and some other neurotransmitter molecules. Dohnalová and colleagues also found that the exercise-induced burst of dopamine activates specific neuronal cell types in a region of the brain called the striatum. Inhibition of dopamine-producing neurons in the ventral tegmental area or blockade of dopamine sensing reduced athletic endurance, indicating that the exercise-induced dopamine surge and subsequent neuronal activity in the striatum are crucial for willingness to maintain body movement. However, when mice lacking gut bacteria exercised, the expression of MAO remained unchanged, and both the dopamine surge and the striatal neuronal activity were blunted compared with what happens in mice that have gut microbes. Restoration of the gut microbiome, inhibition of MAO and an artificially generated increase of dopamine signalling in the striatum were each sufficient to restore exercise performance in mice lacking gut bacteria.

The main communication routes between gut bacteria and the brain include: modulation of immune-system function, direct release of microbiome-produced molecules to the bloodstream and local stimulation of neurons that project to the central nervous system[8]. Dohnalová *et al.* demonstrate that the microbiome uses local neuronal stimulation to access motivational circuits in the brain. Specific sensory neurons — those that express the protein TRPV1, innervate the colon and project to the spinal cord — were stimulated after exercise in conventional mice, but not in those treated with antibiotics. Activation of these sensory neurons in bacteria-depleted animals resulted in restoration of physical performance, a decrease in MAO levels, a burst of dopamine and the triggering of neuronal activation in the striatum.

Furthermore, the authors found that bacterially produced molecules called fatty acid amides (FAA) could activate TRPV1-expressing sensory neurons, and that the abundance of FAA correlated with physical performance. Dietary supplementation of FAA and gut colonization of germ-free mice with FAA-producing bacteria each had the capacity to restore exercise-associated dopamine signalling in the brain and to improve physical performance. The authors discovered that FAA molecules acted on a receptor known as the cannabinoid receptor CB1, which is expressed by sensory neurons. Blockade of this receptor or of CB1-associated signalling inhibited the beneficial effect of FAA supplementation or of FAA-producing bacteria on physical activity.

Dohnalová *et al.* have demonstrated that the circuits involved in the motivation needed to sustain physical activity in mice are modulated by gut microbes. The evolutionary explanation for such regulatory control by microbes on the cognitive function of their host is puzzling. The trillions of microbes in the gut release and regulate a vast repertoire of molecules that can interact with functionally diverse classes of receptors in the host[9]. It is possible that the effect observed is a coincidence that occurs secondarily to the local gut functions of molecules produced by bacteria. Given that TRPV1-expressing sensory neurons also convey pain-related signalling, an alternative explanation might involve a beneficial interdependence in the relationship between gut health and the ability to engage in energy-consuming physical activities.

The psychotropic potential of the microbiome-derived molecules to target the brain, as highlighted by Dohnalová *et al.*, is of great interest for possible therapeutic options, if this phenomenon is also relevant to people. Beyond understanding the pathways that are valuable for encouraging physical activity, the study provides insight into non-invasive methods to access reward circuits in the brain, which are often dysregulated in addictive-behaviour disorders. Although tempting to consider the human implications of this research, gauging the practical relevance of these findings will require extensive further assessment. A variety of other factors influence motivational states in people, requiring a range of strategies to strengthen motivational and reward circuits in unfavourable environments.

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Medical research

Genetics and anatomy sculpt ovarian cancer

Denarda Dangaj Laniti & George Coukos

The therapeutic options available to treat ovarian cancer need improvement. Data that reveal the cellular, molecular and mutational landscape as such tumours grow and spread might aid efforts to develop new targeted therapies. **See p.778**

The most common type of ovarian cancer[1], called high-grade serous ovarian cancer (HGSOC), is challenging from a therapeutic perspective. By the time most individuals are diagnosed with this type of tumour, it has already spread (metastasized) from the primary site to distant regions, seeding cancer cells in multiple abdominal locations (intraperitoneal sites). At that point, symptoms arise because of an accumulation of peritoneal fluid in these areas. On page 778, Vázquez-García *et al.*[2] provide insights into metastatic ovarian cancer.

Key advances[3] have been made in understanding the molecular and genetic alterations that underlie the development of HGSOC, as well as in clarifying how these tumours are recognized by the host's immune system and in characterizing the immune cells in the tumour microenvironment (TME)[4]. However, such information comes mainly from analyses of single sites of tumour growth. Intratumoral heterogeneity, in terms of variation in the tumour cells and immune cells present, is highly prevalent in HGSOC[5], but the consequences of this remain unclear.

So far, variations in the TME cell types across intraperitoneal sites have been thought to arise in a random manner. Vázquez-García *et al.* attempt to decipher the pattern of this diversity. The authors gathered evidence that includes single-cell data on gene and protein expression, and assessed mutations across 160 tumour sites in 42 individuals with ovarian cancer who had not yet received treatment. The authors examined the primary site of tumour growth (the ovary or fallopian tube, or both) and sites to which the tumour had spread, such as the bowel and peritoneum (the membrane that lines the inner wall of the abdomen).

Applying mathematical models used in ecology to measure dissimilarities within and between individuals, the authors show that the TME's cellular constituents in this type of

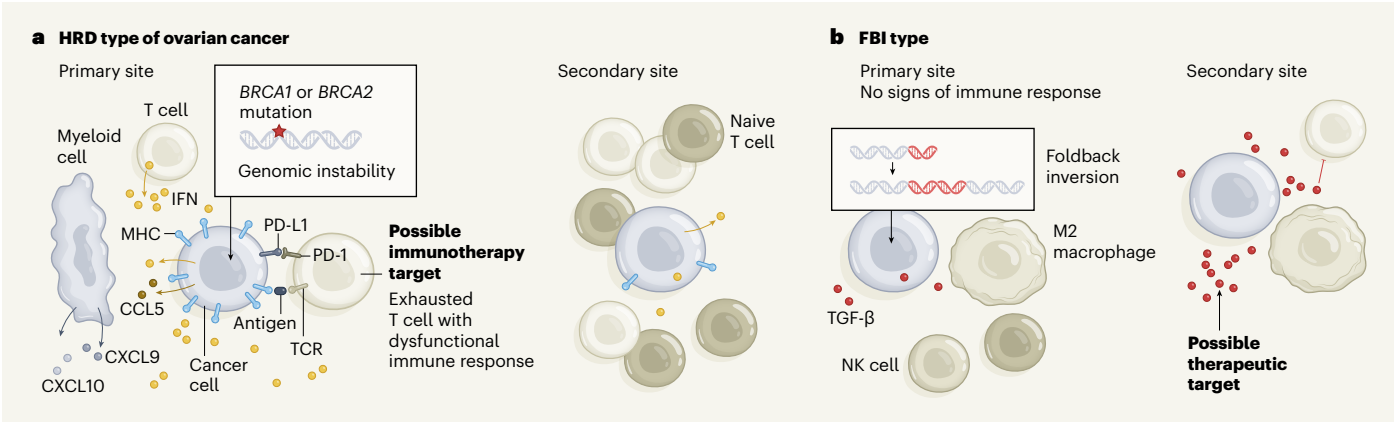

Figure 1 | Human ovarian cancer. Vázquez-García *et al.*[2] examined cancer and immune cells at primary and secondary sites of tumour growth. **a**, The authors observed that tumours associated with mutations in *BRCA1* or *BRCA2* genes (termed HRD tumours) have deficiencies in a DNA-repair process called homologous recombination, which leads to genomic instability. Cancer cells or immune cells (myeloid cells or T cells) at these primary sites express inflammatory molecules such as interferon (IFN), CCL5, CXCL9 and CXCL10. Immune cells called T cells can target cancer after recognizing peptide fragments, called antigens, that bind to the T-cell receptor (TCR) and the major histocompatibility complex (MHC). These T cells became 'exhausted' through interactions with the proteins PD-1 and PD-L1, and immunotherapy might combat this dysfunction. Compared with the primary site, some secondary sites have immune cells called naive T cells, fewer MHC and IFN molecules, and more T cells. **b**, Some tumours (termed FBI tumours) have DNA rearrangements called foldback inversions. Primary sites of FBI tumours contain the immunosuppressive molecule TGF-β and inactive immune cells — naive T cells, natural killer (NK) cells and M2 macrophages. Secondary sites also have M2 macrophages. TGF-β might offer a target for relieving immune-cell suppression.

ovarian cancer vary not only because of their mutational status, as shown previously[6,7], but also as a result of the tumour's anatomical site. This in-depth analysis provides a number of biological insights (Fig. 1).

The presence of immune cells in tumours, described as tumour-infiltrating lymphocytes (TILs), is associated with a longer survival time for individuals with ovarian cancer[8]. A network of cross-talking cells, including those from the tumour and from the immune system (such as myeloid and T cells), has been described[9,10]. The creation of this network[7] is triggered by tumour cells with mutations in the gene *BRCA1*, which have an impaired ability to repair DNA breaks, known as homologous recombination deficiency (HRD). These HRD cells express CCL5 — a type of protein called a chemokine, which induces cell migration[7]. The generation of this network is also enabled by myeloid cells, which respond to the protein interferon by producing other chemokines (such as CXCL9 and CXCL10), which thereby recruit T cells and support them through a process of co-stimulation[7,9,10].

Vázquez-García *et al.* determine the physical position of this T-cell network to be in anatomical sites of primary HRD tumours that exhibit peptide fragments called antigens and that have high levels of surveillance by immune cells (antigen recognition by immune cells can lead to an anticancer defence response). The authors found that the primary sites — regarded as being representative of earlier tumour states — had a high number of dysfunctional 'exhausted' T cells, which are characteristic of a blunted immune response after antigen recognition[10].

These features were accompanied by the activation of various types of myeloid cell, including an increase in the number of certain dendritic cells and macrophages (also known as myeloid cells) that expressed high levels of chemokines, such as CXCL9 and CXCL10. Moreover, the genomic instability associated with loss of BRCA1 protein in primary tumours can result in the abnormal presence of DNA in the cytoplasm. When it is sensed, such DNA drives inflammation in HGSOC cells, resulting in the activation of STING protein and of interferon, which boosts the infiltration of T cells into the tumour[7].

The authors extended their findings by showing that these signatures of an immune response against the cancer were enriched in tumours with the mutational hallmarks of HRD. However, these characteristics were lacking in non-HRD tumours that had other types of genomic abnormality, such as foldback inversion (FBI) structural rearrangements.

Compared with HRD tumours, FBI tumours were instead enriched in particular types of T cell (naive or stem-like T cells and central memory T cells) that seem to be 'bystander' TILs not involved in tumour recognition. These tumours were also populated by immunosuppressive subsets of macrophages, often called M2-like macrophages. Accordingly, compared with FBI tumours, the HRD subtypes exhibited increased signalling through the JAK–STAT inflammatory pathway, mainly in the primary tumours.

The HRD tumours had an accompanying chronic upregulation of interferon signalling in T cells, in cancer cells (which also showed upregulation of the *HLA* genes that encode the major histocompatibility complex (MHC) needed for antigen display) and in cancer-associated myeloid cells. This was seen particularly in 'HRD-Dup' tumours, which exhibit genomic instability in the form of duplications of certain areas of the genome.

Therefore, a particular type of inflammatory response (termed a type I cellular inflammation) of the TME occurs in the context of tumour-cell-intrinsic inflammation that is mediated by interferons and driven by genomic instability (HRD), and in the associated production of a particular type of interferon (type I interferon) by dendritic cells[11]. Moreover, the presence of CD8 T cells and dendritic cells in close proximity to each other — which is needed for the function of these T cells in antitumour defences[10] — was observed mostly in the primary site of HRD tumours.

The metastasis of tumours to secondary sites was associated with evolution of the TME, which seemed to be affected by the particular location of the secondary site of the tumour. The abundance of CD8 T cells in intraperitoneal tumour sites was consistently higher than that in primary tumours, but the capacity of immune cells for tumour recognition was diminished in secondary sites relative to the primary site. This was particularly the case for HRD tumours, which lost their diversity of T-cell states at secondary sites and were notably deficient in exhausted T cells and macrophages — cells that might be reinvigorated through immunotherapy.

What factors might account for this change in the ability of immune cells to recognize tumours? Vázquez-García and colleagues identified a decrease in expression of *HLA* genes in tumour cells at secondary sites as one possible mechanism, through the deletion of a section of a chromosome that contains *HLA* genes. Other mechanisms, such as the silencing of the DNA-sensing and interferon-production pathway by regulating the DNA–protein complex of chromatin (epigenetic regulation), or the loss

of tumour-intrinsic chemokine molecules — might also be involved[7,12].

Local cues from the host tissue could have a role, too, because bowel metastases exhibited an increase in interactions between tumour cells and immune cells — unlike those at adipose-tissue sites, which showed a reduction in tumour–immune cell cross-talk compared with that at the primary site. Notably, intraperitoneal sites of FBI tumours had high levels of expression of TGF-β, a protein that drives immune suppression and T-cell exclusion. Finally, immunosuppressive subsets of immune cells, such as regulatory T cells, suppressive natural killer cells and myeloid cells, were detected in the primary as well as in the secondary sites. Thus, the anatomical site itself could impose distinct pressures that drive and shape specific states of malignant cells.

Although not addressed in this study, epigenetic regulation might be crucial for the acquisition of these shifts in tumour-cell characteristics as the cancer spreads. Simultaneous investigation of various aspects of tumour cells using genomic, epigenomic and transcriptomic analysis will be essential for understanding how such tumour-cell plasticity sculpts the TME in HGSOC.

Vázquez-García and colleagues' work sets the stage for further discoveries and therapeutic development. Clinical trials of immunotherapy for HGSOC, which have so far been performed without using a biomarker strategy to identify individuals who are most likely to respond to therapy, have yielded disappointing results. The authors' findings confirm that people with HRD tumours would be more likely to benefit from an immunotherapy called immune-checkpoint blockade than would those with non-HRD tumours. However, future mechanistic and biomarker-based investigations in this area should consider the complexity of the metastatic process. Combinatorial immunotherapy designs that include more than one type of immunotherapy should take Vázquez-García and colleagues' findings into account, and could investigate TGF-β blockade as a possible strategy for the treatment of FBI tumours. Finally, this work reminds us of the complex nature of HGSOC, and highlights the urgent and still-unmet need for early and curative immunotherapy interventions.

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Ecology

An energetic look at the life in logged forests

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What are the ecological consequences of logging in a tropical forest? A detailed assessment of vegetation growth, bird and mammal numbers, and energy flows in logged and unlogged forests offers some surprising findings. **See p.707**

Hearing the terms tropical forest and logging commonly evokes images of deforestation. Yet most tropical timber is produced by felling only a limited number of trees in a piece of forest, leaving the structure of the forest mostly intact. As long as they are managed well, logged tropical forests also retain most of their species of plants and animals[1]. These forests represent more than one-quarter of all tropical forests worldwide[2] — an area twice the size of Mexico — so they can make an important contribution to nature conservation. Despite this, logged tropical forests are often regarded as being degraded and in need of recovery. On page 707, Malhi *et al.*[3] provide a very different view of these ecosystems. Gathering an impressive number of field observations, the authors reveal that the logged forests they studied harboured more animal species and were ecologically more 'energetic' than were the unlogged forests.

Malhi and colleagues put a huge amount of work into calculating the number of individuals for 144 bird species and 104 mammalian species. They did this in adjacent areas of undisturbed and logged forest in Malaysian Borneo. At 882 locations, the authors installed camera traps — devices that automatically take pictures when animals pass by. In addition, Malhi and colleagues captured small mammals at 1,488 positions; installed bat traps at 336 sites; and counted birds at 356 locations.

The authors then analysed the many thousands of animal sightings to estimate the abundance and diversity of the creatures. Such analyses were supported by progress over the past few years in computational methods for handling wildlife-observation data[4]. Unexpectedly, the team found that the diversity (Fig. 1) and summed weight of birds and mammals was higher in a logged forest than in an unlogged one. This is probably because environmental

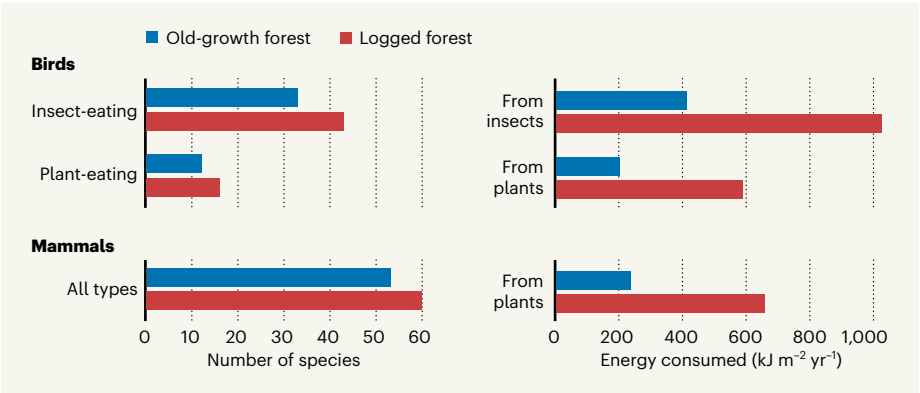

Figure 1 | The effects of logging on birds and mammals in tropical forests. Malhi *et al.*[3] compared logged and unlogged old-growth tropical forest in Malaysia. Surprisingly, the logged sites had a greater number of species than the unlogged sites. For example, logged forests had more species of bird that eat insects or that eat plant material such as fruit and nectar than did the unlogged forests. The authors estimated energy flows through food consumption, and found higher values for logged forests than for unlogged ones. Perhaps logging opens up extra environmental niches that help to boost the forest ecosystem.