cells at the border had unique expression profiles suggestive of immune inhibition. However, patients in this group had increased survival relative to those with mixed tumour and immune cells (survival was not analysed in patients with cold tumours as this group had only five patients).

The authors then looked at the expression of four immune-regulatory proteins that are current therapeutic targets (PD1, PDL1, IDO and LAG3) and found that PD1 and LAG3 were expressed predominantly by immune cells, but PDL1 and IDO were expressed by both tumour and immune cells at similar levels. Furthermore, IDO and PDL1, and LAG3 and PD1, were co-expressed across patients. However, these relationships were not necessarily symmetrical: while many $LAG3^+$ cells were also $PD1^+$, only a small proportion of $PD1^+$ cells were also $LAG3^+$. This suggests ordered or context-dependent expression of these proteins, which may be driven by signals from the microenvironment.

MIBI-TOF analyses might be useful to improve outcomes with immunotherapy. For example, the co-expression of certain immune-regulatory proteins could suggest effective immunotherapy combinations. Potentially therapeutically relevant differences between patients were also observed: in some patients, most PD1 was found on cytotoxic T cells and this correlated with a mixed tumour–immune organization, whereas in others PD1 was predominantly found on T helper cells and this was correlated with a compartmentalized tumour–immune organization. It is possible that these differences could influence the response to checkpoint inhibitors targeting PD1, and might also be linked to survival in the absence of immunotherapy as noted above.

The ability of MIBI-TOF analyses to correlate the expression of multiple biomarkers with tumour architecture should prove useful in delineating how the microenvironment affects tumour progression and therapeutic response.

Sarah Seton-Rogers

ORIGINAL ARTICLE Keren, L. et al. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. *Cell* **174**, 1373–1387 (2018)

high-throughput sequencing) method indicated that CGRP TKO metastases do not have an increase in overall chromatin accessibility or a change in accessible regions relative to primary tumours. RNA sequencing mirrored these results: many genes were differentially expressed between CMV TKO primary tumours and metastases, whereas few differences were observed in the CGRP TKO tumours and metastases.

Interestingly, although tumour cells from both models expressed neuroendocrine genes, CMV TKO primary tumours also had high expression of markers of several other lung epithelial cell types. As such, the authors hypothesized that diverse cells of origin might contribute to the differences in CMV TKO and CGRP TKO tumours. As neuroendocrine cells are rare, this hypothesis could also explain the lower frequency of tumours in the CGRP TKO model relative to CMV tumours, which might be initiated in a larger cell population (or populations). This was supported by a difference in the spatial localization of the different tumours within the lungs, which is also observed in human tumours.

In hopes of pinpointing the cell of origin in the CMV TKO model, the authors targeted Cre expression in alveolar type II cells or club cells in the lung to create different TKO models, but neither led to the high frequency of tumours observed in the CMV TKO mice. Several alternative explanations were also ruled out. Therefore, although different cells of origin seem the most likely explanation for these results, it is still unknown which cell type (or types) initiates the CMV TKO tumours.

This study suggests that there are distinct subtypes of SCLC initiated from different cell types in the lung. Further studies to determine the cell of origin in CMV TKO tumours and to understand potential differences in therapeutic responses of these SCLC subtypes are warranted.

Sarah Seton-Rogers

ORIGINAL ARTICLE Yang, D. et al. Intertumoral heterogeneity in SCLC is influenced by the cell type of origin. *Cancer Discov.* https://doi.org/10.1158/2159-8290.CD-17-0987 (2018)
FURTHER READING Gazdar, A. F. et al. Small-cell lung cancer: what we know, what we need to know and the path forward. *Nat. Rev. Cancer* **17**, 725–737 (2017)

IN BRIEF

TUMOUR SUPPRESSORS

SPOP mutations disrupt phase separation

Speckle-type POZ protein (SPOP) is the substrate-binding subunit of a cullin 3 (CUL3)-based E3 ubiquitin ligase complex and is commonly mutated in prostate cancer, as well as in other solid tumours. SPOP mutations block substrate recruitment and lead to the accumulation of various proto-oncogenic proteins, but how SPOP recruits substrates is not known. Bouchard, Otero et al. find that substrate binding is necessary for SPOP complexes to accumulate in membrane-less organelles formed by phase separation. Cancer-associated SPOP mutations disrupt SPOP–substrate co-localization and phase separation, thus reducing ubiquitylation and degradation of substrates. This better understanding of the molecular mechanisms involved in substrate accumulation in SPOP-mutant cells might inform the development of therapies for cancers driven by SPOP mutations.

ORIGINAL ARTICLE Bouchard, J. J., Otero, J. H. et al. Cancer mutations of the tumor suppressor SPOP disrupt the formation of active, phase-separated compartments. *Mol. Cell* **72**, 19–36.e8 (2018)

TUMOUR IMMUNOLOGY

New targets for cancer immunotherapy

Resistance to immune checkpoint inhibitors has hampered their clinical success. Thus, there has been an impetus to find new targets acting on tumour-specific T cells. One set of potential targets are the CD33-related sialic acid-binding immunoglobulin-like lectins (Siglecs), which function as pattern recognition immune receptors. Siglecs bind to a variety of sialoglycan ligands, which serve as self-associated molecular patterns. Stanczak et al. identified that Siglec-9 is upregulated on tumour-infiltrating T cells from patients with non-small-cell lung cancer (NSCLC) and colorectal and ovarian cancer compared with the low-level expression on normal T cells. Moreover, in patients with NSCLC its expression was correlated with decreased survival. The sialoglycan–Siglec pathway was shown to mediate immune evasion in vivo and, importantly, could be targeted both in vitro and in vivo to improve anticancer immune responses.

ORIGINAL ARTICLE Stanczak, M. A. et al. Self-associated molecular patterns mediate cancer immune evasion by engaging Siglecs on T cells. *J. Clin. Invest.* https://doi.org/10.1172/JCI120612 (2018)

PROTEIN TRANSLATION

Oncogenic mRNA modification explained

The N^6-methyladenosine (m^6A) methyltransferase METTL3 promotes translation of oncogenes and is tethered to respective promoters. The mechanism by which m^6A modification of mRNA through METTL3 promotes translation of target mRNAs has been identified in a recent paper published in *Nature*. Choe, Lin et al. show that METTL3 can only promote translation if bound to the 3′ untranslated region near the stop codon of the target mRNA. METTL3 interacts with the eukaryotic translation initiation factor 3 subunit h (eIF3h) in close proximity to the cap-binding protein, thereby promoting mRNA looping. eIF3h was needed for METTL3-mediated enhanced translation of a wide range of genes involved in tumour progression and apoptosis, including bromodomain-containing protein 4 (BRD4). METTL3 overexpression promoted invasion of mouse embryonic fibroblasts in vitro and tumour growth in vivo, for which interaction with eIF3h was required. Whether this interaction is targetable remains to be shown.

ORIGINAL ARTICLE Choe, J., Lin, S. et al. mRNA circularization by METTL3–eIF3h enhances translation and promotes oncogenesis. *Nature* **561**, 556–560 (2018)