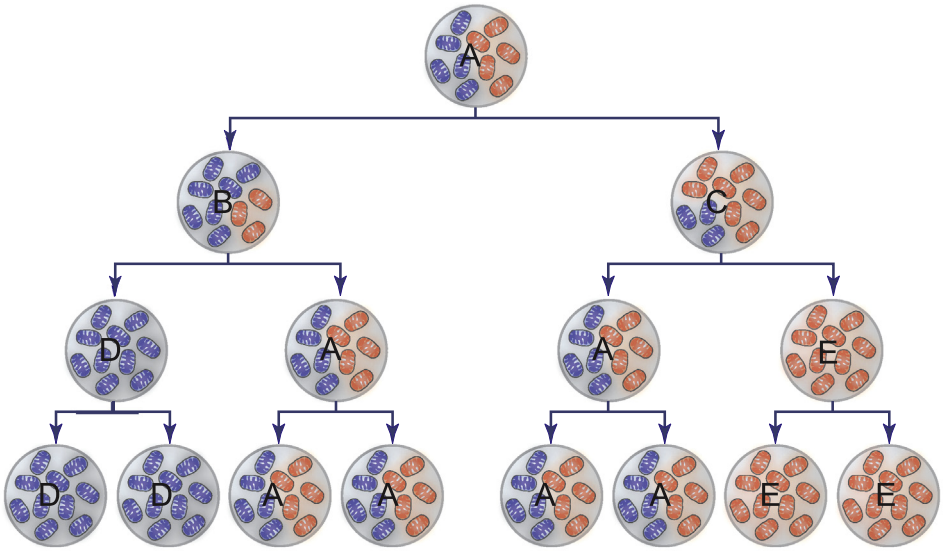


**Fig. 3.** Generation of malignant and benign cells from a malignant cell line (see footnote 3). (A) De-differentiated heteroplasmic cells with continuously activated genes that generate mitosis=malignant. (B) Daughter of A with a spatially clumped minority of renegade mitochondria can generate one heteroplasmic daughter and one daughter that is homoplastic for wild type mitochondria. (C) Daughter of A with a spatially clumped minority of wild type mitochondria can generate one heteroplasmic daughter and one daughter that is homoplastic for renegade mitochondria. (D) De-differentiated cell homoplasmic for wild type mitochondria=benign cancer cell. (E) De-differentiated cell homoplasmic for renegade (new wild type) mitochondria=relatively benign cancer cell.

heteroplasmicity would often be resolved in favor of mutant mitochondria … which would account for the fact that mitochondrial DNA can evolve about 10x faster than nuclear DNA in sexually reproducing species.

The above suggestion about TDF's, GDF's and cytokines comports with the observation that substantially differentiated teratomas are seldom malignant, while relatively undifferentiated teratomas are less common and are typically malignant.

This perspective also complements the observation that pituitary tumors which generate excessive amounts of growth hormone cause conditions like acromegaly and gigantism but are otherwise benign, while malignant pituitary tumors are extremely rare and do not generate excessive growth hormone. The American Cancer Society estimates that about 20% of adult humans host a small, benign pituitary tumor … small enough to not cause a mechanical problem near the tight space of the *stella turcica*, and not 'functional' enough to cause growth abnormalities. If there is a genetic propensity for developing such tumors (see Couldwell and Cannon-Albright, 2014), 20% is too high a frequency to have evolved by genetic drift. Perhaps those tumors are naturally selected because they produce enough non-'misexpressed' growth hormones (Tykwinska et al., 2013; Vanhara et al., 2012), and stimulate sufficient and appropriate cytokines/GDF's/TDF's to re-differentiate malignant cells to states that re-enable apoptosis (Jones et al., 2015) … and so protect against malignant cancer.

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