You can be replaced: Immune cells compensate for defective DNA repair factor

September 4 2008

A new mouse model has provided some surprising insight into XLF, a molecule that helps to repair lethal DNA damage. The research, published by Cell Press in the September 5th issue of the journal *Molecular Cell*, suggests that although XLF shares many properties with well known DNA repair factors, certain cells of the immune system possess an unexpected compensatory mechanism that that can take over for nonfunctional XLF.

Genetic instability can lead to multiple problems, including cell death and many forms of cancer. Therefore, it is absolutely critical for cells to have both the means to constantly survey genes for damage and the mechanisms to repair broken DNA. Currently, there are six well characterized classical non-homologous end-joining (C-NHEJ) factors that repair double strand breaks (DSBs) in mammalian cells.

Lymphocytes, a type of immune cell, use a kind of genetic shuffling called variable, diversity, joining V(D)J recombination. This gene shuffling occurs during lymphocyte development and helps to produce diverse immune system cells that can recognize all sorts of different foreign substances, called antigens, that might pose a threat to the organism. Previous work in mice has shown that deficiency of C-NHEJ factors results in a severely compromised immune system, because of incomplete V(D)J recombination, along with increased sensitivity to cellular ionizing radiation (IR) and genomic instability.

Some recent studies have suggested that XLF may serve as an additional

C-NHEJ factor. "We know that XLF mutations in humans lead to decreased numbers of lymphocytes and a somewhat less severe form of immunodeficiency," says senior study author Dr. Frederick W. Alt from the Howard Hughes Medical Institute and Harvard Medical School. "While a role of XLF in C-NHEJ might explain lower than normal numbers of lymphocytes in human XLF-mutant patients, the reason for their relatively mildly impaired lymphocyte development is not clear."

To examine XLF function, Dr. Alt and colleagues generated and characterized XLF-mutant mice. XLF-deficient mouse cells were IR sensitive, had substantial genomic instability and displayed major defects in the ability to repair DSBs. Surprisingly, however, mature lymphocyte numbers were only modestly decreased in the XLF-deficient mice and developing B cells exhibited nearly normal V(D)J recombination. This finding was in direct contrast to results seen in previously characterized C-NHEJ-deficient mice. Further, on a tumor suppressor p53-deficient background, XLF-deficient mice were not prone to lymphomas as were C-NHEJ-deficient mice, even though they were just as likely to develop non-immune cell tumors.

The findings demonstrate that although the XLF-deficient mice share many characteristics associated with C-NHEJ-deficient mice, lymphocytes have a distinct developmental signature when it comes to XLF. "Together, our results implicate XLF as a C-NHEJ factor, but also indicate that developing mouse lymphocytes harbor cell type specific factors/pathways that compensate for absence of XLF function during V(D)J recombination," explains Dr. Alt.

Source: Cell Press

Citation: You can be replaced: Immune cells compensate for defective DNA repair factor (2008,