PANCREATIC CANCER

Inherited pancreatic cancer risk

A new case–control study published in *JAMA* finds that germline mutations in six cancer predisposition genes are significantly associated with pancreatic cancer. Of 3,030 patients with pancreatic ductal adenocarcinoma (PDAC), 5.5% had germline mutations in one of the six genes. Among the 3,030 patients, 7.9% of those with and 5.2% of those without a family history of PDAC had a mutation in one of the six genes.

Testing for cancer predisposition gene mutations can be valuable in optimizing cancer care, for example for prevention and screening. However, the utility of this approach in PDAC is still unclear. Chunling Hu and colleagues have now evaluated the association between inherited germline mutations in known cancer predisposition genes and the risk of PDAC. In their case–control study including 3,030 patients with PDAC at different disease stages, the researchers analysed patient sequencing data of 21 genes that are implicated in susceptibility to solid tumours in comparison with publicly available reference data from a total of 176,241 controls. Six genes were significantly associated with PDAC compared with controls: *CDKN2A*, *TP53*, *MLH1*, *BRCA2*, *ATM* and *BRCA1*. Overall, 5.5% of the tested patients had deleterious mutations in one of the six predisposition genes, and 7.9% of 343 patients with and 5.2% of 2,687 patients without family history of pancreatic cancer had a mutation in one of these six genes. Furthermore, among 495 patients who had previously been diagnosed with a different cancer, 8.1% had alterations in these genes.

> “5.5% of the tested patients had deleterious mutations in one of the six predisposition genes”

Evaluation of patient characteristics showed that advanced disease stage, history of other cancers, family history of breast cancer or common epithelial cancers and younger age at diagnosis were significantly associated with mutations in the six predisposition genes. Specifically, *BRCA2* alterations were significantly associated with an earlier age at PDAC diagnosis (mean age 60.5 years versus 63.3 years; $P = 0.01$). In addition, only patients with *CDKN2A* alterations were more likely to have a family history of pancreatic cancer (OR 7.91, 95% CI 2.19–28.57; $P = 0.005$). Analysis of mutation status and overall survival showed no statistical significance: median overall survival of patients with and without mutations was 13.6 months versus 11.4 months, respectively.

These findings provide new insights into the effect of germline mutations on the risk of developing PDAC and, pending further research, might inform future genetic testing guidelines for this disease.

Clemens Thoma

ORIGINAL ARTICLE Hu, C. et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. *JAMA* **319**, 2401–2409 (2018)

NEUROGASTROENTEROLOGY

Microbiota modulate ENS maturation

According to a new study, the maturation of the adult enteric nervous system (ENS) in mice is regulated by the gut microbiota via a mechanism involving serotonin (5-HT) release and activation of the 5-HT_4 receptor.

Following postnatal colonization by gut microbiota, the ENS undergoes extensive further development. Studies have also suggested that the adult ENS is capable of maturation and plasticity, but the mechanisms responsible remain unknown. Now, after noticing that germ-free (GF) mice had ENS abnormalities, a team of researchers examined how the gut microbiota affect ENS maturation.

“For this study, we used GF mice, which we colonized with the microbiota from age and sex-matched donors,” explains author Filipe De Vadder. “We found that GF mice have a larger pool of neuronal precursors, which express the Nestin protein, but after colonization the proportion of $Nestin^+$ neurons decreased.” These findings suggested that mouse ENS neurons acquire a mature phenotype after colonization, which was also accompanied by increased intestinal transit.

To examine the role of mucosal 5-HT in the ENS, which is implicated in neurogenesis and synthesized by TPH1, neural density was quantified in *Tph1*-knockout mice. When GF mice deficient in TPH1 were colonized with donor microbiota, a decrease in myenteric neurons was observed. “We concluded that mucosal 5-HT has a neuroprotective role in the first days of colonization, which is a novel finding,” reports De Vadder. The team also examined the role of neuronal 5-HT in the ENS. “We found that, just like mucosal 5-HT the microbiota was able to

COLORECTAL CANCER

IEC mitophagy promotes anti-tumour immunity

A new study has uncovered a link between mitophagy in intestinal epithelial cells (IECs) and the induction of anti-tumour immune responses in colorectal cancer (CRC).

Commonly activated in CRCs, the STAT3 transcription factor promotes transcription of genes involved in immunosuppression, cell survival and proliferation. Florian Greten and colleagues had first explored how STAT3 signalling in IECs altered development of inflammation-associated CRC. “However, the vast majority of colorectal tumours develop as sporadic cancers in the absence of chronic inflammation,” says Greten. “Therefore, we wanted to examine whether STAT3 had a role in these tumours as well.”

To probe this question, the researchers administered the mutagen azoxymethane to mice with or without intact STAT3 in IECs and assessed subsequent tumour development. All wild-type mice developed tumours, whereas tumorigenesis was completely prevented in mice lacking STAT3 in IECs. Histological analysis showed that loss of STAT3 in IECs was associated with $CD3^+$ T cell accumulation, which indicated an adaptive immune response against mutated IECs deficient in STAT3.

Switching to a genetic mouse model of CRC driven by overactive β-catenin, a feature of ~80% of human CRCs, Greten and colleagues found that IEC-specific STAT3 deficiency markedly improved survival and induced an adaptive immune response. In this model, the researchers next explored how STAT3 loss induced effective immune responses. Importantly, histopathological examination