

A Correlation between Mismatch Repair Systems and Tolerance to DNA Damage by Alkylating Agents in Human Tumor Cells

By
HALIMA A. ALSINI

Submitted as a Partial Fulfillment of the Requirement
For the Degree of
MASTER OF SCIENCE IN BIOCHEMISTRY

SUPERVISORS
Mohammad S. Alanazi (PhD)
Sibghat-Ulla Lari (PhD)

Department of Biochemistry
College of Science, King Saud University
Riyadh, Saudi Arabia

Zulqa'ada 1425H
January 2005

SUMMARY

To understand the mechanism(s) by which a tumor cell gains resistance to cell killing by chemotherapeutic drugs, we studied the integrity of mismatch repair (MMR) enzymes using human tumor cells. Thus, it is postulated that the anomaly in the mismatch repair or defects in the corresponding repair enzymes may correlate with resistant phenotype of the derivative cell lines.

The aim of this study is to establish a relationship between the mismatch repair and tolerance to DNA damage induced by SN1 alkylating agents in human cells.

The aim was fulfilled by measuring the sensitivity of these tumor cells toward alkylating agents, microsatellite instability assay as a measure of general mismatch repair, and by the ATP dependent G:T incision assay.

We found a strong correlation between defective mismatch repair systems and drug-resistant phenotype in some human tumor cells (brain tumor cell line derivative A1235-MR4) whereas it was absent in some other type (colon carcinoma HT29 cell line and derivative HT29-TGR).

Given these findings, it is concluded that the human cells have more than one mechanism; (i) MMR-dependent; and (ii) MMR-independent for protection against alkylation damages such as m6G and 6TG, a structurally similar adducts. In case of the former mechanism, an offensive O⁶-mG:T (C) adduct is recognized by the cellular MMR followed by cell death through activation of apoptotic machinery. The latter mechanism that operates in human tumor cells against 6TG (possibly O⁶mG) without involving MMR is a provocative proposition and thus requires further understanding of the mechanism.