Nature Reviews Cancer | AOP, published online 5 October 2012; doi:10.1038/nrc3381

DNA DAMAGE

The enemy within

> Fanconi anaemia DNA repair pathways together with aldehyde dehydrogenases ... protect HSCs against damage induced by reactive aldehydes.

K. J. Patel and colleagues have previously shown that a mouse model that lacks one of the Fanconi anaemia genes (*Fancd2*) combined with the loss of aldehyde dehydrogenase 2 (*Aldh2*) has developmental defects and an increased risk of developing leukaemia. These results indicate that the Fanconi anaemia DNA repair pathway might be particularly important in preventing DNA damage induced by endogenous reactive aldehydes that are generated as part of normal metabolic processes. The *Fancd2*$^{-/-}$*Aldh2*$^{-/-}$ mice are a useful mouse model of Fanconi anaemia that parallels the human disease, despite the fact that mutations in ALDH2 are not evident in this disease. Further study of these mice has shown that some of them also develop aplastic anaemia, another common facet of Fanconi anaemia in humans.

In *Fancd2*$^{-/-}$*Aldh2*$^{-/-}$ mice that have not developed T cell leukaemia, the levels of all blood cell types are reduced compared with controls. Six of 29 older *Fancd2*$^{-/-}$*Aldh2*$^{-/-}$ mice developed anaemia with hypocellular bone marrow and extramedullary haematopoiesis — pathological features of aplastic anaemia. Immunohistochemistry revealed high levels of bone marrow cells expressing γH2AX (a surrogate for the presence of DNA double-strand breaks) and cells undergoing apoptosis. Flow cytometry using a variety of haematopoietic differentiation markers indicated that the highest levels of γH2AX expression were present in cell populations enriched in haematopoietic stem and progenitor cells (HSPCs). What might be inducing this damage? Exposure of *Fancd2*$^{-/-}$*Aldh2*$^{-/-}$, *Fancd2*$^{-/-}$, *Aldh2*$^{-/-}$ and wild-type bone marrow cells to acetaldehyde *in vitro* followed by transplantation into lethally irradiated syngeneic mice indicated that the short-term haematopoietic stem cell (ST-HSC) population was substantially reduced in *Fancd2*$^{-/-}$*Aldh2*$^{-/-}$ bone marrow cells exposed to acetaldehyde. Moreover, the use of Aldefluor, a fluorescent marker of aldehyde dehydrogenase activity, indicated that the loss of ALDH2 in long-term HSCs (LT-HSCs) removes most of the aldehyde dehydrogenase activity of these cells, in agreement with the high levels of ALDH2 expression in wild-type LT-HSCs.

The consequences of *Fancd2* and *Aldh2* loss on the HSC population are also evident in young mice. The use of competitive repopulation assays in lethally irradiated mice indicated that the frequency of LT-HSCs in *Fancd2*$^{-/-}$*Aldh2*$^{-/-}$ bone marrow was reduced 638-fold compared with wild-type bone marrow. Although loss of either *Aldh2* or *Fancd2* also reduced the number of LT-HSCs, the effect of the combined loss of these genes is synergistic in LT-HSCs.

These results add weight to the hypothesis that patients with Fanconi anaemia mutations develop anaemia and/or leukaemia because of the need for Fanconi anaemia DNA repair pathways together with aldehyde dehydrogenases to protect HSCs against damage induced by reactive aldehydes.

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ORIGINAL RESEARCH PAPER Garaycoechea, J. I. *et al.* Genotoxic consequences of endogenous aldehydes on mouse haematopoietic stem cell function. *Nature* 26 Aug 2012 (doi:10.1038/nature11368)