

MODULATION OF DNA REPAIR AND RADIATION CLASTOGENICITY BY THE HISTONE DEACETYLASE INHIBITOR TRICHOSTATIN A IN ATAXIA TELANGIECTASIA (AT) LYMPHOBLASTOID CELL LINES

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Ataxia Telangiectasia (AT) is an autosomal recessive disorder characterised by acute cancer predisposition and sensitivity to ionizing radiation (IR) revealed with an enhancement of chromosomal instability. Even though AT cell lines rejoin the majority of double strand breaks (DSBs) with normal kinetics via non homologous end joining (NHEJ) repair pathway, the rejoining of about 15% of IR induced DSBs require ataxia telangiectasia mutated (ATM) protein [Foray et al., *Int. J. Radiat. Biol.* (1997): 72, 271-283; Riballo et al., *Mol. Cell* (2004): 16, 715-724]. Moreover, DSBs persisting in the presence of an ATM inhibitor localise to heterochromatin suggesting that ATM is required for repairing DSBs arising within or close to heterochromatic DNA regions [Goodarzi et al., *Biochem. Soc. Trans.* (2009): 37, 569-576].

In order to study the impact of chromatin compaction on chromosomal instability in AT cells, the response to Trichostatin A (TSA), a histone deacetylase inhibitor, was investigated in normal and AT (carrying different mutations in ATM gene) lymphoblastoid cell lines testing its effect on both DNA repair and chromosomal aberrations (ChA) induced after G₁ and G₂ X-ray exposure. The preliminary results show an enhanced repair capability and a different modulation of chromosomal aberrations in AT cell lines depending on the cell-cycle phase exposed to radiation. These results need to be further investigated in order to better clarify the nature of the modulation of both DNA repair and radiation clastogenicity found in AT cells analysing the epigenetic modifications in presence of TSA. The effect of TSA in AT cells could represent a tool for further research on the possible pharmacological applications of TSA in the A-T therapy.