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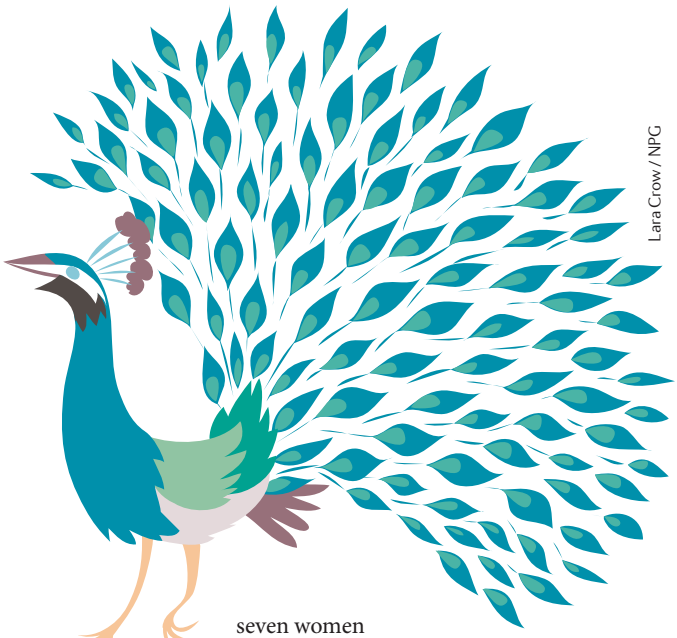
HEPATOCELLULAR CARCINOMA

Gender differences



Lara Crow / NPG

Epidemiological data have shown that women have a lower risk of hepatocellular carcinoma (HCC) than men. This gender bias has been attributed to female sex hormones, as HCC incidence markedly increases in postmenopausal women who do not take hormone replacement therapy (HRT). Hartwell *et al.* have investigated this connection further.

The pituitary gland is required for gender-dependent differences in HCC, so the authors hypothesized that the responsible hormone might be prolactin (PRL), which responds to oestrogen and is expressed at higher peak levels in hormonally active females compared with males. Interleukin-1β (IL-1β) can promote inflammation, which can lead to liver tumorigenesis. The authors showed that in cultured hepatocytes treated with IL-1β, p38 MAPK stress signalling, nuclear factor-κB (NF-κB) and AKT are activated, and this is disrupted by PRL treatment.

To determine how PRL interferes with these pathways, the authors first examined upstream receptors. Ligands to IL-1 receptor (IL-1R), Toll-like receptor 4 (TLR4), tumour necrosis factor receptor 1 (TNFR1) and TLR3 activated innate immune signalling, and PRL treatment blocked all of these except signalling through TLR3. TNF receptor-associated factors (TRAFs), which anchor signalling modules in complexes called 'trafasomes', are involved in the PRL-sensitive pathways but not TLR3 signalling, and the authors showed that PRL increased the rate of trafasome degradation following IL-1β treatment, thus attenuating activation of p38, NF-κB and AKT in hepatocytes.

Reduced activation of p38, NF-κB and AKT signalling was observed in female, but not in male, mice following treatment with IL-1β. MYC expression is increased in response to these three signalling pathways and is upregulated early in hepatocarcinogenesis in male mice. However, there was no gender difference in HCC incidence in mice constitutively expressing MYC in hepatocytes, in agreement with the upstream position of trafasome signalling relative to MYC activation. Furthermore, female *Prl*$^{-/-}$ mice had increased incidence and aggressiveness of liver tumours following treatment with the carcinogen diethylnitrosamine (DEN); interestingly, loss of *Prl* also accelerated DEN-induced tumorigenesis in males. Liver tissue samples from seven women and seven men without evidence of liver disease also showed evidence of increased activation of inflammatory pathways in males but not in females, indicating that male livers might have a higher sensitivity to inflammatory stimuli.

As HRT is not a viable option in men, the authors tested the ability of the dopamine D2 receptor antagonist domperidone (which increases serum PRL levels) to prevent the progression of DEN-induced preneoplastic liver lesions in mice. Male mice that were treated with domperidone had PRL levels similar to that of female mice and were significantly protected from HCC development (22% incidence of HCC versus 100% in control mice). Overall, these data suggest that increasing PRL levels in men, and also in postmenopausal women, might help to reduce HCC incidence.

Sarah Seton-Rogers

> female *Prl*$^{-/-}$ mice had increased incidence and aggressiveness of liver tumours

ORIGINAL RESEARCH PAPER Hartwell, H. J. *et al.* Prolactin prevents hepatocellular carcinoma by restricting innate immune activation of c-Myc in mice. *Proc. Natl Acad. Sci. USA* **111**, 11455–11460 (2014)