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Whispering sweet somethings

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Author
Tlsty, Thea

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Ever-improving molecular techniques are providing tantalizing glimpses of the gut ecosystem[11]. With the launch of the Human Microbiome Project[12], which plans to characterize the human microbiota and analyse its role in human health and disease, we are set to see considerable advances in understanding how host–microbial interactions may affect human health. When such information will translate into new therapeutic approaches is, however, anyone's guess. ■

Marika C. Kullberg is in the Immunology and Infection Unit, Department of Biology, University of York, and The Hull York Medical School, PO Box 373, York YO10 5YW, UK.
e-mail: mk512@york.ac.uk

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CANCER

Whispering sweet somethings

Thea Tlsty

That genetic mutations contribute to cancer is undisputed. What now emerges is that a cancer cell's microenvironment has a much stronger hand in the course a cancer takes than previously thought.

The goal of personalized medicine is to tailor a treatment to a specific cellular target at the appropriate stage of a disease, thus 'defusing' the disease process. Cancer is an example of the way in which multifaceted approaches to attaining this goal are emerging. We have come to appreciate that a tumour is a collection of diverse cells — cells carrying cancer-causing mutations and the cells of its immediate microenvironment — that act in concert towards disease progression[1,2]. Three studies[3–5] illustrate how these cells collude, and focus on the contribution of non-tumour cells.

Within tissues, epithelial cells are supported by a connective framework called the stroma, which itself consists of specific cells, such as fibroblasts, endothelial cells and immune cells, as well as the extracellular matrix. Physiological processes occurring in this compartment, for example the development of new blood vessels in response to oxygen shortage, and host immune responses, could dictate cancer progression.

Writing in *Nature Medicine*, Finak *et al.*[3] set out to examine how gene-expression profiles in cells of the stroma are affected by cancer. Comparing morphologically normal and tumour stroma from the breast tissue of patients with breast cancer, they identify gene-expression patterns that are strongly associated with a specific outcome of the disease and that could be used as predictors of disease progression.

One specific predictor, a group of 26 genes that the authors call the stroma-derived prognostic predictor (SDPP), stratifies the risk of breast-cancer progression using molecular markers that are independent of — but add power to — both standard clinical prognostic factors, such as the presence or absence of tumour cells in adjacent lymph nodes, and the more recently described[6] predictors based on gene expression. SDPP identifies stromal subtypes that have gene-expression profiles relating to a good or poor outcome of breast cancer.

The clinical significance of work such as that of Finak *et al.* is twofold. First, discerning the subtleties of cell–cell interactions within the microenvironment of a malignant lesion (a localized, disease-associated change in a tissue) will indicate which particular therapy might be most effective for the specific biology of that tumour. Second, such insights could provide targets for developing new therapies. Finak *et al.* find that SDPP is not affected by treatment, suggesting that existing therapies do not target host responses that affect SDPP genes.

Reporting in *Proceedings of the National Academy of Sciences*, Postovit *et al.*[4] use a contemporary approach to address the question of the stromal contribution to cancer malignancy. In this exciting study, the authors use an *in vitro* three-dimensional model that exposes cancer cells to the microenvironment to which human embryonic stem cells are normally exposed; they were hoping to identify conditions in the stroma that suppress malignant characteristics of cancer cells.

Stromal cells surrounding embryonic stem cells secrete a protein factor called Lefty, which inhibits the Nodal protein. Nodal, which during embryonic development prevents stem-cell differentiation, is abnormally expressed in human tumour cells, causing malignancy[7]. Postovit and colleagues found that metastatic tumour cells do not express Lefty. Their results strongly support stromal regulation of malignancy and indicate that Lefty has a suppressive effect on cancer cells. The authors' work also suggests that factors secreted by the tumour stroma, and their derivatives, could be used as treatments to 'reprogramme' the differentiation of malignant cells, suppressing tumour development and growth.

Although modulating tumour properties in invasive cancers — as discussed in the Finak and Postovit papers[3,4] — could reduce the associated morbidity and mortality, early diagnosis and prevention are even more effective means of preventing cancer-associated death. To address the clinical problems of cancer at these early stages, understanding the molecular processes underlying cancer initiation and progression is crucial. A paper by Hu *et al.*[5] published in *Cancer Cell* addresses the mechanism of breast-cancer transition from a localized (*in situ*) lesion to an invasive form.

The authors used a cell line that, when injected into mice, mimics aspects of an early, non-malignant form of human breast cancer called ductal carcinoma *in situ* (DCIS)[8], by forming non-invasive lesions in the animals' mammary gland. They next studied the role of myoepithelial cells in these lesions in suppressing the transition of DCIS to malignancy. (Myoepithelial cells separate the basement membrane of the duct from the epithelial cells that face the duct lumen.)

Hu and colleagues' functional analysis of cell-type-specific gene expression identified several pathways that could be essential for interactions between stromal fibroblast cells and myoepithelial cells in controlling the integrity of a tissue's basement membrane. These pathways, which modulate myoepithelial-cell differentiation, are mediated by essential signalling molecules such as TGF-β, Hedgehog, cell-adhesion molecules and the gene transcription factor p63. Malfunction of these signalling pathways leads to the loss of myoepithelial cells and subsequent invasion of the basement membrane by their adjoining epithelial cells, which respond to signals originating from fibroblasts. Determining whether the loss of myoepithelial cells is a cause or a consequence of the transition from *in situ* disease to invasive cancer will help to dictate therapeutic strategies.

Myoepithelial cells secrete a protein called maspin, which inhibits degradation of the extracellular matrix, an event thought to be essential for the transition from *in situ* cancer to an invasive form[9]. Moreover, this crucial tumour-suppressor protein is postulated to affect tissue invasion, programmed cell death and blood-vessel development. Hu and colleagues[5] identified several extracellular-matrix metalloproteins that are implicated in cancer transition to the invasive state, but maspin is not one of them. Perhaps distinct subtypes of pre-malignant tumours use different pathways for the transition. Recent characterization of

DCIS tissue has indicated that it shows the same changes in gene-expression patterns as those seen in fully invasive tumours.

Understanding DCIS transition to invasive breast cancer is of tremendous importance. In the past two decades, the reported incidence of DCIS in the Western world has increased rapidly because of regular mammography screening. But only a small fraction of patients with DCIS will develop invasive disease or die of it[10], as the vast majority have the tissue surgically removed and are then unlikely to develop subsequent tumours. This also means that additional treatment after surgery might be redundant. Nonetheless, after surgery, many women receive at least one of three regimens — radiation therapy, hormonal therapy or chemotherapy. At present, no criteria can consistently identify which women diagnosed with DCIS are most likely to benefit from these additional treatments. Identification of factors associated with subsequent invasive events could help classify women's individual risk for subsequent tumours and their response to therapies so as to avoid over- or under-treatment.

These three studies[3–5] begin to deliver on the promise of basic research in characterizing the tumour microenvironment and the application of that knowledge in the clinic. Molecular markers in epithelial cells that predict which DCIS lesions will subsequently become invasive tumours are being found[11]. By integrating such information with other data on the tissue microenvironment, researchers could identify additional molecular markers, thus improving prediction of future tumour formation and pointing the way to personalized treatment. The whisperings of molecular dialogue that go on between malignant cells and their microenvironment also hold information that can be used to categorize patients into those who need more, or less, aggressive therapy, identify patients for clinical trials, and develop new therapeutic approaches. These whisperings might even provide clinically important information before an invasive tumour can form. ■

Thea Tlsty is in the Department of Pathology, University of California, San Francisco, 513 Parnassus Avenue, San Francisco, California 94143-0511, USA.
e-mail: thea.tlsty@ucsf.edu

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EVOLUTIONARY BIOLOGY

Sex ratios writ small

Jos. J. Schall

The evolutionary theory of sex ratios should apply to all creatures, both great and small. Experimental studies of the proportions of male to female sex cells of malaria parasites deliver cheering results.

Charles Darwin, the man of 'enlarged curiosity', was particularly curious about sex. He wondered, for example, why males and females are equally abundant in so many species in which males can mate with multiple females. Aren't males in surplus and a waste for such species? Darwin provided an answer, but was concerned primarily with human sex ratios. The question extends to even the single-celled protists, and on page 609 of this issue[1] Reece *et al.* revisit this venerable problem with a study of sex ratios in a protist that is both complex and lethal — the *Plasmodium* parasite that causes malaria.

Plasmodium prospers by replicating asexually within its vertebrate host, but also produces male and female gametocyte cells for transmission to a blood-feeding insect vector. Sex occurs within the vector, after each female gametocyte develops into a single female gamete, and each male yields several male gametes[2]. Intuition suggests that a *Plasmodium* infection's transmission success into the vector would be greatest when just enough male gametocytes are present to mate with all the females. Female-biased sex ratios are indeed common, but an apparent surplus of male gametocytes is routinely seen in some *Plasmodium* species, and gametocyte sex ratio varies among and even within infections over time[2–6]. Sex-ratio theory, a mainstay of modern evolutionary biology, offers explanations for these observations, but experimental verification has long been lacking.

Reece *et al.*[1] report that rodent malaria parasites follow sex-ratio theory quite well. Their elegant experiments show that each parasite clone shifts its ratio of male and female gametocytes according to the density of gametocytes in the blood, the fecundity of each male gametocyte and the likelihood of selfing (that is, union of male and female cells from the same clone). But *Plasmodium* also surprises with an additional talent — the parasite seems to detect kin and non-kin in the infection, and even the proportions of each.

Darwin provided a verbal explanation for the occurrence of equal proportions of males and females (Carl Düsing supplied the algebraic treatment a decade later)[7]. When sex ratio is biased, the less-common gender will have, on average, higher fitness, strictly because it will claim more offspring in the next generation. Mothers that produce offspring of the less-common gender would thus expect more 'grand offspring'. The equilibrium sex ratio would be 1:1. Almost a century later, W. D. Hamilton recognized that this model holds only for outbred populations[8]. In a species that reproduces in patches in which sisters mate only with brothers, a mother's fitness depends on reducing competition among her sons for mates. Thus, just enough sons should be produced to mate with all the daughters. As the degree of mating between siblings declines within patches, the sex ratio should shift towards more equal representation of males and females. Humans show a 1:1 sex ratio because we are so well outbred.

Hamilton's model fits the life history of malaria parasites[9]. All mating of *Plasmodium* gametes occurs in a single blood meal within the vector. If an infection consists of a single genotype, or clone, of parasites, the optimal sex ratio for that clone would be one male gametocyte to **f** female gametocytes, where **f** is the fecundity of the male, or the number of gametes it produces. In mixed-clone infections, the optimal sex ratio for each genotype depends on the likelihood of selfing, and will shift appropriately towards more males.

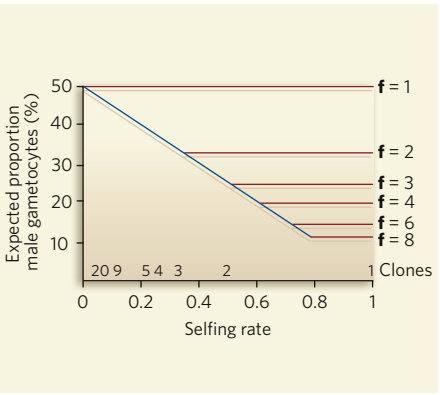

Figure 1 | A theory under test. Reece and colleagues[1] find that sex-ratio theory[2] predicts the proportion of malaria parasites' male gametocytes within a vertebrate host. The selfing rate depends on the number of genetically distinct clones and their proportions. Shown here are the expected rates of selfing with equal proportions of 1 to 20 clones. The fecundity of each male gametocyte (**f**) is the number of viable gametes produced per cell. With high fecundity (**f** = 8), and only one clone present, just enough males (11%) will be produced to mate with all the females within the insect vector. With low fecundity or many clones, the gametocyte sex ratio tilts towards higher production of males. (Figure redrawn from refs 2 and 4.)