Germany, and at Kiel University.
e-mail: gul@sail.msk.ru

1. McCarthy G. D., Haigh, I. D., Hirschi, J. J.-M., Grist, J. P. & Smeed, D. A. *Nature* **521,** 508–510 (2015).
2. Knight, J. R., Allan, R. J., Folland, C. K., Vellinga, M. & Mann, M. E. *et al. Geophys. Res. Lett.* **32,** L20708 (2005).
3. Delworth, T. L. & Mann, M. E. *Clim. Dynamics* **16,** 661–676 (2000).
4. Latif, M. *et al. J. Climate* **17,** 1605–1614 (2004).
5. Gulev, S.K., Latif, M., Keenlyside, N., Park, W. & Koltermann, K. P. *Nature* **499,** 464–467 (2013).
6. Latif, M. in *Ocean Circulation and Climate* 2nd edn (eds Siedler, G., Griffies, S., Gould, J. & Church, J.) (Academic, 2013).
7. Booth, B. B. B., Dunstone, N. J., Halloran, P. R., Andrews, T. & Bellouin, N. *Nature* **484,** 228–232 (2012).
8. Curry, R. G. & McCartney, M. S. *J. Phys. Oceanogr.* **31,** 3374–3400 (2001).
9. Hurrell, J. W. *Science* **269,** 676–679 (1995).
10. Sutton, R. T. & Hodson, D. L. R. *Science* **309,** 115–118 (2005).
11. Zhang, R. & Delworth, T. L. *Geophys. Res. Lett.* **33,** L17712 (2006).

CANCER METABOLISM

A waste of insulin interference

Many people with cancer die from a wasting disorder called cancer-associated cachexia. Two studies in fruit flies show that inhibition of insulin signalling causes cachexia-like organ wasting.

ERWIN F. WAGNER & MICHELE PETRUZZELLI

It is estimated that up to 30% of people with advanced-stage cancer are killed not by the tumour itself, but by a metabolic disorder called cancer-associated cachexia (CAC)[1,2], which is characterized by systemic inflammation, weight loss, body-fat atrophy and skeletal-muscle wasting. Cachexia is also a feature of several chronic conditions[2,3], including heart failure, lung disease and infectious diseases such as HIV. At present there is no cure for CAC and no biomarkers are available for identifying patients at risk of developing the disorder. Thus, there is a need to better understand the origins of cachexia, its systemic progression and the molecular pathways involved in its development. Two papers[4,5] in *Developmental Cell* now report that interference with insulin signalling in the fruit fly *Drosophila melanogaster* induces systemic organ wasting reminiscent of human cachexia.

The cancer-causing protein Yap1 is part of the Hippo signalling pathway, which induces cell proliferation, in part by increasing signalling by insulin and by a related protein, insulin-like growth factor 1 (IGF1) (ref. 6). Kwon *et al.*[4] investigated the systemic changes caused by intestinal activation of Yorkie, an equivalent of Yap1, in fruit flies. The authors report that activation of Yorkie in the gut causes over-proliferation of intestinal cells, and leads to the secretion of ImpL2, an insulin growth factor binding protein (IGFBP) that inhibits insulin and IGF1 signalling. Secretion of ImpL2 in the intestine caused systemic wasting in muscles and distant organs, including the ovaries and the fat body (an organ analogous to vertebrate fat and the liver). This remarkable finding implies that over-proliferation in a given tissue can lead to distant metabolic changes and wasting symptoms, similar to human cachexia.

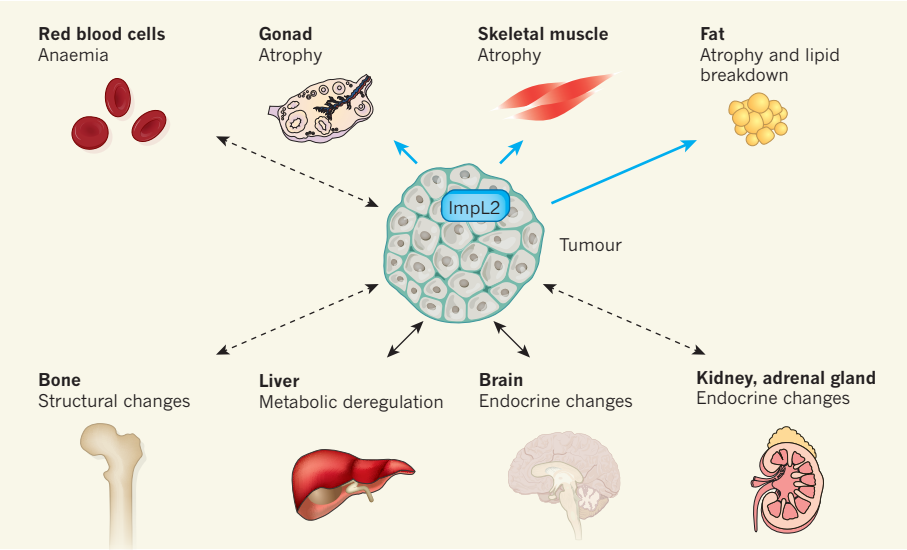

Figure 1 | Systemic metabolic changes in cancer. Cancer-associated cachexia is defined by harmful abnormalities that are brought about by factors secreted by the growing tumour, and by adaptive responses in host tissues. Solid double-headed arrows indicate that the molecular mechanisms underpinning the trait (which are thought to be bidirectional) have been defined, whereas dashed double-headed arrows indicate that causative factors remain unknown. Kwon *et al.*[4] and Figueroa-Clarevega and Bilder[5] demonstrated that the protein ImpL2, which is secreted from hyperproliferating tissues and tumours, impairs insulin signalling in fruit flies. This interference is the cause of atrophy in skeletal muscle, fat and gonadal tissues (indicated by the blue arrows, which are unidirectional to reflect the fact that bidirectional interactions have little time to become established in the fly studies.)

Using a different fly model, Figueroa-Clarevega and Bilder[5] find evidence to corroborate Kwon and colleagues' study. They transplanted tumours into adult flies, and found that malignant, but not benign, tumours caused wasting of fat, muscle and gonadal tissue. Furthermore, the tumours induced down-regulation of the insulin signalling pathway in peripheral organs, leading to insulin resistance in these regions. Investigating the differences between benign and malignant tumours, the authors found that *ImpL2* was one of the genes most upregulated in malignant tumours. They demonstrated that overexpression of ImpL2 in specific tissues in flies without tumours led to wasting in distant locations. However, inhibition of ImpL2 in flies with tumour transplants only partially ameliorated wasting, suggesting that other molecular interactions between the tumour and the host remain to be discovered.

Notably, the systemic wasting traits described in the two papers correlate with other features that are associated with high blood sugar. Furthermore, this wasting is independent of changes in food intake or local damage to organs at the site of tumour growth. This, taken together with the other results, indicates that factors secreted from tumours or hyper-proliferating tissues in *D. melanogaster* perturb systemic metabolism and induce wasting in distant organs.

Insulin resistance is common in patients with cancer, and may contribute to skeletal-muscle wasting in mouse models of CAC[7]. Previous studies[7] of how tumour-derived factors affect the organism have primarily focused on a group of cell-signalling molecules called pro-inflammatory cytokines, which promote systemic inflammation. Alterations in systemic

metabolism that arise as a consequence of tumour growth have been regarded as secondary effects of inflammation. The current studies provide evidence that impaired insulin signalling is itself a direct cause of CAC development. However, whether insulin resistance is sufficient to cause cachexia in model systems other than fruit flies remains to be demonstrated.

Insulin and IGF1 signalling are key regulators of tissue mass in both flies and mammals, and it is possible that IGFBPs are differentially regulated in cancers that are associated with cachexia compared with those that are not. Little is known about the regulation of ImpL2 in flies and mice, but it is probable that stress factors, which activate inflammatory pathways and Hippo signalling[6], could induce ImpL2 expression. It is interesting that other tumour-specific proteins, such as the *Drosophila* cytokine Upd2, are unable to induce organ wasting in flies, whereas the equivalent protein in mice, IL-6, is a mediator of CAC[8]. Surprisingly, a role for the immune system is not discussed in the two papers despite inflammation being an accepted hallmark of cachexia.

These two studies highlight the importance of studying the metabolic response to cancer. Although our knowledge of the metabolism of cancer cells themselves is steadily improving, the characterization of organism-wide metabolic changes in response to cancer is still incomplete (Fig. 1). The focus of cancer research is gradually expanding, from the cancer cell to the tumour microenvironment, to the system as a whole. Supporting the need to study organism-wide metabolism, abnormal alterations in organs at a distance from the primary tumour that are independent of the process of cancer metastasis have been described[8–10]. Remarkably, targeting such alterations has therapeutic value in mice, ameliorating total body-weight loss and skeletal-muscle and adipose-tissue atrophy, without directly affecting the mass of the tumour[8–10]. The tiny fruit fly nicely illustrates the value of broadening our horizons to encompass the organism as a whole, and of using animal models of cancer to explore this macroenvironment. ■

Erwin F. Wagner *is in the Cancer Cell Biology Programme, CNIO, Madrid 28029, Spain.*
Michele Petruzzelli *is in the Department of Oncology, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.*
e-mails: ewagner@cnio.es; mp753@cam.ac.uk

1. Tisdale, M. J. *Physiol. Rev.* **89,** 381–410 (2009).
2. Fearon, K., Arends, J. & Baracos, V. *Nature Rev. Clin. Oncol.* **10,** 90–99 (2013).
3. Argilés, J. M., Busquets, S., Stemmler, B. & López-Soriano, F. J. *Nature Rev. Cancer* **14,** 754–762 (2014).
4. Kwon, Y. *et al. Dev. Cell* **33,** 36–46 (2015).
5. Figueroa-Clarevega, A. & Bilder, D. *Dev. Cell* **33,** 47–55 (2015).
6. Strassburger, K., Tiebe, M., Pinna, F., Breuhahn, K. & Teleman, A. A. *Dev. Biol.* **367,** 187–196 (2012).
7. Fearon, K., Glass, D. J. & Guttridge, D. C. *Cell Metab.* **16,** 153–166 (2012).
8. Petruzzelli, M. *et al. Cell Metab.* **20,** 433–447 (2014).
9. Kir, S. *et al. Nature* **513,** 100–104 (2014).
10. Das, S. K. *et al. Science* **333,** 233–238 (2011).

MICROBIOLOGY

Taking the bad with the good

Modelling of the interactions between antibiotic production and antibiotic degradation reveals that these opposing activities are key to maintaining diversity in microbial communities. SEE LETTER P.516

CARL T. BERGSTROM & BENJAMIN KERR

We commonly expect competitive ecological interactions to be transitive: if ravens displace crows and crows displace jays, then ravens should displace jays as well. But the world does not always work this way. Increasingly, researchers are finding intransitive relationships, in which ravens displace crows, which displace jays, which in turn displace ravens. Intransitive relationships occur in animals[1,2], plants[3,4] and microbes[5,6]. Theoretical models show that species abundances can cycle in intransitive communities, in principle preserving species diversity[7,8]. However, in finite populations, extinction can readily occur when one type cycles to low abundance. On page 516 of this issue, Kelsic *et al.*[9] model an intransitive system in which microbial species produce antimicrobial compounds and exhibit differing sensitivities to the products of their competitors. By demonstrating that antimicrobial degradation can stabilize a multispecies community, the authors suggest a new solution to the puzzle of how bacterial diversity is maintained[10].

To illustrate Kelsic and colleagues' model, consider the rock–paper–scissors (RPS) scenario familiar to many as a game. Imagine three microbial species called Rock, Paper and Scissors, each of which produces a unique antimicrobial compound and is immune to its own toxin. If Rock kills Scissors, Scissors kills Paper and Paper kills Rock, we have the standard situation (Fig. 1a). Each bacterial species must protect itself from the toxin of its victim; for example, Scissors protects itself from Paper's toxin. Kelsic *et al.* focused on a neglected aspect of this protection: it may be non-excludable, meaning that protection may spill over to other species.

Such 'leakiness' may occur if a cell degrades the antimicrobials of a competing species by secreting enzymes that do the job externally, or by deactivating the competitor's antimicrobials once they have entered the cell[11]. Either way, the concentration of the antimicrobial in the environment is reduced. The RPS scenario can be adapted to account for this leakiness. For instance, when Scissors protects itself from Paper's toxin, partial protection would extend to Rock as well — here, Scissors inadvertently helps its own enemy (Fig. 1b, orange line). Kelsic and colleagues develop a mathematical model showing that the 'public good' of leaky protection and the 'public bad' of toxin production can interact to permit stable coexistence between multiple species.

Models with diffusible public goods and public bads are complicated. To improve our intuition about Kelsic and colleagues' model, let us reframe this population-level interaction as a two-player game. Instead of having many toxic microbes interacting with one another simultaneously, we consider pairwise interactions between individuals, each of whom play one of the RPS strategies. Players meet at random and receive a pay-off of 1 for winning or drawing and 0 for losing. They then replicate according to their pay-offs, and faithfully pass on their strategies to their offspring. A population of individuals playing this game undergoes unstable cycles; this scenario corresponds to the mathematical model developed by Kelsic *et al.* when there is no leaky protection. If instead the pay-off for winning is 2, drawing is 1 and losing is 0, we have the RPS game more commonly studied in the literature; this version has neutrally stable cycles[8]. Whether the cycles are neutrally stable or unstable, two of the three strategies will eventually be lost in a finite population (Fig. 1a).

Now suppose that we add one or more 'bystanders' to the game. Within the pair, a would-be winner is ineffectual if its enemy is standing by, and the game ends in a draw. With one or two bystanders, randomly chosen from the population, the chances of having a bystander that can interfere are too low to alter the dynamics qualitatively. But with more bystanders, the dynamics change completely: the community can approach a stable balance