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Editorial

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Mitochondrial Insult and Revenge in Tumorigenesis

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Early detection and monitoring of aggressive diseases are major challenges in cancer research and require development of signature biomarkers. It is now well accepted that the superior intellect of a cancer cell is governed not only by the nuclear genome alterations but also mitochondrial genetic changes as envisioned long ago by Otto Warburg [1,2]. Fortunately, in this century, Warburg has been revisited and regarded as one of the hallmarks of cancer [3]. Following these footprints, mitochondrial DNA (mtDNA) alterations (mutation and copy number) are emerging as a novel and attractive tool for biomarker development along with nuclear DNA markers [4].

Mitochondria are unique organelles within the cells by virtue of their own DNA and are an integral part of the oxidative phosphorylation system (OXPHOS) for generating cellular ATP [4]. They are key regulators of OXPHOS and composed of five complexes (I-V), assembled from multiple polypeptides, some encoded by mtDNA and others by nuclear DNA (nDNA) [4]. The human mtDNA is a 16.5 kb double stranded closed circular molecule which codes for the 12S and 16S rRNAs, 22 tRNAs and 13 proteins essential for the mitochondrial respiratory complex [4]. Most human cells contain hundreds of copies of mtDNA and nearly all of these mtDNA copies are identical, i.e., homoplasmic at birth [4]. The mtDNA follows a strictly maternal mode of inheritance. The mutation rate in mtDNA is approximately 10 times higher than nDNA and much easier to detect because of the high copy number in a cancer cell. Somatic mtDNA mutation was first reported in colorectal cancer from the laboratory of Dr. Bert Vogelstein [5]. Since then, mtDNA mutations were reported in various tumors including head and neck, esophageal, thyroid, bladder, lung, prostate, liver, esophageal, breast, gastric, renal cell and various hematological malignancies [4]. Remarkably, some of these tumor-derived mutations were readily detectable in the corresponding urine, normal appearing surgical margins and salivary rinse samples [6-8]. Moreover, introduction of some of these mutations in cancer cells resulted in enhanced tumor growth and metastasis [9-12]. Apart from the mtDNA mutation, increased or decreased mtDNA copy number reflecting mitochondrial dysfunction has also been detected in various cancers [4]. Additionally, the correlation between cancer associated key nuclear genes such as EGFR, PSA and mtDNA mutation has also been established in lung and prostate cancer respectively [10,13].

Undoubtedly, mitochondrial DNA alterations are the key components of tumorigenesis in concert with nuclear genetic alterations and would be examined in greater detail in the coming decades. Precise molecular mapping of mtDNA changes and delineating their role in human cancers could be of immense value to develop strategies for early detection, monitoring and therapeutics. However, in light of the recent findings of erroneous mutation reporting in various cancers [4], adequate caution should be exercised for the assessment of mtDNA mutation in clinical samples.

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