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Editorial

When numbers matters: mitochondrial DNA and gliomagenesis

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Besides being crucial for cellular bioenergetics, mitochondria are key players in many pathophysiological processes: from cell death to autophagy, immunity.[1] In cancer, not only they regulate the evasion from apoptosis that characterizes most tumor cells, but they are also crucial for the metabolic switch from oxidative to glycolytic.[2] Among all other organelles, mitochondria are peculiar because they harbor their own DNA (mtDNA), whose replication is tightly controlled and concerted with the biogenesis of the vast majority of mitochondrial proteins that are encoded by the nuclear DNA. It is therefore no surprise that mtDNA copy number deregulation alters mitochondrial and cellular functions. For instance, mtDNA mutations and copy number expansions and depletions are common features of cancer cells. Remarkably, mtDNA copy number has been reported to be increased in some tumors and decreased in other. Additionally, mtDNA-depleted cancer cells grow at a lower rate and are more resistant to chemotherapeutic agents compared to their parental cell lines.[3] Therefore, although many evidences suggest mtDNA copy number variations in tumorigenesis, their role in tumor formation and growth is still intensively debated.

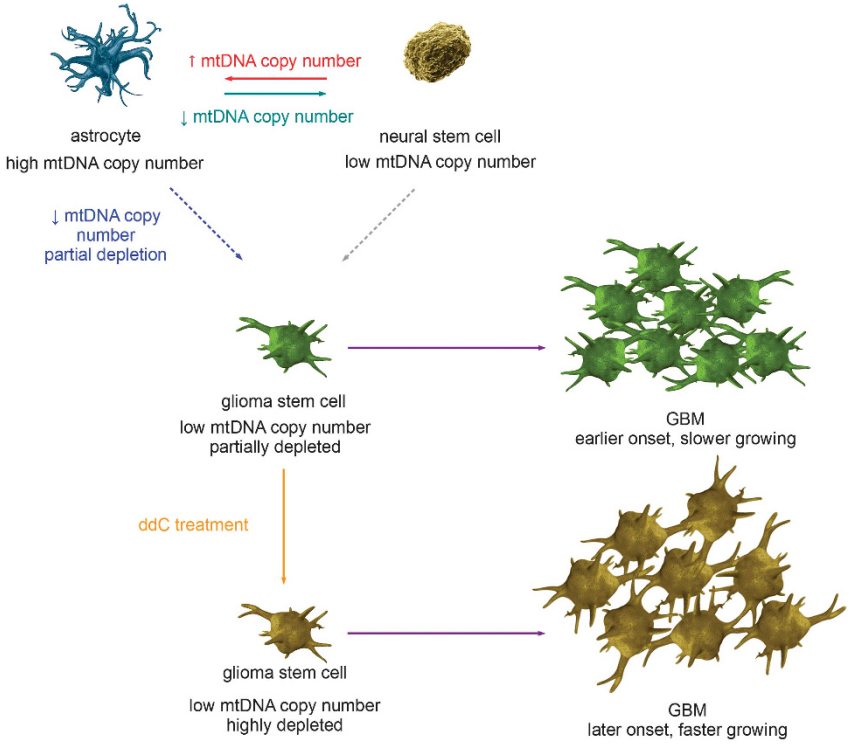

Figure 1 During differentiation, neural stem cells expand their mtDNA copy number in order to sustain mitochondrial biogenesis. Glioma stem cells, which might derive from adult neural stem cells or dedifferentiating astrocytes, have a reduced stem potential compared to neural stem cells possibly due to an incomplete nuclear reprogramming and a partial reduction of mtDNA copy number. Partial mtDNA depletion in GBM cells gives rise to cancer with later onset and subsequent faster growth compared to their 100% mtDNA GBM counterparts

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In this issue of *CDD*, Dickinson *et al.*[9] investigate the role of mtDNA copy number in gliomagenesis and further explore their intriguing hypothesis of the 'mtDNA set point'.[4–6] Accordingly to their previous publications, after fertilization, glycolytic embryonic stem cells (ESCs) progressively reduce their mtDNA copy number until they reach the so-called 'mtDNA set point', the minimal mtDNA content per cell that ensures adequate mtDNA replenishing after cell division and that sets the point for the subsequent proper expansion of mtDNA pool in differentiating cells. This mtDNA expansion would sustain proper mitochondrial biogenesis and the switch from glycolysis to oxidative metabolism occurring during differentiation.

Dickinson and colleagues assess the effect of mtDNA copy number on stemness and differentiation potential of glioblastoma multiforme (GBM) cell lines. They demonstrate that defective mtDNA copy number reduces astrocytic differentiation of GBM cells compared to human neural stem cells (hNSCs). In line with their 'mtDNA set point' theory, they suggest that GBM cells are less 'stem' and unable to regulate their mtDNA content tightly in order to ensure proper differentiation. Additionally, they show that a minimal mtDNA copy number is required to maintain GBM cells in the stem-like state and that mtDNA depletion impacts on stemness. Remarkably, they demonstrate that different levels of mtDNA depletion regulate the expression of stemness *versus* differentiation genes. Moreover, under basal condition only partially mtDNA-depleted GBM cells can recover their mtDNA copy number, whereas differentiation can promote effective mtDNA replenishment even in seriously mtDNA-depleted GBM cells.

Dickinson *et al.*[9] go on to asses the impact of mtDNA copy number on tumorigenesis *in situ* by implanting mtDNA-depleted GBM cells into nude mice. This approach shows that unexpectedly, frequency of tumor formation is inversely proportional to the degree of mtDNA ablation: the lower the ablation degree, the higher the frequency of tumor formation. This work demonstrates a link between mtDNA copy number and tumor formation and sheds light on the apparently contradictory data reported in literature. In particular, the authors show a relationship between mtDNA depletion and stemness/differentiation and between mtDNA depletion and cancer growth rate. Their results suggest that different degree of mtDNA depletion might differentially impinge on tumor development and that the mtDNA levels might be modulated during tumorigenesis. Additionally, the nuclear background, different among different glioma cells, and cancer cells in general, might influence how mtDNA depletion affects tumorigenesis. For instance, p53 and Ras, two almost invariantly mutated gene in cancer, have been reported to regulate mtDNA replication and mitochondrial biogenesis[7,8] and their status might interplay, or determine, the mtDNA changes reported here. Furthermore, the link between differentiation/stemness stage and mtDNA levels suggests that even within the same tumor type mtDNA depletion could differentially affect tumor growth, depending on its developmental stage and grade.

How the expansion of mtDNA copy number during differentiation promotes mitochondrial biogenesis and hence mitochondrial oxydative phosphorylation which sustains differentiation, is unclear. Depletion of mtDNA levels in GBM cells, instead of increasing their stemness, disrupts their stem-like state and induce an anomalous differentiation. This suggests that precise mtDNA content is required to maintain stemness. Additionally, differentiation might not only rely solely on oxidative phosphorylation, which is depressed in mtDNA-depleted cells, but also on other mitochondrial functions such as, for example, morphology. However and surprisingly, Dickinson *et al.*[9] conclude that mtDNA depletion does not alter OPA1 processing and mitochondrial morphology. Further experiments are required to more precisely link mtDNA depletion-induced loss of stemness to other key mitochondrial functions, like regulation of calcium signaling, of apoptosis, or of cell motility.

In conclusion, the work by Dickinson *et al.*[9] further develops the intriguing hypothesis that the 'mtDNA set point' is a check point for stemness, proper differentiation and tumorigenesis. Their work opens the possibility that somehow mtDNA content controls tumorigenesis (see Figure 1).

Conflict of Interest

The authors declare no conflict of interest.

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