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Highlights from this issue

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LUMINAL

Shanghai fever—a *Pseudomonas aeruginosa* enteric disease

Shanghai fever, first documented in 1918, is a syndrome comprising fever, diarrhoea and sepsis, and is caused by enteric *Pseudomonas aeruginosa* infection. Community-acquired cases were subsequently reported in children without pre-existing conditions, primarily from Taiwan, Hong Kong and China. The disease usually leads to serious complications and is associated with high mortality. Sadly our understanding of this disease is still incomplete and its pathogenesis remains unknown. In this issue of *Gut*, Chuang et al present the most comprehensive study to date on the clinical features of Shanghai fever (table 1) and the host and microbial factors associated with the infection. The data presented offer a glimmer of hope in the fight against this deadly disease.

In colon cancer, it's not just if a gene is mutated, but where, that matters

Cancer in general is viewed as being predominantly a disease that results from alterations in genes. Many of the oncogenes and tumour suppressor genes

involved in colorectal cancer have been identified over the last three decades, although the role they play in tumour formation is still being defined. One of the most common tumour suppressor genes mutated in colorectal cancer is *FBXW7*. *FBXW7* is classified as a tumour suppressor, but it has an unusual mutation spectrum whereby loss-of-function mutations are unusual. Instead, most mutations are mono-allelic missense changes involving specific arginine residues at β -sheet propeller tips that allow the *FBXW7* protein to recognise its substrates. The Tomlinson lab now provides evidence that the effect of mutant *FBXW7* on intestinal tumorigenesis is dependent on the type of *FBXW7* mutation and that deletion of *FBXW7* has a much weaker effect on tumour formation than the common missense mutation. The missense mutation causes elevated levels not only of classical *FBXW7* substrates such as cyclin E and Myc, but also of *Klf5* and *Tgif1*, in both adenomas and normal intestine. These results suggest that targeted therapies need to take into account the specific mutations in cancer and how they act if they are going to be used to the best advantage (see figure 1).

New insights into genetic factors that affect the risk of colorectal cancer

Genome-wide association studies have identified a large number of single nucleotide polymorphisms (SNPs) associated with a wide array of cancers, including colorectal cancer. Several of these variants appear to be important in many different types of cancer, which suggests pleiotropic effects of the SNPs and shared biological mechanisms among different tumour types. Based on this observation, a research team led by Dr Ulrike Peters hypothesised that SNPs previously associated with other cancers may additionally be associated with colorectal cancer. They conducted a large scale study of 18 different cancers in almost 55 000 people to identify novel SNPs that may be involved in colorectal cancer. They found SNPs on chromosome 8q24, a prostate cancer susceptibility region that correlated with colorectal cancer risk, expanding our understanding of genetic factors that affect the risk of colorectal cancer. This information promises to ultimately be useful for individually tailoring colorectal cancer prevention programmes (see figure 2).

Table 1 Clinical features of patients with Shanghai fever

Clinical manifestation	Number (%)
Initial presentations	
Fever and diarrhoea	25 (93)
Dyspnea/cyanosis	2 (7)
Fever	27 (100)
Diarrhoea	26 (96)
Watery	18 (67)
Greenish	12 (44)
Mucoid	11 (41)
Bloody	7 (26)
Vomiting	12 (44)
Dyspnea	10 (37)
Seizure	7 (26)
Shock	22 (81)
Necrotising enteritis	23 (85)
Bowel perforation	9 (33)
Ecthyma gangrenosum	17 (63)

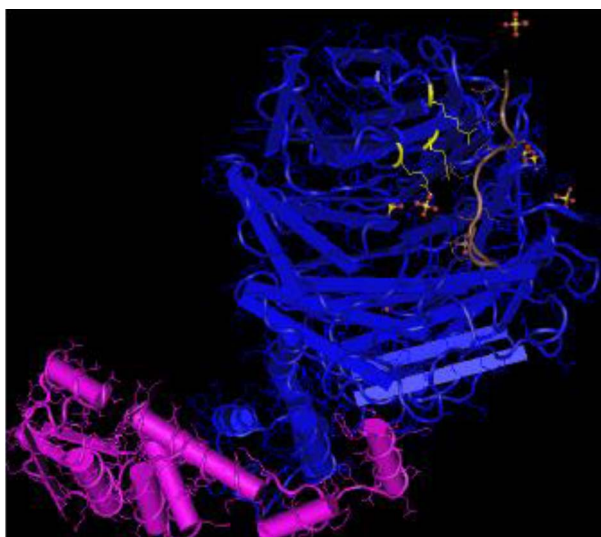


Figure 1 Structural model of *FBXW7* protein. The pink residues comprise the F-box domain, blue the WD40 domain, yellow arginines 465, 479 and 505 and brown the CPD sequence of cyclin E. Arginines 465, 479 and 505 are found at the apex of the β -propeller sheets.

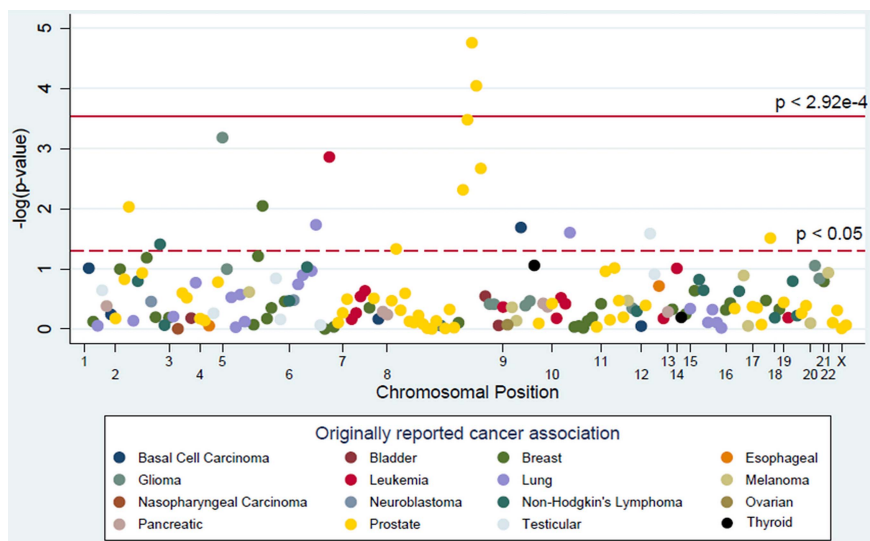


Figure 2 Manhattan plot of the meta-analysis association between risk variants of 18 other cancers and colorectal cancer. The solid line is the Bonferroni-corrected significance threshold. Each association is coloured according to the cancer for which the SNP was originally reported, and positioned on the x-axis according to its genomic position.

ENDOSCOPY

Improving adenoma detection rate—more by the endoscopist than by the endoscope?

Numerous studies have looked into technical endoscope features which might increase adenoma detection rate (ADR), considered to be the main outcome parameter of colonoscopy, especially screening colonoscopy. New technologies such as narrow band imaging (NBI) or—from a different company—Fujinon intelligent chromoendoscopy (FICE) have been introduced to improve image contrast and the hope was that adenomatous lesions,

especially the flat ones would be more easily recognised. However, both techniques have been shown in previous randomised trials not to confer any benefit over white light endoscopy in terms of finding more adenomas. This was again confirmed by a large study from Korea comparing NBI and FICE with white light endoscopy; there was no difference between experts and non-experts in that respect. It is likely that more substantial changes of endoscope technology also incorporating some form of the so-called red flag techniques are necessary to significantly increase ADR (see page 785).

HEPATOLOGY

What clinicians should now about hepatocellular carcinoma

With great pleasure we would like to draw your attention to this masterly review (see page 844) by three most respected authorities on HCC: Jordi Bruix from the BCLC, Greg Gores from the Mayo Clinic and Vincenzo Mazzaferro from the National Tumour Institute, Milan. HCC is the main cause of death in patients with cirrhosis. This timely update covers the standard and the most recent developments regarding screening and diagnosis, molecular pathogenesis and profiling, risk stratification, non-surgical treatment, surgery and liver transplantation. The focus is on treatment. Controversial issues are highlighted and new concepts for second line pharmaceutical treatment are provided. A great pleasure to read!

A role of imbalanced RNA editing in HCC

The role of DNA mutations for hepatocarcinogenesis is well known. However, RNA editing may be equally important. The most prevalent RNA editing in humans is governed by the ADAR (Adenosine deaminase acting on RNA) enzyme family. This exciting pioneer study from Hong Kong (see page 832) employing large scale sequencing unravels an ADAR editing imbalance of potential clinical relevance in HCC. The findings could stimulate the development of early biomarkers for HCC and may even open new therapeutic avenues. Please also read the insightful commentary by Dr Fortes on page 709.