TABLE 1 Mutation rates in mismatch binding-defective strains

RajiMex$^-$ and RajiF12

Cell line	Mutation frequency ($\times 10^{-6}$) Day 20	Day 36	Day 50	Mutation rate (per cell per generation)
RajiMex$^-$	4.5 ± 1.6	10.5 ± 5	16.5 ± 2.5	2.1×10^{-7}
RajiF12	23.0 ± 11.2	37.1 ± 9.5	42.7 ± 8.5	7.5×10^{-7}

CHOMT$^+$ and derived strains

Cell line	Cultures	Number of resistant colonies per culture: Range	Mean	Variance	P_0	Mutation rate (per cell per generation)
CHOMT$^+$ Clone B (expt 1)	39	0–55	6.4	127	0.31	$2.4 \times 10^{-7} \pm 0.5$
CHOMT$^+$ Clone B (expt 2)	38	0–51	6.1	99	0.31	$2.4 \times 10^{-7} \pm 0.5$
BS11	40	0–225	12.8	43	0.50	$1.4 \times 10^{-7} \pm 0.3$

Three RajiMex$^-$ and three RajiF12 subclones were isolated by plating in 96-well plates. Single colonies were picked and cultured. Exponential growth was maintained by daily dilution. On days 20, 36 and 50 after the initial subcloning, cells from each of the six subclones were plated at two different dilutions in duplicate 96-well plates in the presence of 5 $\mu g\,ml^{-1}$ 6-thioguanine. Positive wells were scored after a further 10 days incubation. Plating efficiency for all clones in non-selective conditions was determined similarly. Mutation frequencies were calculated from the Poisson distribution and were not significantly different at any of the sample times for each set of three subclones and data have therefore been pooled. Values are ±s.d. when appropriate. The generation time of each RajiMex$^-$ and RajiF12 clone was determined from growth curves to be 18 h. Mutation rates in CHOMT$^+$, clone B and BS11 were determined by Luria–Delbrück fluctuation analysis[20]. Cells were plated in α-MEM containing 4 μM thymidine and 10% fetal calf serum at 100 cells per 6-cm plate and grown to 3×10^6 cells per plate. Each culture was then distributed equally among five 10-cm plates containing medium supplemented with 8-*aza*-adenine. The mutation rate (μ) was calculated from $\mu = MC^{-1} \ln 2$, where C is the number of cells plated in selective medium and M is the mean number of mutations per culture ($M = -\ln P_0$, where P_0 is the number of cultures containing no mutants). Standard deviations were calculated according to ref. 21.

Correction of mismatches is likely to involve the concerted action of several different proteins and these five lines could be defective in other steps in the same pathway. Elucidation of the functions of the *E. coli* mismatch repair proteins MutH, MutS and MutL was facilitated by defined mutant strains[19]. No simple selection for mammalian cell lines defective in mismatch correction exists but the isolation of methylation-tolerant cells is straightforward. The implication of defective mismatch correction in alkylation tolerance offers a new approach to investigation of DNA mismatch correction in mammalian cells. □

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