> internationally renowned experts convened to share their knowledge

The afternoon started with Mark Emberton and Laurence Klotz, who led an informal discussion on active surveillance. This interlude was followed by a set of presentations on high-risk and metastatic disease given by Anthony D'Amico and Martin Gleave. This session was concluded by Alberto Bossi and Declan Murphy debating metastasis-directed therapies.

The final day of the summit included a set of talks on metastatic prostate cancer given by Michael Hofman, Anthony D'Amico, Noel Clarke and Silke Gillessen. Aptly, the final talks of the summit were on hot topics and controversies in prostate cancer.

The last words were given by Derya and Markus, who concluded this stimulating meeting of fantastic talks and in-depth discussions by thanking the organizers, panel and attendees. We look forward to the next Hamburg Prostate Cancer Summit, when it returns after a few years' hiatus.

*Louise Stone*

> In their simulation, extracellular acidosis caused by amplified tumour glycolysis dynamically modulated the macrophage phenotype

levels of infiltration were seen at the point of progression to high-grade adenocarcinomas and invasion. By contrast, in mice treated with $NaHCO_3$, macrophage infiltration into the stromal compartment and tumour incidence were reduced and prostate interglandular structure appeared normal.

To clarify the functional relation between the acidic pH and the associated TAM phenotype, the researchers developed an in silico approach, which enabled assessing tumour development with acid-induced macrophage responses 'switched off'. In their simulation, extracellular acidosis caused by amplified tumour glycolysis dynamically modulated the macrophage phenotype. In the presence of acidosis and resultant phenotype modulation, tumours grew more quickly, as visualized by significantly different Kaplan–Meier curves ($P < 0.001$).

*Clemens Thoma*

**ORIGINAL ARTICLE** El-Kenawi, A. et al. Acidity promotes tumour progression by altering macrophage phenotype in prostate cancer. *Br. J. Cancer* https://doi.org/10.1038/s41416-019-0542-2 (2019)

DEVELOPMENT

# Gut–gonad communication masculinizes metabolism

New data published in *Cell* report that testicular signals control carbohydrate metabolism in male *Drosophila*, which in turn controls food intake and spermatogenesis, suggesting the existence of a gut–gonad axis, whereby the testis alters metabolism to regulate its own function.

Researchers from the Gut Signalling and Metabolism team at the MRC London Institute of Medical Sciences demonstrated a male-biased pattern of gene expression in the *Drosophila* gut for genes encoding carbohydrate (sugar) metabolism. This sexually dimorphic expression was spatially restricted to the posterior R4 region of the midgut. Using RNA-sequencing analysis, they showed that these genes were upregulated in female flies that lacked *tra*, a gene that controls feminization in *Drosophila*. Generation of knock-in and knockout alleles for *tra* and its binding partner *tra2* showed that the sex bias for sugar metabolism gene expression could be controlled: *tra* and/or *tra2* mutation upregulated the expression of the sugar genes in (masculinized) female flies, whereas ectopic *tra* expression in (feminized) male flies reduced their expression to amounts comparable to that of a female. Interestingly, *tra* knockdown in specific cells of the intestinal epithelium did not identify a specific site for this effect, suggesting that the male bias in sugar genes is controlled outside the gut.

Thus, the team went on to consider the 3D arrangement of gene expression within the body as a starting point for investigating an origin for the male bias effect. The close proximity of the R4 gut region to the testicular apex led them to hypothesize that the testis itself might be controlling sugar gene expression. By disconnecting gonadal sex from somatic sex, they showed that masculization of the female gonad in female flies led to a male-like sugar gene expression pattern in the gut.

"Our study illustrates the overlooked influence of sex (through the action of the sex chromosomes or sex organs) in the biology of adult somatic cells," commented first author Bruno Hudry.

To identify the pathway responsible, the group knocked down components of signal transduction pathways that had shown sexual dimorphism in earlier experiments; only disruption of the JAK–STAT pathway reduced the male bias in sugar gene expression. Furthermore, downregulation of JAK–STAT signalling in the R4 midgut of male flies reduced food intake, whereas exacerbation of JAK–STAT signalling in the same region increased food intake, an effect shown to be mediated by citrate. Thus, the team proposed a model in which male-biased activation of JAK–STAT signalling in the R4 region upregulates intestinal sugar gene expression to produce cytosolic citrate, which is exported into the circulation to promote food intake.

Hypothesizing that citrate might be affecting the testis itself, the team knocked down the citrate transporter *Indy*, which did not seem to affect testicular architecture; however, it did reduce spermatocyte numbers, suggesting that citrate is required for spermatogenesis.

In addition to its role in spermatogenesis, these data raise some interesting questions regarding the further roles of citrate in *Drosophila* and in humans — for example, in the prostate, where citrate levels are 1,000-fold higher than in plasma. The team are now working on a number of knockdown models to investigate the functions of citrate in the testis and to determine whether this role is observed only in *Drosophila* or if it is conserved across species.

*Annette Fenner*

**ORIGINAL ARTICLE** Hudry, B. et al. Sex differences in intestinal carbohydrate metabolism promote food intake and sperm maturation. *Cell* **178**, 901–918 (2019)