European Journal of Cancer, Vol. 35, No.9, pp. 1407–1408, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

Letter

PII: S0959-8049(99)00126-4

Comments on: *Mutations in Mitochondrial Control Region DNA in Gastric Tumours of Japanese Patients*, Tamura, *et al. Eur J Cancer* 1999, 35, 316–319

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In a recent issue of the *European Journal of Cancer*, Tamura and colleagues [1] reported mutations in mitochondrial control region DNA in 2/45 gastric tumours (4.4%). The two mutations were detected in the hypervariable regions HV1 and HV2; a G to A transition at nucleotide position 16129 and a 1 bp A deletion at nucleotide position 248, respectively. Despite the high percentage of replicative error negative (RER-) tumours (only 8/45 tumours exhibited an RER+ phenotype), the two cases with mtDNA mutations were RER- carcinomas. Tamura and colleagues [1] suggested that the observation of carcinomas with mtDNA instability that do not exhibit nuclear microsatellite instability might be explained by alterations of a mismatch repair system that would act specifically in mitochondrial genome integrity, namely a MSH1-like enzyme [2].

The results we have recently obtained partly confirm and partly diverge from the results reported by Tamura and colleagues [1]. We searched for the mitochondrial common deletion (Δ4977 mtDNA) in a series of 32 primary gastric carcinomas. 10/32 primary gastric carcinomas (31.3%) had microsatellite instability (RER+ phenotype) evaluated according to the methods previously described [3]. The detection of Δ4977 mtDNA was performed on DNA extracted from microdissected frozen tissues as previously described [4], using two sets of primers: Mitout-F -5′-cccaactaaatactaccgtatgg-3′ and Mitout-R -5′-ggctcaggcgtttgtgtatgat-3′ (outside the Δ4977 mtDNA) and Mitin-F -5′-ctgagccttttaccactccag-3′ and Mitin-R -5′-ggtgattgatactcctgatgcg-3′ (within the Δ4977 mtDNA). In the wild type mtDNA (wt mtDNA) only the Mitin primer set gives a PCR product with 142 bp. In cases with the Δ4977 mtDNA, Mitin primers amplify a 142 bp target sequence and Mitout primers an aberrant PCR product with 214 bp (Figure 1). We detected Δ4977 mtDNA in 17/32 primary sporadic gastric carcinomas (53.1%) (Table 1). The high frequency of large mtDNA deletions found in our series in comparison with the low frequency of mtDNA point mutations in the series of Tamura and colleagues [1], suggests that gastric cancer is more prone to have gross genetic alterations of

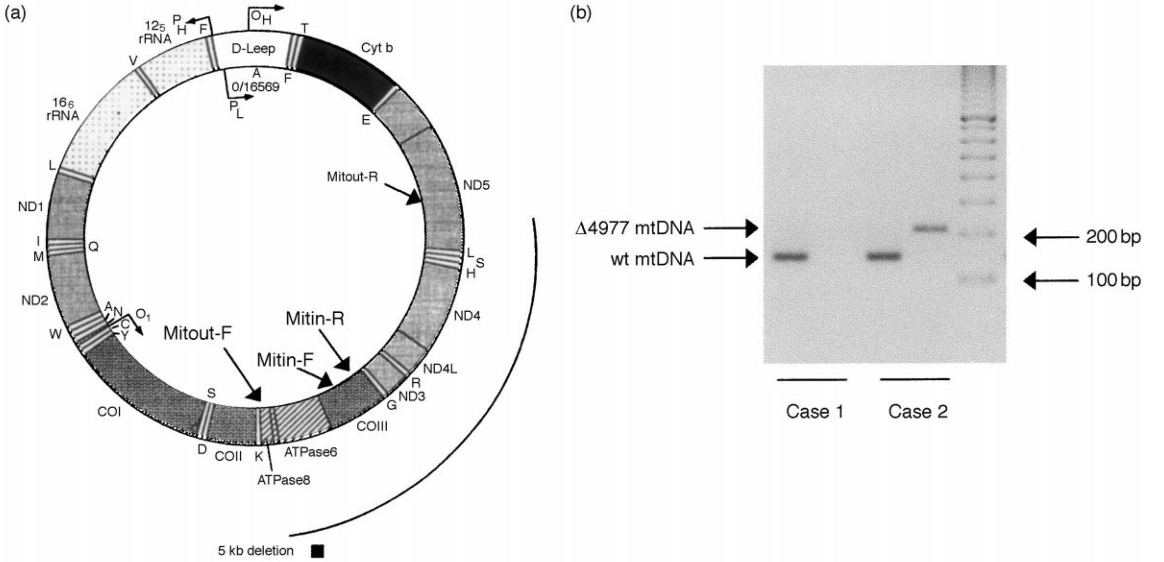

Figure 1. (a) Human mtDNA map showing the location of mitochondrial genes. Arrows represent the localisation of the primers (Mitin and Mitout) used for amplification. The out line represents the Δ4977 mtDNA. (b) Analysis of mtDNA PCR products. Case 1 showing only Mitin amplification is negative for Δ4977 mtDNA and Case 2 showing both Mitin and Mitout amplification is positive for Δ4977 mtDNA.

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Received 6 Apr. 1999; accepted 13 May 1999.

Table 1. *Relationship of RER phenotype and* Δ4977 *mtDNA in 32 gastric carcinomas*

RER+ phenotype	Del Mit+ (*n* = 17)	Del Mit− (*n* = 15)	Total (*n* = 32)	*P* value*
Positive	1	9	10	0.0010
Negative	16	6	22	

**P* value was obtained using the Chi-square test with Yates correction.

mtDNA than to exhibit signs of fine genetic instability. This assumption is supported by the findings of Burgart and colleagues [5], who detected a 50bp mtDNA deletion in 4/32 gastric carcinomas (12.5%) of the cardia. The same does not hold true in colorectal carcinomas where somatic point mutations of mtDNA appear to be much more prevalent than mtDNA deletions [6].

In keeping with the results of Tamura and colleagues [1] who found mtDNA mutations only in two RER- tumours, almost every carcinoma of our series displaying Δ4977 mtDNA were also RER- (16/17 tumours) (94.1%) ($P = 0.001$) (Table 1).

The inverse association found by Tamura and colleagues [1] and ourselves, between RER+ phenotype and mitochondrial alterations (somatic point mutations and Δ4977 mtDNA), remains to be clarified. We think it cannot be ascribed to a different DNA mismatch repair gene defect, namely MSH1, as it was suggested by Tamura and colleagues [1] because if that were the case, one would expect the occurrence of mtDNA alterations regardless of genetic nuclear instability. Alternatively, we think it is tempting to hypothesise that such an inverse relationship may reflect a putative lethal effect caused on the neoplastic cells by the association of mtDNA deletions and DNA repair deficiency, but this possibility remains to be proven.

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