LETTER TO THE EDITOR

Pitfalls for Common Mitochondrial DNA Deletion (ΔmtDNA4977) As a Biomarker of Cancer

To the Editor:

The human mitochondrial deletion (mtDNA4977) is a 4977-bp deletion that originates between two 13-bp direct repeats (1) beginning at nucleotide positions 8470–8482 and 13447–13459. The deletion encompasses five tRNA genes and seven genes involved in oxidative phosphorylation (OXPHOS) such as ATPase 8, ATPase 6, cytochrome oxidase III, NADH dehydrogenase subunit 3 (ND3), ND4L, ND4 and ND5, respectively. The latter group of genes is essential for protein synthesis of the mitochondria. As reported previously, the deletion may confer a strong metabolic disadvantage to mtDNA (2). The ΔmtDNA4977 deletion leads to a fusion of ATPase8 and ND5 genes (2), resulting in the impairment of mitochondrial respiration and a decrease in ATP synthesis (3). Mitochondria produce ~90% of the energy (ATP) via oxidative phosphorylation (OXPHOS) for cellular functions and has a role in the bioenergetics of cancer cells (4). ΔmtDNA4977 has been reported to occur in various human cancer cells such as gastric cancer (2,5), colorectal cancer (6,7), thyroid cancer (8), paired oral cancer and precancerous lesions (9).

Recent studies have also consistently shown that the incidence of ΔmtDNA4977 was lower in tumors than that in adjacent nontumoral tissues such as gastric cancer (2,10), adjacent normal gastric tissues, and normal gastric mucosa of noncancer patients (11), lung carcinoma (12), breast cancer (10,13), colorectal cancer as well as head and neck tumors (10). However, the role of ΔmtDNA4977 in carcinogenesis remains largely unknown (14).

The reason for the low incidence of ΔmtDNA4977 in tumors than in adjacent nontumoral tissues was hypothesized by Kamalideghghan et al. (2006) that cells initially with ΔmtDNA4977 transform to tumoral cells and the existed deletion conferred metabolic disadvantage. Thus, cells containing this deletion would be overgrown by other cancer cells without the deletion. Therefore, the presence of ΔmtDNA4977 was found to be low in tumoral cells (2). In another study, Tao et al. (2011) indicated that the level of ΔmtDNA4977 deletion decreased as the stage advanced in colorectal cancer (7). Other studies showed that the ΔmtDNA4977 has an obvious correlation with aging (15,16) and histological type (2), but there was no correlation between this deletion and certain clinical parameters like age, gender, tumor location and tumor size (2).

In cancer cells, some of the pyruvate is converted to lactate by lactate dehydrogenase-A, regenerating the NAD⁺ necessary to maintain glycolysis. However, the slower rate through which OXPHOS generates ATP in normal cells does not appear to be able to keep up with the bioenergetic needs of a cancer cell, thus leading to a decrease in mitochondrial membrane potential, cessation of cell growth, and inhibition of tumorigenesis. As a result, the percentage level of ΔmtDNA4977 is less common and intolerable in tumoral tissues (2) than in normal tissues. On the other hand, ΔmtDNA4977 is possibly intolerable in cancer cells due to metabolization of pyruvate to lactate than through the TCA cycle and the OXPHOS process in mitochondria. Therefore, ΔmtDNA4977 has no specific primary role either in the early or advanced stage of cancers but has possible secondary effects reflected in the carcinogenesis process.

Conflict of Interest

The authors declare no conflict of interest.

References


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