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Variations in ALL responses to Daunorubicin exist independently of genetic variation in the ATM gene

Statement of the Problem: Daunorubicin (DNR) is commonly used in the treatment of acute lymphoblastic leukaemia (ALL). Various DNR mechanisms of action have been proposed and its action is likely to be multi-modal. The ataxia–telangiectasia mutated (ATM) protein initiates DNA repair and apoptosis as well as the upregulation of anti-oxidant proteins. Genetic alteration in ATM is common in ALL and these may result in cells which are more sensitive to oxidative stress and are likely to undergo altered DNA repair and apoptosis. Thus, it may be hypothesized that the responses of ALL cell lines to DNR would depend on alterations to the ATM gene.

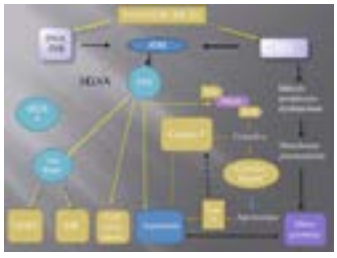
Purpose: The purpose of this study was to identify functional mutations in ATM gene in three ALL cell lines and to correlate these to the cellular responses to DNR.

Methodology: Three ALL cell lines (CCRF CEM, MOLT 4 & SUP-B15) were examined following 4 hours treatment with DNR chemotherapy and varying recovery periods. Methods used were MTT assay, ATM gene sequencing, Western blot, γH2AX assay, ROS assay and apoptosis assays.

Results: SUP-B15 showing significantly more resistance to DNR compared to the other cell lines. There were no mutations in the ATM coding region of all three cell lines. ATM and its downstream targets p53 and SOD2 were found to be phosphorylated in all cells except p53 was not phosphorylated in SUP. DNR induced apoptosis similarly in all cell lines but there were variations in ROS levels in response to DNR.

Findings: Although no variations in ATM were identified, repair of DSBs was slower in SUP-B15 and it exhibited prolonged elevation of ROS levels. DNR induced apoptosis similarly in all lines.

Conclusion & Significance: It can be concluded that the increased resistance to DNR seen in the SUP-B15 line could be due to variations in its DNA repair pathways or in its anti-oxidant pathways independently of ATM.



Biography

Hussain M Al Aamri qualified from the Institute of Health Sciences (IHS), Sultanate of Oman. He was posted in Pathology Department at Royal Hospital in Muscat. He was then transferred to Samail Hospital where he became Lab-in charge and was an active member of different committees and established a Blood Bank. In 1998, he went to UK for approximately four years and pursued BSc and MSc in Immuno-Haematology. After returning, he was posted at the IHS as Tutor and has been involved in teaching different subjects including Haematology, Pathology, Parasitology, and Microbiology. In 2007, he obtained Master and Post-graduate diploma in Medical Education from University of Dundee, Scotland. He was a supervisor of many theses. He is a member of different committees at IHS and has a membership in some medical societies. Currently, he is in the last year of his PhD at Latrobe University, Australia.

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