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The Fanconi Pathway Counteracts the Toxic Effects of Naturally Produced Aldehydes

Crossan, G.*[1]; Langevin, F.P.[1]; Arends, M.J.[2]; Patel, K.J.[1]
[1]MRC Laboratory of Molecular Biology, Cambridge, United Kingdom; [2]University of Cambridge, Cambridge, United Kingdom

Fanconi anaemia (FA) is a genetically complex, recessive DNA repair deficiency syndrome. Patients with FA have multiple congenital abnormalities, an extreme pre-disposition to cancer, and develop bone marrow failure.

FA deficient cells spontaneous accumulate chromosomal aberrations and are extremely sensitive to a class of chemotherapeutic agents - DNA crosslinkers e.g. Cisplatinum. However chemotherapeutic agents are not common environmental mutagens therefore the FA pathway cannot have evolved to repair DNA damage caused by these drugs.

We have recently shown that FA deficient cells are hypersensitive to simple reactive aldehydes (Nature 2011;475:53-8). We find that the acetaldehyde catabolising enzyme Aldh2 is required for the development of FA deficient embryos in mouse. This shows that the endogenous production of acetaldehyde is sufficient to cause genotoxicity which is repaired by the FA pathway. Mice deficient in both Aldh2 and the key FA gene Fancd2 can be generated but are developmentally compromised and rapidly succumb to acute leukaemia. We expand on these results to show that there is an essential requirement for the collaboration of aldehyde catabolism and DNA repair to maintain the haematopoieitic stem cell pool and to suppress leukaemogenesis.

Acetaldehyde is not only produced as a by-product of cellular metabolism but is generated during alcohol catabolism. Aldh2-/-Fancd2-/- embryos are extremely sensitive to *in utero* exposure to alcohol mimicking Foetal alcohol syndrome. Furthermore exposing adult Aldh2-/-Fancd2-/- mice to alcohol precipitates bone marrow failure within 10 days.

Taken together these data shed light on the endogenous source of DNA damage which the FA pathway evolved to counteract. Furthermore this work has significant public health implications as acetaldehyde is generated during alcohol catabolism with 540 million people carry inactivating mutations in the Aldh2 gene.