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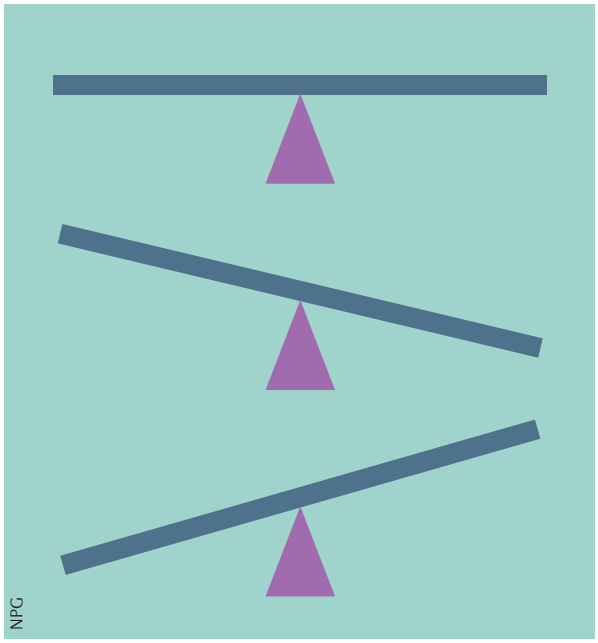
CANCER RISK

Generating tumours: it's all in the balance

There is debate about the influence of intrinsic and extrinsic factors (such as exposure to carcinogens) that drive tumorigenesis and thus influence cancer incidence in an organ-specific and age-associated manner. An important intrinsic risk factor has been proposed to arise from the accumulation over time of random mutations that result from errors in stem cell division. Extrinsic factors may also influence the accumulation of mutations and thus cancer risk.

Zhu *et al.* generated mice in which PROM1$^+$ cells (which are considered to be stem cells) can be inducibly labelled with green fluorescent protein (GFP). GFP expression in PROM1$^+$ cells was induced in neonatal and adult mice, which were subsequently allowed to age for 180 days (young mice) and 600 days (aged mice), respectively, before their organs were harvested for lineage tracing. They found that PROM1$^+$ cells in young mice had a higher generative capacity than those from adult mice and that there was variation in PROM1$^+$ cell generative capacity in different organs.

> balance between mutation accumulation and generative activity of stem cells may therefore explain the organ-specific differences in cancer incidence



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Next, the authors introduced various conditional oncogenic mutations, resulting in 316 tumours in 280 mice. Interestingly, few or no tumours developed in the salivary gland, kidney, brain or pancreas. Some PROM1$^+$ cell populations were more susceptible than others to transformation, regardless of the oncogenic mutations that were introduced. Mathematical modelling was used to assess whether PROM1$^+$ cell population size, proliferative capacity and/or generative capacity are related to tumorigenesis in each organ. They found that generative capacity correlated with susceptibility to tumorigenesis, such that organs with the smallest PROM1$^+$ cell populations were the most likely to develop tumours.

Focusing on liver cancer, they demonstrated that liver damage (induced by partial hepatectomy or exposure to the carcinogen DDC) substantially increased the number of liver tumours derived from PROM1$^+$ cells with oncogenic mutations. This indicates that in the liver, the reactivation of generative capacity of PROM1$^+$ stem cells (to repair damaged tissue) increases their susceptibility to tumorigenesis, and thus both generative capacity and tissue damage — intrinsic and extrinsic factors — are important for tumorigenesis.

Zhu *et al.* artificially introduced oncogenic mutations to assess tumorigenesis in different organs — but might organ-specific differences in mutation type and rate of mutation influence cancer risk *in vivo*? To address this, Blokzijl *et al.* assessed the variation of mutations in stem cells of the small intestine, colon or liver from 19 individuals aged 3–87 years. They expanded the stem cells into 45 clonal organoid cultures, which enabled the authors to carry out whole-genome sequencing.

The number of somatic point mutations in the stem cells correlated with age for all of the organs, with ~36 mutations occurring each year. The mutation spectra for the stem cells from each organ were similar between individuals and did not change with age. The liver, colon and small intestine have different cancer incidences, with colon having the highest cancer incidence. Therefore, although mutations accumulate with age in these three organs, this does not explain the differences in cancer incidence.

The mutation spectra in the small intestine and colon stem cells were similar, but they were considerably different from that of the liver stem cells. The mutations in small intestine and colon stem cells were mostly the result of spontaneous deamination of methylated cytosine, resulting in T:G mismatches that become 'fixed' in the DNA as a result of DNA replication before repair. These mutations occurred mostly in late-replicating regions of DNA (indicating reduced repair of these regions), which tend to be non-gene-encoding. In the liver, the somatic mutations occurred mostly in transcribed DNA through an unknown mutagenic process.

Therefore, Blokzijl *et al.* have shown that the accumulation of mutations with age can be driven by proliferation and cell-intrinsic mutagenic processes, as well as by extrinsic factors. Zhu *et al.* demonstrated that generative capacity of oncogenically mutated stem cells is also important. Generative capacity may be intrinsic to the organ and it may be induced by the repair of tissue damage resulting from extrinsic factors. This balance between mutation accumulation and generative activity of stem cells may therefore explain the organ-specific differences in cancer incidence and thus cancer risk.

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ORIGINAL ARTICLES Blokzijl, F. *et al.* Tissue-specific mutation accumulation in human adult stem cells during life. *Nature* **538**, 260–264 (2016) | Zhu, L. *et al.* Multi-organ mapping of cancer risk. *Cell* **166**, 1132–1146 (2016)
FURTHER READING Alderton, G. K. Debating the odds. *Nat. Rev. Cancer* **16**, 68 (2016)