patients with ovarian cancer would yield better results. From the same cohort, 43% of plasma samples from patients with ovarian cancer tested positive, whereas 40% of corresponding Pap brush samples were positive for genetic mutations. The positive Pap brush samples only partially overlapped with the positive plasma samples from the same patients, leading to an overall positivity rate of 63% for the detection of ovarian cancer based on Pap brush and plasma samples.

Although the moderate sensitivity for the detection of ovarian cancer might have multiple underlying causes that need further investigation, overall, this study offers promising opportunities for improving the screening for endometrial and, potentially, ovarian cancers through modification of the routinely used Pap test.

Ulrike Harjes

ORIGINAL ARTICLE Wang, Y. et al. Evaluation of liquid from the Papanicolaou test and other liquid biopsies for the detection of endometrial and ovarian cancers. *Sci. Transl Med.* **10**, eaap8793 (2018)

Fc receptor on NK cells), the researchers showed that Fc receptor engagement was not required for NK cell-mediated killing of A375 cells or for therapeutic efficacy in the B16F10 metastasis model. However, the mutant mAb was not as effective as 7C6, indicating that engagement of Fc receptors also has a role.

Finally, if immunocompromised mice reconstituted with human NK cells were intravenously injected with human melanoma cells, the 7C6 mAb reduced metastases to the lung and other organs. Interestingly, liver metastases were reduced by 7C6 even in the absence of NK cells, and this effect depended on liver-resident macrophages.

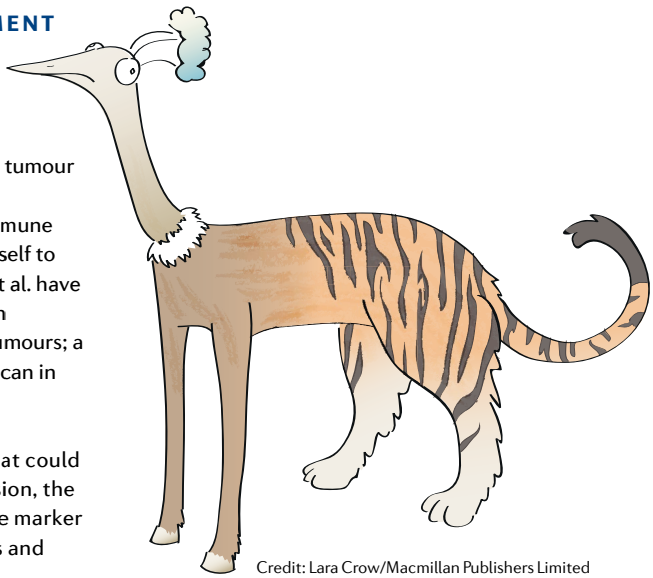
These data indicate that preventing the loss of immunostimulatory ligands on tumour cells can reactivate antitumour immune responses and that antibodies such as 7C6 might be useful as immunotherapies.

Sarah Seton-Rogers

ORIGINAL ARTICLE Ferrari de Andrade, L. et al. Antibody-mediated inhibition of MICA and MICB shedding promotes NK cell-driven tumor immunity. *Science* **359**, 1537–1542 (2018)

TUMOUR MICROENVIRONMENT

Cell genesis



Credit: Lara Crow/Macmillan Publishers Limited

Immune cell populations recruited to the tumour microenvironment (TME) can profoundly influence cancer progression. Equally, immune cells can be reprogrammed by the TME itself to promote cancer progression. Now, Han et al. have discovered a new immune cell population induced outside of the TME by primary tumours; a circulating factor secreted by these cells can in turn support tumour growth.

To search for novel cellular subsets originating in the main lymph organs that could have a systemic role in tumour progression, the researchers used the common leukocyte marker CD45 to screen for known immune cells and previously unidentified non-leukocyte populations in the spleen, draining lymph node and bone marrow of tumour-bearing mice. Using the Hepa cell line to create a syngeneic orthotopic mouse model of hepatocellular carcinoma (HCC), it was shown that the proportion of all known immune cell subsets in the enlarged spleen significantly decreased during HCC progression. However, 4 weeks after tumour challenge, an expanded population of $CD45^-$ non-leukocyte cells was detected in the spleen of mice. The phenotype of these cells was defined by the expression of erythrocyte and megakaryocyte markers, including Ter-119, CD41, CD71 and CD44. The authors named this cell population Ter erythroblast-like, as their transcriptome shared similarities with megakaryocyte–erythroid progenitor cells from the bone marrow. Importantly, Ter-cells were specifically induced by tumours as they were not found in the spleens of normal mice and, moreover, originated exclusively within the spleen as they were not induced in HCC-bearing mice that had undergone splenectomy before injection of Hepa cells. Ter-cells were also found in the spleens of mice bearing EG7 T cell lymphoma and B16 melanoma tumours, high-lighting that the generation of this cell subset was not exclusive to HCC.

Investigating the emergence of Ter-cells revealed that SMAD3 activation and transforming growth factor-β (TGFβ) signalling were required, as both *Smad3*-knockout mice bearing Hepa cell tumours and mice injected with *Tgfb*-knockout Hepa cells had a reduced ability to form splenic Ter-cells. The authors went on to show that whilst Ter-cells did not affect host antitumour immunity, they did exhibit increased expression of the neurotrophic factor artemin (encoded by *Artn*). Accordingly, elevated levels of serum artemin were detected during HCC progression in the mouse model, which could be effectively abolished with splenectomy before tumour challenge.

Using in vitro assays with Ter-cells demonstrated that Ter-cells could increase Hepa and EG7 cell migration and invasion and that this effect could be reversed with a neutralizing antibody to mouse artemin. Similarly, in vivo injection of Ter-cells increased Hepa and EG7 tumour growth and reduced survival of mice, a phenotype that could be opposed by caudal vein injection of a neutralizing antibody to mouse artemin. Additionally, Hepa tumour growth was inhibited in *Artn*-knockout mice implying that Ter-cell-derived artemin and not cancer cell-derived artemin was responsible for the observed tumour progression. Mechanistically, the authors found that artemin promoted HCC survival through phosphorylation of caspase 9 and promoted invasion through expression of TRIO and F-actin-binding protein (TRIOBP) and integrin β5.

These findings in cancer mouse models prompted the authors to examine samples from patients with HCC. This analysis confirmed the presence of CD235A (the human orthologue of Ter-119) and $artemin^+$ cells in the spleen. Furthermore, increased artemin and TGFβ levels in the serum and higher expression of the artemin receptor GFRα3 in HCC tissues all correlated with poor prognosis.

This study proposes that splenectomy might be a viable clinical option for patients with advanced HCC to treat not only the associated symptom of splenomegaly but also to slow tumour progression.

Anna Dart

ORIGINAL ARTICLE Han, Y. et al. Tumor-induced generation of splenic erythroblast-like Ter-cells promotes tumor progression. *Cell* **173**, 634–648 (2018)