makes up the whole nanolaser array. This is the basis for the authors' ability to synchronize the phases of the nanolasers. As they increased the number of nanolasers emitting light with a synchronized phase, the authors found that the directionality of the light emitted was enhanced. The intensity pattern of the pump laser was carefully engineered to enable the nanoarrays to shine in particular patterns, and to ensure that light from individual nanolasers combined constructively.

Luan *et al*. showcased the reconfigurability of their technique by using their nanolaser arrays to form the distinct shapes of letters in the Roman alphabet, such as P, K and U (the abbreviation of Peking University in Beijing, with which the authors are affiliated). They also configured more intricate patterns resembling the Chinese characters for 'China'. The authors demonstrated the scalability of the method by achieving single-mode lasing in a large pattern comprising more than 160 synchronized nanolasers with high-spatial and spectral coherence. All the lasers emitted light with the same frequency and polarization, while maintaining a constant relative phase that maximized directionality and brightness.

The key innovations of Luan and colleagues' work lie in the reconfigurability and scalability of the nanolaser arrays, but the method offers other practical advantages. Existing lasers based on photonic crystal cavities localize light only under stringent conditions, and the flat-band mechanism underlying the authors' approach dispenses with these requirements, offering increased flexibility for both design and fabrication.

It would be preferable to excite the moiré system electrically, instead of using an external pump laser, but this would require carefully designed electrical interfaces and further chemical engineering. Another unresolved issue involves how to make the lasers as robust to defects and perturbations as those that are based on topological principles in photonics[8–12].

Looking forwards, various photonic devices have already profited from the integration of discoveries made by physicists, and by technologies devised in photonics and materials science research. We imagine that Luan and co-workers' ingenious application of moiré flat bands will open an avenue for exploring smaller, smarter and more powerful laser sources, lighting our way towards a brighter future.

Liqin Tang and **Zhigang Chen** are in the MOE Key Laboratory of Weak-Light Nonlinear Photonics, TEDA Applied Physics Institute and School of Physics, Nankai University, Tianjin 300457, China.
e-mails: tanya@nankai.edu.cn; zgchen@nankai.edu.cn

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Cancer

Harmful tumour–kidney interactions identified

Pierre Leopold

Fatal renal dysfunction is often associated with tumour development. Fly and mouse data reveal evolutionarily conserved mechanisms that link tumours to renal failure and offer potential for future therapeutic approaches. **See p.425**

Kidney dysfunction or injury is commonly found in people who have cancer, contributing to illness and mortality[1]. Kidney disease can be the consequence of chemotherapy treatments, which in many cases induce toxicity during the elimination of these drugs in the kidney. Alternatively, the tumour can obstruct or compress the urinary tract (tissues including the prostate or bladder), which in turn can drive alterations in kidney function. An intriguing further scenario is now coming to light, with the discovery of tumour-produced molecules that modify host metabolism and organ physiology. On page 425, Xu *et al*.[2] report a study in flies and mice that provides key advances in our understanding of tumour-associated renal dysfunction.

"This finding raises the prospects of new therapeutic opportunities."

A cancer-induced wasting syndrome called cachexia occurs at advanced stages of the disease. It is characterized by a substantial loss of weight, muscle and fat mass — often associated with conditions such as the eating disorder anorexia nervosa — by a lack of energy (asthenia) and by renal failure. No effective treatment is available for cachexia, which is responsible for up to 20% of deaths associated with cancer[3,4]. The reasons for the drastic metabolic switch observed in host tissues are not understood. However, over the years, a direct role for tumours in producing and secreting 'cachectic factors' involved in tumour–host interactions has emerged[5]. Knowledge of the molecular mechanisms of renal dysfunction in cachexia is limited, so progress is needed from studies of animal models.

Lately, fruit flies (*Drosophila melanogaster*) have emerged as a valid biological model for studying tumour-induced metabolic changes[6]. Fly tumours can be induced genetically, both in juveniles (larvae) and in adults. In both cases, metabolic modifications across the body are observed that mimic cancer-induced cachectic syndromes. The powerful genetic tools developed for this model system have enabled the identification of cachectic factors produced by tumours that are responsible for metabolic transformations. Many of these molecules are evolutionarily conserved between flies, mice and humans, raising hope for the development of innovative therapeutic approaches.

Xu and colleagues studied tumours of the adult fly gut (Fig. 1) obtained after expressing an activated form of the evolutionarily conserved transcription factor protein Yorkie–Yap/Taz (the activated form is termed Yki^{3SA}) in intestinal stem cells (ISCs). These tumours induce severe cachectic syndromes associated with an accumulation of abdominal fluid, called bloating, which is a sign of impaired fluid excretion. By blocking expression of genes encoding ligands (proteins that can bind to receptors) in ISC-derived tumours, the authors identified an antidiuretic hormone (one that reduces urine output) called ITP as a potent inducer of tumour-associated bloating. They found that the hormone affects neither tumour growth nor other wasting syndromes.

ITP was previously described as a fly hormone produced by specialized neurons with functions similar to those of the human hormonal systems (vasopressin and

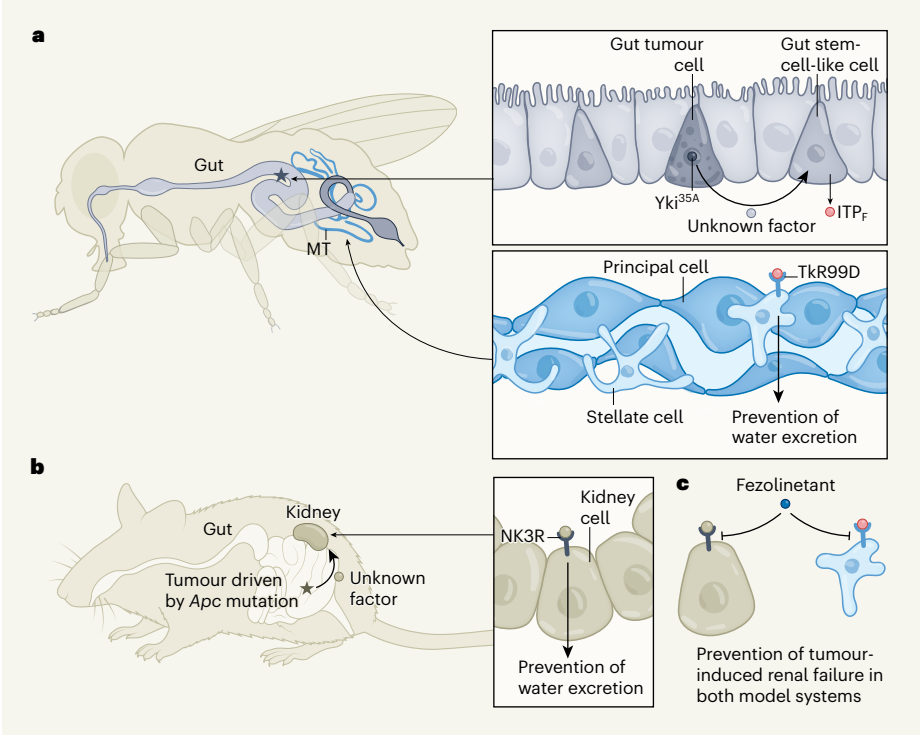

Figure 1 | An evolutionarily conserved pathway that drives kidney dysfunction when a tumour is present in the body. Xu *et al.*[2] describe a pathway that harms kidney function in tumour-bearing flies and mice. Kidney dysfunction contributes to the illness and death of people who have cancer. **a**, In flies, gut tumours, driven by the activated form of a transcription factor (a mutated protein termed Yki^{3SA}), through the action of an unknown factor, drive stem-cell-like cells in the gut to produce a hormone termed ITP_F. This acts on the fly equivalent of the kidneys — the Malpighian tubules (MT), which form from stellate cells and principal cells. ITP_F binding to the receptor TkR99D on stellate cells prevents water excretion (diuresis) and promotes bloating. **b**, TkR99D is evolutionarily conserved in mice, which have a corresponding receptor called NK3R that is expressed in the kidney. Mice that develop a gut tumour driven by a mutation in the gene *Apc* release an unknown factor that acts on NK3R to prevent diuresis. **c**, Fezolinetant is an inhibitor of TkR99D and NK3R that abolishes tumour-induced renal failure in both animal models. This finding raises the prospects of new therapeutic opportunities.

renin-angiotensin systems) that respond to low-water stresses[7]. Xu *et al.* now show that a long version (isoform) of the protein, called ITP_F, is produced by stem-like cells in the middle region of the gut that are distant from the tumour, indicating a yet-unidentified mechanism for remotely inducing ITP_F production. In line with its role as an anti-diuretic hormone, the expression of ITP_F in secretory tissues such as the fat body (the insect equivalent of vertebrate adipose and liver tissue) or the muscles is sufficient to perturb excretion and promote bloating.

The Malpighian tubules are the fly's renal system; they are composed of principal cells and stellate cells, which function in excretion and water balance. Using biosensors and genetic analysis, Xu and colleagues found that adding ITP_F to dissected Malpighian tubules activated what is termed the cGMP signalling pathway, specifically in stellate cells. This required the genes *NOS*; *Gycβ100B*, which encodes an enzyme called guanylyl cyclase; and *foraging* and *Pkg21D*, which are cGMP-dependent enzymes called kinases.

The authors also found that TkR99D, a type of receptor called a G-protein-coupled receptor, is a membrane-associated receptor for ITP_F. TkR99D is present on the surface of stellate cells, and is required for bloating to occur in tumour-bearing animals expressing Yki^{3SA}, although it is dispensable for water balance in control animals. Interestingly, Xu and colleagues show that the peptide tachykinin, which is a normal ligand for TkR99D, interacts with this receptor in tumour-bearing animals and alleviates the effects of ITP_F on bloating.

TkR99D is functionally equivalent to the mammalian protein neurokinin B receptor (NK3R), which is highly expressed in mouse renal tubules. This functional similarity was confirmed by the inhibition of bloating in tumour-bearing flies treated by the NK3R inhibitors fezolinetant or pavinetant. This led Xu and colleagues to investigate the role of NK3R in renal dysfunction associated with tumour development.

Using a mouse colon-cancer model (with a mutation in the gene *Apc*) that promotes severe cachexia and renal dysfunction, the authors observed a strong and selective amelioration of renal dysfunction after injection with NK3R inhibitors; this did not affect other cachectic syndromes. Of note, neurokinin B, the normal ligand for NK3R, did not alleviate renal dysfunction in tumour-bearing mice, nor did it induce water imbalance in control animals — indicating that a yet-unknown ITP_F-like ligand for NK3R is responsible for mouse kidney failure associated with tumour development. Remarkably, inhibiting NK3R alleviated renal failure in several mouse tumour models. These included ones that used injection of mouse cancer cells (foregastric carcinoma cells and lung carcinoma cells), injection of human colorectal cancer cells and transplants of human gastric tumours. However, this alleviation of renal failure in mice did not occur when transplanted human liver tumours were used, suggesting the existence of alternative molecular mechanisms.

This study advances our understanding of tumour-associated kidney failure, and identifies NK3R as a potential target for therapeutic treatments. Notably, fezolinetant is approved in the United States for treating post-menopause symptoms. The identification of one or several NK3R ligands produced by tumours that induce renal failure will provide further insight into the physiology of tumour–host interactions, as well as pinpointing other drug targets. The work also exemplifies how the fruit fly has emerged as a powerful model system for unravelling aspects of cancer physiology involving cross-organ communications that have high physiological relevance for mammalian systems.

Pierre Leopold is at the Institut Curie, PSL Research University, CNRS UMR3215, INSERM U934, UPMC Paris-Sorbonne, 75005 Paris, France.
e-mail: pierre.leopold@curie.fr

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