**Mechanisms underlying cellular responses of cells from haemopoeitic tissue to low dose-low LET radiation**

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Radiation-induced responses at the cellular and whole body levels are influenced by genetic predisposition, with implications for environmental and potentially, diagnostic exposures. Currently, the extent to which genetic background play a role in the mechanisms and signalling pathways involved in radiation-induced delayed Genomic Instability (GI) is not fully understood.
In previous studies, our results have shown that the CBA/H and C57BL/6 mouse strains, have differing sensitivities in the induction of radiation-induced genomic instability (RIGI) in terms of chromosomal instability, following exposure to high dose-high LET and high dose-low LET radiation (>3Gy X-ray). To further our understanding of possible mechanisms by which, genetic factors influence the induction of GI following low dose-low LET radiation exposure, in the current study, haemopoeitic tissue/cells from these two mouse strains, were exposed to a range of X-ray doses (0.01, 0.1, 1.0 and 3.0Gy). Key biological endpoints including: chromosomal analysis, detection of apoptosis, cytokine analysis and gene array analysis, were conducted to assess early (2hr and 24hr) and delayed (15 population doublings (15 pd)) post-irradiation responses.

Our results identified clear differences between the two mouse strains, across all biological approaches. Chromosomal instability was found to be induced in both strains of mice following exposure to X-rays down to 0.01Gy. Delayed chromosomal instability was demonstrated at higher levels and of a higher complexity in terms of the number of aberrations per cell in the cells from C57 mice, compared to those from CBA mice. Data from analysis of apoptosis by annexin V indicated strain-specific differences at the delayed time point, with baseline and overall levels of apoptotic cells found to be higher in C57 cells, across all X-ray doses.
The ELISA technique was used to investigate the levels of TGF-β and TNF-α cytokines; the data suggest strain differences in both cytokines. Levels of TGF-β were consistently higher in CBA cells across all doses and time-points whereas TNF-α levels were higher in C57 cells, in particular at the delayed time-point. Gene array analysis of the low X-ray dose exposure from the early time-point, showed relatively high levels of change in metabolic pathways in both mouse strains, although at higher levels in the C57 cells. CBA cells in contrast, showed higher levels of degradation pathway changes. Analysis of high X-ray dose exposure from the early time-point, showed C57 to have high levels of changes in the degradation pathways, whilst CBA cells showed high levels of change in

signalling pathways. Metabolic pathway changes were also seen in relatively high levels across both strains.
Strain differences were also observed at the delayed time point after low X-ray dose exposure, CBA cells demonstrated higher levels of change in repair pathways in compared to C57 cells.

Specific gene analysis from gene array data, at early time-point following low and high dose exposure, showed lower levels of NF-kβ and Bcl-xl (both down regulated by TGF-β) in CBA cells, a finding supported by ELISA data which showed higher levels of TGF- β in CBA cells compared to C57 cells. These results suggest that the ELISA and gene array data provide complementary and strongly associated evidence when compared in this study.

In conclusion, low dose-low LET radiation in the form of X-rays induced delayed genomic instability in both CBA/H and C57BL/6J haemopoeitic stem cells. Using several biological approaches, some key strain-specific differences have been identified. Furthermore, differences in cytokine levels and gene expression indicate alternatives in both signalling pathways and mechanisms linked with the induction of non-targeted radiation and genetic dependency.

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