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Deep Insight Section

Mitochondrial DNA mutations in cancer: causality or association?

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There is probably no need to explain that mitochondria are essential for the functioning of the eukaryotic cell: they provide energy through oxidative phosphorylation. Mitochondria are the site of synthesis of many molecules and are also involved in apoptosis. All mammalian eukaryotic cells - in particular somatic cells with some exceptions such as red blood cells - contain mitochondria: there are several hundred to several thousand. Human mitochondria contain their own circular genome, 16568 base pairs long, encoding 13 proteins of the respiratory chain, 2 rRNAs and 22 tRNAs. The 13 proteins are components of four respiratory complexes participating in oxidative phosphorylation, but many other proteins of the respiratory chain are encoded in the nucleus and complex II is only made up of nuclear-encoded proteins (Anderson et al., 1981; Andrews et al., 1999).

The belief that mitochondria are involved in cancer is quite old - Warburg (1956) proposed in the early 20th century that cancer was due to the lack of oxidative respiration. Cancer cells performed glycolysis even when oxygen was present. The general idea has been discussed in many papers. This phenomenon, as often in cancer, is not as simple as it was believed to be (Mullen et al., 2011; Ward and Thompson, 2012). The glycolytic phenotype, combined with glutaminolysis, is a way to provide the rapidly dividing cells with building blocks from molecules which are not degraded to carbon dioxide and water in this way.

Interest in mitochondrial DNA (mtDNA) mutations was aroused much later, there were early papers pointing out that mitochondria were altered in oncocytomas. But the turning point was a paper by Vogelstein's group (Polyak et al., 1998) reporting that mutations in sequences of tumor mtDNA were found (but not in appropriate control tissues). These mutations were homoplasmic, which means that all mtDNA molecules carried the mutation. At this point many groups started to look for these mutations in many different types of cancer. Currently, a Medline query of "mitochondrial DNA mutations cancer", June 2012, gives 1279 hits.

To try to summarize this amount of data is difficult. Mitochondrial DNA has been hailed as an excellent marker for detecting tumors, as a possible site of attack for anti-cancer drugs. A whole issue of Oncology and several books have been devoted to mitochondria and cancer.

To discuss these papers in more detail, some more information on mitochondrial DNA is required. At present, this molecule has been sequenced in many thousands of individuals. But even earlier partial sequences and restriction analysis led to the grouping of various subgroups of mtDNA sequences into groups of related sequences with a common ancestor called: haplogroups. Mitochondrial DNA originated in Africa from where it spread to other continents. In Europe, for instance, haplogroups H, U, I, J, K, V, X, T and W are the most common. Each haplogroup is composed of subhaplogroups, very numerous for instance in the case of haplogroup H. As mitochondrial DNA is maternally inherited, which does not recombine (but it is still not a closed matter), there is a set of characteristic mitochondrial DNA positions for each haplogroup. As mitochondrial DNA is easy to analyze, many papers have appeared linking various haplogroups to both positive (longevity) and negative (increased frequency of Alzheimer's disease etc.) effects (Wallace, 2005).

In general, mtDNA sequences are compared to a reference sequence, called the Cambridge Reference Sequence (CRS), originally determined by Sanger and co-workers (Anderson et al., 1981) and corrected later

(revised Cambridge sequence, rCRS, Andrews et al., 1999). It is important to understand that this comparison is for the sake of standardization, but it really does not mean anything, except that the analyzed DNA is not the same as that of the standard. Essentially, in recent papers, a full classification up to subhaplogroups is made on the basis of the sequence of the entire mitochondrial genome; but for "older" papers (a field started in the late 1990s), often only parts of the sequence were analyzed.

There are many papers stating that various mutations have been found in tumors which were not found in an appropriate control tissue. Here we come to one of the numerous problems with many of the published papers - the ones we will discuss is appropriate reference material, appropriate control tissue, appropriate number of analyzed samples and appropriate standards of analysis.

The reference material has been mentioned above - it is the rCRS. However, comparison of patients' mtDNA sequences to the rCRS is not sufficient to warrant conclusions that these differences have anything to do with cancer - they are simply different from the reference sequence, as are most analyzed mitochondrial DNAs. This has not been understood by some of the authors.

The second problem is standards. Salas, Bandelt and co-workers (Salas et al., 2005; Bandelt and Salas, 2009) have pointed out that in many of the papers combinations of haplogroup-specific sites are found in some mtDNA sequences which can only be explained as a mix-up or contamination of the analyzed samples. Such mtDNA molecules would not exist in a cell. These authors even go as far as to discredit essentially all or most of the papers in the field. This is perhaps extreme, as especially in more recent papers careful analysis with assignment to subhaplogroups is made, but it does suggest that the papers should be read with caution.

The appropriate healthy control tissue is also a problem. In some papers tumor margins are taken, but the theory of field cancerization (Dakubo et al., 2007) indicates that tissues at the boundary of a tumor are not necessarily normal, and this may also be true for the mitochondrial DNA that they contain. Blood is a commonly used control and is generally acceptable. There is some concern that it may contain tumor-derived cells or DNA, but these levels of contamination are not expected to be high.

The next problem is a statistical one - how many samples have to be analyzed to give a reliable result? This is of less importance for mutations, and of more importance for papers analyzing whether the fact that an individual has a given haplogroup affects his risk of getting a defined type of cancer. This has been investigated for many cancers and many haplogroups,
but generally on groups of patients and controls which Samuels et al. (2006) consider much too small to draw reliable conclusions from.

Many reviews have been published concerning mtDNA and cancer, but in very few of them did the authors check the original data, thus what is discussed in many of them may be the result of analyzing a mixture of true and false results.

In a review analyzing numerous mutations Brandon et al. (2006) put forth the hypothesis that most mutations found in mtDNA in cancer occur at the sites which are polymorphic in the human population - that is the sites which changed in human evolution. This has been also stated by other authors. Briefly, most of these mutations would not have strong effects on mitochondrial function, though mutations with strong effects have been shown to occur in early stages of thyroid cancer. It is very difficult to comment on this as reanalyzing all the published data would be a daunting task, this may not, however, be true for all types of cancers. Elegant analysis performed by Skonieczna et al. (2012) for colon cancer and a paper on oncocytomas (Pereira et al., 2012) have shown that in these two types of tumors, which were analyzed by the new high-throughput sequencing techniques, the mutations which are found in the tumors but not in control tissue are severe mutations, which would certainly impair oxidative phosphorylation. More data are required to determine whether these two types of tumors are special or whether simply better data is available for them. Many of the mutations found by high-throughput sequencing techniques are heteroplasmic (He et al., 2010), that is the mtDNA is a mixture of mutated and unmutated molecules. In many cases heteroplasmy below a certain level would not have been detected by Sanger sequencing, and this is the way most of the data in the literature were obtained.

Another point worth mentioning is whether these mutations have any selective value for the tumor. Though instinctively the idea of the selection of a mutation which somehow drives a cancer cell is appealing, there are mathematical models indicating that homoplasmy can be established starting by chance with a single mutation, without any need for selective advantage (Chinnery et al., 2002).

Of course a mathematical model cannot be proof of anything taking place in a living cell, but it
certainly is an indication of the possibility that at least some mutations in mtDNA in cancer cells are there for no special reason.

One of the more important facts concerning mitochondria and cancer is the fact that mutations in nuclear genes which are components of complex II of the respiratory chain cause various types of tumors. These mutations have been found in all four subunits of succinate dehydrogenase as well as in fumarate hydratase. They cause paragangliomas, leiomyomas and myomas, and the mechanism is believed to be
through altering the stability of HIF1 alpha through indirect action by fumarate (Baysal et al., 2000; Baysal,

2006; Bardella et al., 2011; Burnichon et al., 2010). As these complex II mutations affect the mitochondrial respiratory chain this is proof that mutations acting on mitochondria can cause cancer. However, this does not resolve the problem of the role of mutations in mitochondrial DNA.

Is there any evidence that mtDNA mutations affect carcinogenesis or other processes taking place in tumors? There are some data which are intriguing. Petros et al. (2005) have shown in a mouse model that when cells of the prostate cancer cell line PC3 are introduced into nude mice, the presence of a well known 8993 NARP mutations (in ATP6, which causes the disease neurogenic ataxia with retinitis pigmentosa) in the mtDNA causes tumors which grow 7 times faster that tumors differing only by the absence of this mutation from mitochondrial DNA. Moreover, the same mutation was shown to stimulate cell growth in a bone stromal environment (Arnold et al., 2009). In a similar set of experiments Shidara et al. (2005) have shown that the same mutation present in HeLa cell mitochondria causes resistance to apoptosis in tumors growing in nude mice in comparison to the results obtained with HeLa cells containing wild type mitochondrial DNA. This is interesting, but as the 8993 mutation has never been found in tumors this does not show how a mutation which is present in a natural tumor would act.

While it is difficult to prove the involvement of mtDNA mutations in triggering oncogenesis, there is increasing evidence of their significance for tumor growth and metastatic potential and its regulation (Shidara et al., 2005). The first suggestions that mtDNA mutations may play a role in metastasis came from the comparison of frequency of somatic mtDNA mutations in lung carcinoma at different stages of tumor formation. It positively correlated with cancer progression as well as with metastatic potential (Matsuyama et al., 2003). However, such analysis could not be considered as a proof, and needed to be confirmed experimentally.

Ishikawa and Hayashi (2009, 2010) addressed this problem with a set of experiments based on cybrids. As there is no way to transform mammalian mitochondria, cybrids or transmitochondrial hybrids are a very useful tool for exploring the role of mtDNA mutations. It is possible to obtain cells devoid of mitochondrial DNA called rho0 cells, generally by prolonged growth in the presence of ethidium bromide. Such cells can be repopulated by mitochondria derived from other cells, which were enucleated to eliminate the influence of the nuclear component. Cybrids have the nucleus from rho0 cells and the mitochondria of choice. To find the role of mtDNA mutations, exchange experiments were performed between cell lines with high and low metastatic capability. Both cell lines were depleted of mtDNA to create rho0 cells. Then the rho0 cells from a low metastatic cell lines derived from a lung carcinoma were fused with high metastatic cytoplasts (cells with removed nuclei) and the other way round: rho0s from high metastatic cell line were fused with low metastatic cytoplasts. The metastatic potential was evaluated in mice and it correlated with the presence of "metastatic" mtDNA and not with the "metastatic" nucleus. Together with the metastatic potential, complex I deficiency observed in the original high metastatic cell line (but not in a low metastatic one) was transferred. The finding was confirmed for another pair of high/low metastatic cell lines with/without complex I deficiency respectively derived from fibrosarcoma with similar effect. For both "metastatic" mitochondria, mutations in mtDNA complex I genes were found (Ishikawa et al., 2008a). Similar experiments were performed for other cancer cells like breast cancer (Imanishi et al., 2011).

These experiments confirmed in a very elegant way the involvement of mtDNA mutations in metastasis, but the mechanism still may be questioned. As mitochondria as a whole and complex I in particular are important reactive oxygen species (ROS) generators in the cell this was one of the first concepts to explain mitochondrial participation in metastasis. ROS are natural candidates as they are known to be an important cell signaling factors involved, among others, in cell cycle control and apoptosis - both disturbed in carcinogenesis.

Higher levels of ROS are frequently observed in cancer cells but the source and the way of action seem to be pleiotropic and involve several mechanisms like hypoxia, paradoxically causing increased ROS production, hypoglycemia, oncogenes and transcription factors (like RAS, MYC, p53) and others together with mtDNA mutations. The multiple possibilities have been reviewed in detail by Ralph et al. (2010) and Fogg et al. (2011). To present some examples of mitochondrial ROS involvement: a coincidence of elevated ROS production, mitochondrial defect and enhanced tumorigenesis was shown in a mouse model of intestinal carcinoma (APCMin/+ mice) crossed to produce APCMin/+ Tfam+/- mice.

TFAM (mitochondrial transcription factor A) is responsible for mtDNA transcription and maintenance. Homozygous knockout of the gene is lethal, but heterozygotes are viable, with no phenotype besides up to 50% mtDNA depletion. Interestingly, APCMin/+ Tfam+/- mice showed increased tumor number and growth as well as ROS production. The role of ROS in APCMin/+ model was proven by targeting catalase to mitochondria which resulted in reduction of tumorigenesis (Woo et al., 2012). Similarly SOD inactivation led to increased transformation of irradiated mouse embryonic fibroblasts. Increased ROS was observed as well by the Hayashi group in cybrid experiments but some aspects of ROS measurement methods have been questioned (Zielonka and Kalyanaraman, 2008).

At the end it is worth pointing that some activity of respiratory chain is required for metastatic potential.

Rho0 cells do not generate elevated ROS and do not grow in an anchor-independent way as cancer cells (Weinberg et al., 2010). Similarly, heteroplasmic mutations (frameshifts and nonsense) in ND5 mitochondrial gene (complex I) show higher ROS production and tumor growth than the same mutations in a homoplasmic state (Park et al., 2009). Again, no enhanced ROS and high metastatic potential was observed for the cells with large mtDNA deletion in cybrid system (Ishikawa et al., 2008b). This effect may be easily explained: as the respiratory chain is a ROS producer, when it is completely inactive ROS are not elevated and do not influence tumor formation and metastasis.

Another interesting matter is not mutations but haplogroups and polymorphisms. For a long time the different mitochondrial haplogroups were believed to have no effect on the phenotype of the individual in whose organism they occurred. Some papers have suggested that some haplogroups are responsible for more uncoupled mitochondria, which could have consequences for their "owners" in respect to their utilization of food, and could affect aging and susceptibility to various mitochondrial diseases, especially Leber's hereditary optic neuropathy, a disease for which mitochondrial DNA mutations in complex I are necessary but not sufficient and one of the predisposing factors is the haplogroup in which the mutation is present (Wallace, 2005; Singh and Kulawiec, 2009; Kulawiec et al., 2010). There are some papers indicating functional differences between haplogroups, though the differences have not really been proven. However, the literature on haplogroup associations with various diseases is also abundant (Medline gives 77 hits for mitochondrial haplogroup association disease). This has all the problems of association studies and few of them have been performed on groups which are sufficiently large to warrant definitive conclusions. Samuels et al. (2006) have stated that in order to ascertain an association with a common haplogroup with a 95% certainty 2000 patients and controls would have to be analyzed, very few studies had even a quarter of the required number of cases.

Breast cancer is a good example how confusing the data can be. The site 10398 is polymorphic - in some haplogroups an A is present in this position, in others a G. There are serious and well-documented papers showing an association of the A with breast cancer in African women (Canter et al., 2005; Darvishi et al., 2007), though this has not been confirmed by other studies (Setiawan et al., 2008). On the other hand, we have shown the association of a G in this position with breast cancer in Polish women (Czarnecka et al., 2010). What does this mean? Perhaps only that the association is not as simple as it appears - the effects of the nucleotide in this position either are spurious or due to complex interactions with nucleotides at other positions in the mitochondrial genome and also with the nuclear genes.However, some of the results are interesting, Booker et al. (2006) have shown associations of haplogroup U with renal and prostate cancer (relative risk of about 2), we have shown various haplogroup associations for vulvar cancer, endometrial cancer and breast cancer (reviewed in Czarnecka and Bartnik, 2011). In our analysis we did not find many mutations, but what seemed to be true was that many of the samples from the patients contained very rare polymorphisms of mtDNA - not found or only very rarely found in the existing mitochondrial DNA databases. Herrnstadt and Howell (2004) have suggested that rare polymorphisms are something which is common in many diseases, and would be a sign of poorer fitness, somehow conducive to a number of disease processes.

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