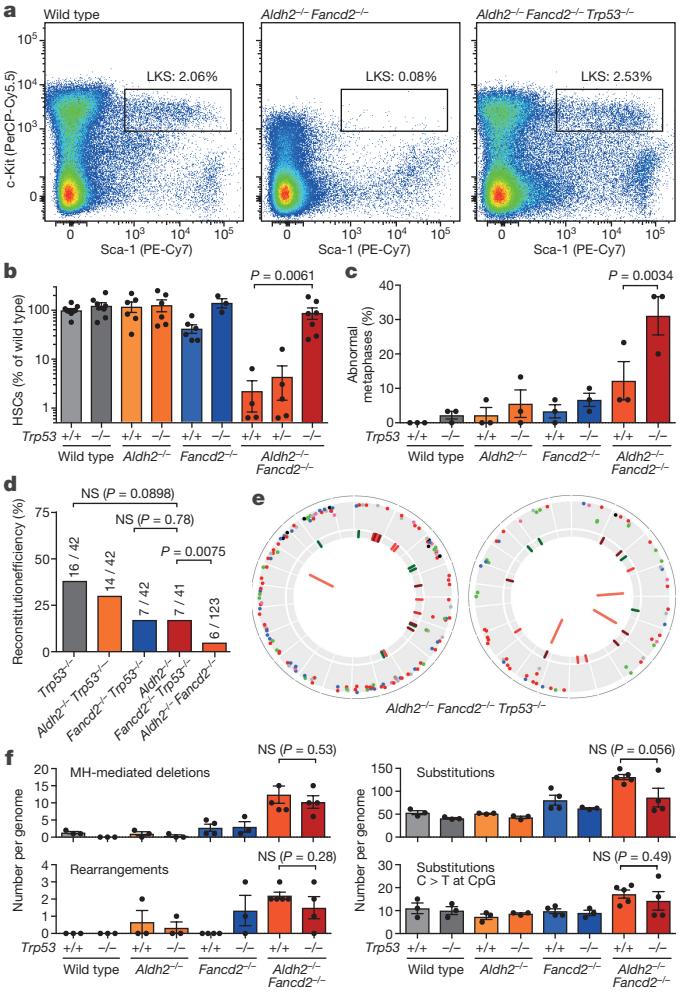

Figure 6 | A p53 response depletes aldehyde-damaged HSCs. **a**, Representative flow cytometry plot of HSPCs (LKS). **b**, Quantification of HSCs as determined by flow cytometry (*P* calculated by two-sided Mann–Whitney test; data shown as mean and s.e.m.; $n = 9, 8, 6, 6, 6, 3, 4, 5$ and 7 mice, left to right). **c**, Frequency of abnormal metaphases in bone marrow cells (*P* calculated by two-sided Fisher's exact test; data shown as mean and s.e.m.; 3 mice per genotype, 30 metaphases per mouse). See Extended Data Fig. 8b–d for a complete list of rearrangements. **d**, Proportion and number of irradiated recipients that were positive for reconstitution by transplantation of single HSCs (*P* calculated by two-sided Fisher's exact test). **e**, Mutations in two $Aldh2^{-/-}Fancd2^{-/-}Trp53^{-/-}$ HSCs. **f**, Number of microhomology-mediated deletions, rearrangements, substitutions and clock substitutions per genome (*P* calculated by two-sided Mann–Whitney test; data shown as mean and s.e.m.; $n = 3, 3, 3, 3, 4, 3, 5$ and 4 HSC genomes, left to right).

Discussion

These results outline the mechanisms by which the mouse haematopoietic system and, more specifically, blood stem cells respond to an endogenous and alcohol-derived source of DNA damage. Primary protection against acetaldehyde is provided by ALDH2-mediated detoxification and, when this is lost or saturated, acetaldehyde damages DNA. The Fanconi anaemia pathway is the principal mechanism to counteract this damage, but NHEJ and homologous recombination can also deal with these lesions. These results therefore illustrate that coordinated pathway choice is critical for maintaining genome stability upon aldehyde exposure. The Fanconi anaemia pathway prevents aldehyde lesions from degenerating into DSBs, the illegitimate repair of which leads to a characteristic pattern of mutagenesis in HSCs (Extended Data Fig. 11). Aldehydes are capable of forming a diverse range of DNA lesions—from base adducts to DNA–DNA or DNA–protein crosslinks. The known molecular function of the Fanconi anaemia pathway suggests that the most physiologically toxic lesion caused by aldehydes may be a DNA interstrand crosslink. However, if it is indeed an interstrand crosslink, then the factors involved in the translesion synthesis or homologous recombination processes are distinct from the previously described mechanism of interstrand-crosslink repair[6,14,15,28]. It will be important to resolve the nature of the lesion and the precise mechanics of its repair.

HSCs mutated by aldehydes are functionally compromised and display myeloid bias. The p53 response is critical in driving the loss in number and function of HSCs. Although *Trp53* deletion rescues HSC defects, this, paradoxically, does not result in further genomic instability at the single HSC level. It is important to emphasize, however, that the pool of HSCs is larger, and therefore there is still an overall increase in mutation. Nevertheless, our work implies that the relationship between p53, DNA repair and genome stability is more complex in stem cells than previously appreciated. The central role for ALDH2 in removing genotoxic aldehydes has implications for the more than 540 million people who are deficient in ALDH2 activity. Alcohol exposure in such individuals may cause DNA DSBs and chromosome rearrangements[3]. This large population may also be susceptible to alcohol-induced age-related blood disorders. More generally, this research provides a simple plausible explanation for the established epidemiological link between alcohol consumption and enhanced cancer risk[4,29].

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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