# Plenary Session

## EACR Award Lecture

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### DNA damage responses in cells derived from breast cancer patients displaying radiosensitivity

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**Purpose:** Normal cells respond to ionising radiation (IR) with the inhibition of cell cycle progression, the processing of DNA damage or the induction of apoptosis. Defects in any of these processes have been shown to be important in cancer development. The DNA-dependent protein kinase (DNA-PK) and the ataxia-telangiectasiazx gene product (ATM) have been found to play key roles in this cellular DNA damage response and act in distinct pathways. The DNA-PK protein has been shown to be involved in the processing of DNA double-strand breaks and in apoptosis, whereas the ATM protein acts upstream of p53 in the control of cell cycle progression and possibly apoptosis. Recently, we have found that the gene product defective in cells derived from Nijmegen Breakage Syndrome patients acts also upstream of the p53-mediated DNA damage response to IR. Persons heterozygous for the *ATM* gene, present at about 1% of the population, have been estimated to account for up to 8% of all breast cancer cases. This could imply that female *ATM* heterozygotes might face special hazards from routine diagnostic or therapeutic procedures involving radiation. Clinically, it is apparent that a significant proportion of breast cancer patients (up to 16%) after treatment with radiotherapy show an exaggerated acute or late reaction of normal tissues. It is believed that this "over-reacting" group may represent individuals having a sub-optimal DNA damage response. To examine this, we have evaluated the functionality of the DNA damage response pathways in lymphoblastoid cell lines derived from breast cancer patients displaying radiosensitivity.

**Methods:** Radiosensitivity of the lymphoblastoid cell lines established from breast cancer patients "over-reacting" (EORTC grade III) to radiotherapy has been determined by measuring the colony-forming ability of the cells after exposure to IR. The modulation of p53 protein levels and the induction of transcription of the WAF1(p21) gene after exposure to IR was determined by western and northern blot analysis. The overall DNA-PK activity was assayed in cell extracts by measuring the phoshorylation of a protein substrate.

**Results and conclusions:** Enhanced radiosensitivity was found for all the lymphoblastoid cell lines established from these breast cancer patients which correlates very well with the adverse skin reaction observed in these patients. These results suggest that the lymphoblastoid cell lines are a good model for studying the DNA damage response after exposure to IR. DNA-PK activity was found to be normal in all breast cancer cell lines examined and appears not to be an explanation for the observed radiosensitivity. Changes in p53 levels after exposure to IR was found to be significantly reduced in all the breast cancer cell lines examined. However, the induction of WAF1(p21) mRNA, which is transcriptionally regulated by p53, was found to be normal. These results suggest that G1-S cell cycle regulation is normal and that additional genetic factors are involved in the induction of WAF1(p21) mRNA. The transcription factor IRF-1, which has recently been shown to also be involved in the induction of WAF1(p21) mRNA and in apoptosis after exposure to IR, is presently being studied. Since, ATM and p53 are also involved in cell cycle checkpoints other than in G1-S, abnormalities in cell cycle progression and apoptosis following exposure to IR are presently also being studied by FACS analysis, as is the ATM gene expression.

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No abstract