Formaldehyde induced endogenous DNA damage disrupts blood regeneration, nutritional homeostasis and promotes ageing

S-01.3-3

K. Patel[I]

[I]MRC Weatherall Institute of Molecular Medicine, Oxford, United Kingdom

Endogenous DNA damage is an important and dominant cause for the accumulation of mutations in all organisms. This can be seen in the mutation signatures associated with cells obtained from aged animals and in most cancers. The established factors and processes that cause endogenous DNA damage are oxygen, water, structured DNA and DNA replication and transcription. However, a fundamental question is whether there are other factors that are prevalent drivers for endogenous DNA damage and whether DNA repair pathways mitigate against such damage. Our research has identified that simple aldehydes such as formaldehyde and acetaldehyde are produced in our cells that can cause DNA damage possibly through the formation of DNA crosslinks. We uncovered that a two-tier protection mechanism (aldehyde detoxification and DNA repair) ensure that these metabolites do not cause DNA damage and mutations. I will discuss how this two-tier protection mechanism ensures this protection and how its dysfunction damages blood regeneration, alters nutritional homeostasis, causes kidney failure and neurodegeneration. This research therefore defines endogenous aldehyde, particularly formaldehyde, as an important prevalent source of endogenous DNA damage, and thus manipulating the original source of these reactive chemicals might provide a means to preserve blood, renal and brain function over time.