Alcohol by-product destroys blood stem cells

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(Medical Xpress)—Scientists at the Medical Research Council (MRC) Laboratory of Molecular Biology have found that stem cells in the body's 'blood cell factory'—the bone marrow—are extremely sensitive to the main breakdown product of alcohol, which causes irreversible damage to their DNA.

New research in mice, published today in *Nature*, shows that this damage is normally kept in check by two vital control mechanisms: an enzyme that mops up the toxic breakdown product (acetaldehyde) and a group of proteins that recognise and repair damaged DNA. Mice lacking both these protective mechanisms develop bone marrow failure, due to obliteration of their blood stem cells.

The findings provide the first explanation of why the bone marrow fails in patients with a rare genetic condition called Fanconi anaemia (FA). People with this disease inherit mutations in one or more of the FA genes, which leads to inactivation of the 'repair kit' that would fix DNA damage caused by acetaldehyde. As a result, FA patients suffer from developmental defects, bone marrow failure and an extremely high risk of blood and other cancers.

If replicated in humans, the findings may also be significant for around a quarter of a billion people worldwide with alcohol-induced "Asian flush syndrome". These individuals are deficient in the enzyme (ALDH2) that removes toxic acetaldehyde and may therefore be unusually susceptible to DNA damage. The authors believe that alcohol consumption in this population may result in permanent damage to their blood stem cells,

increasing their risk of blood cancers, bone marrow failure and accelerated ageing.

Dr KJ Patel, who led the research at the MRC Laboratory of Molecular Biology, said: "Blood stem cells are responsible for providing a continuous supply of healthy blood cells throughout our lifespan. With age, these vital stem cells become less effective because of the build up of damaged DNA. Our study identifies a key source of this DNA damage and defines two protective mechanisms that stem cells use to counteract this threat.

"Last year we published a paper showing that without this two-tier protection, alcohol breakdown products are extremely toxic to the blood. We now identify exactly where this DNA damage is occurring, which is important because it means that alcohol doesn't just kill off healthy circulating cells, it gradually destroys the blood cell factory. Once these blood stem cells are damaged they may give rise to leukaemias and when they are gone they cannot be replaced, resulting in bone marrow failure.

"The findings may be particularly significant for a vast number of people from Asian countries such as China, where up to a third of the population are deficient in the ALDH2 enzyme. Alcohol consumption in these individuals could overload their FA DNA repair kit causing irreversible damage to their blood stem cells. The long-term consequences of this could be bone marrow dysfunction and the emergence of blood cancers."

Sir Hugh Pelham, Director of the MRC Laboratory of Molecular Biology, said: "This study provides much sought-after explanation of the biology underpinning the devastating childhood disease Fanconi anaemia. In future this work may underpin new treatments for this genetic disease, which currently is associated with a very poor prognosis. It also helps to inform large numbers of the global population, who are

deficient in the ALDH2 enzyme, that drinking alcohol may be inflicting invisible damage on their DNA."

More information: The paper, entitled 'Genotoxic consequences of endogenous aldehydes on mouse haematopoietic stem cell function', is published in *Nature*. dx.doi.org/10.1038/nature11368

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