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### DECODING THE METHYLOME IN MANTLE CELL LYMPHOMA: CLOSE INFLUENCE OF B-CELL DIFFERENTIATION AND CLINICAL RELEVANCE

The hallmark of mantle cell lymphoma (MCL) is the t(11;14)(q13,q32) translocation, which leads to the juxtaposition of *CCDN1* to the IgH promoter locus, resulting in cyclin D1 overexpression. However, studies from transgenic mouse show that additional secondary genetic events are required for oncogenic transformation. Epigenetic dysregulation is an important mechanism of oncogenesis and tumour progression, but there are only few genome-wide studies of DNA methylome in MCL and mainly focused on promoter regions. In an elegant article published in *Cancer Cell*, Queirós *et al*<sup>1</sup> studied the genome-wide methylation profiles of 82 MCL cases using microarray containing approximately 450 000 CPG sites across the genome. They developed a novel computational strategy to isolate tumour DNA methylation changes from normal cells, in a so called ‘in silico purification’. Based on this strategy, the MCL samples were clustered into two groups—C1 and C2, which display similar methylation patterns to normal germinal centre (GC) inexperienced and GC experienced B cells, respectively, indicating a different B-cell origin. Both groups were highly heterogeneous and this also translated into distinct clinical–biological features, as IgVH mutational status, *SOX11* expression, nodal presentation and worse survival for C1 patients.

To identify tumour-specific alterations (TSA) from their normal counterpart, the authors compared data obtained from the MCL tumour cells with those coming from different B-cell subpopulations, ranging from haematopoietic progenitor cells to plasma cells. They found that 61%–79% of methylation changes CpGs overlapped with those acquired during B-cell differentiation and were enriched for enhancer elements, whereas the rest of 21%–39% were strictly tumour specific. Overall, hypomethylation in MCL in both the B-cell-related compartment changes and the TSA was enriched in enhancer elements. On the other hand, hypermethylated CpGs in the B-cell related were located in

H3Hk27me3-repressed and poised promoters, whereas TSA were mostly associated with poised promoters. Furthermore, one patient forms each C1 and C2 groups were subjected to whole-genome bisulfite sequencing. By using the haematopoietic progenitor cells as a point of reference, they showed that up to 92% of differentially methylated regions overlapped with those acquired during B-cell differentiation, and TSA were rare event. However, when they compared these TSA with the histone modification patterns, the authors were able to identify recurrent TSA that may have functional impact. Thus, a cluster of hypomethylated TSA located 650 kbp from *SOX11* was identified only in *SOX-11* expressing cases and showed enhancer elements. Finally, the authors showed that epigenetic burden as the number of differentially methylated sites had a prognostic impact in terms of survival, as C1 group had a worse survival than C2 patients. Within the C2 group, epigenetic changes identified a subset of patients with increased cell proliferation. Epigenetic burden was also found to be the strongest independent marker for clinical outcome in multivariate analysis, which included six important variables. This work outlines two important conclusions: first, the importance of performing an integrative whole-genome analysis combining methylation, histone modifications, 3D looping and gene expression to identify distant regulatory elements associated with MCL, and second, the extensive epigenetic changes and their clinical impact on survival is opening up the idea that some patients may benefit from drugs acting at the epigenetic level. Therefore, further methylation studies are needed in the context of well-designed clinical trials with new targeted agents, such as B-cell-receptor-targeted agents.

### HOW TO USE IMMUNOTHERAPY IN THE PERIOPERATIVE SETTING: NEOADJUVANT IMMUNOTHERAPY SEEMS TO BE MORE EFFICACIOUS THAN ADJUVANT IN ELIMINATING MICROMETASTATIC DISEASE

The use of immunotherapy is progressively expanding for the treatment of advanced cancers. However, its role as complementary

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to surgery to help in controlling micrometastatic disease is far from being established, except for adjuvant ipilimumab in melanoma. Investigators from Queensland University in Australia in cooperation with researchers at the University of Juntendo in Japan developed two animal models, to which triple negative breast cancer tumours were implanted to study the potential advantage of immunotherapy as neoadjuvant versus postoperative.<sup>2</sup> In a first setting of experiments, they applied depletion of regulatory T cells as the simplest manipulation and most effective immunotherapy to relieve tumour-induced immunosuppression, given it suppresses the antitumour activity of different immune cell types. The authors demonstrated that a proportion of mice that received neoadjuvant or adjuvant depletion of T regulatory cells had significantly improved long-term survival (>250 days) compared with the control group that received phosphate buffer solution (PBS), where all mice died by day 100. More striking was the result from the neoadjuvant T regulatory cells-depleted group, where almost all mice (19/20) displayed long-term survival compared with adjuvant T regulatory cells-depleted mice.

However, the benefit of neoadjuvant immunotherapy was not limited to regulatory T cells depletion, which is, at this moment, not feasible in the clinic, but included also the use of anti-PDL1 antibodies as well as anti-CD137. When both tumour models were treated in the neoadjuvant setting with the combination of both agents, the survival of treated animals was significantly superior to those treated postoperatively. The authors also showed that the improvement in survival in favour of the neoadjuvant immunotherapies was not due to differences in micrometastatic tumour burden. When mechanistic studies were performed, neoadjuvant immunotherapy depends on CD8<sup>+</sup> cells and interferon. Interestingly, neoadjuvant immunotherapy clearly increases tumour-specific CD8<sup>+</sup> cells in peripheral blood and organs such as lung and liver. Moreover, mice with high levels of tumour-specific CD8<sup>+</sup> T cells in blood, when measured early after neoadjuvant immunotherapies, were predicted to survive long term, indicating that those CD8<sup>+</sup> T cells could be potential biomarkers for outcome. In an accompanying editorial by Melero *et al*<sup>3</sup> the findings of this study are underscored and the importance of conducting clinical studies to assess the value of neoadjuvant immunotherapy is reinforced.

## LIQUID BIOPSIES TO DETECT DIFFERENT DNA COPY NUMBER PROFILES IN PATIENTS WITH CHEMOSENSITIVE VERSUS CHEMOREFRACTORY SMALL CELL LUNG CANCER

The genomic landscape of small cell lung cancer (SCLC) is not as well characterised, as compared with non-SCLC. This fact may be due by the scarcity of surgical resections and in general by the poor quality of tumour biopsies in this disease. However, some studies indicate that more than 90% of patients with SCLC do present mutations in RB1 and p53. However, studies relating specific genetic abnormalities with clinical outcome in SCLC are limited. To expand on the knowledge of this area, investigators

at the University of Manchester recently published a report in *Nature Medicine* to describe genomic alterations able to distinguish between chemosensitive and chemorefractory SCLC using circulating tumour cells (CTCs), which are frequently present in this type of tumour.<sup>4</sup> The authors examined copy-number alterations in CTCs from pretreatment SCLC blood samples. After studying a training set, they developed a classifier based on copy-number alterations. When applying this classifier also to a validation set of patients, they were able to identify chemosensitive versus refractory tumours in 83% of them. Progression-free survival was significantly superior in patients classified as chemosensitive. Of interest, a group of patients initially considered as chemosensitive became resistant after several months of standard chemotherapy and were reanalysed according to the copy-number classifier. None of them acquired the chemoresistant genotype initially detected in primary resistant patients, indicating, therefore, different mechanisms for primary versus acquired resistance.

The authors underlined the major advantage of blood sampling for CTC profiling, indicating the ease of availability of longitudinal samples to investigate tumour evolution and mechanisms of acquired chemoresistance. The results presented demonstrate that genetic changes in baseline CTCs correlate with clinical outcome, and they represent a first step towards the identification of an objective biomarker that may define the chemosensitivity of an individual's SCLC before the start of treatment. As the understanding of this difficult disease evolves, the authors anticipate that a more precise molecular classification of patients with SCLC will emerge and be of value for the stratification of patients in clinical trials and the development of precision medicine.

**Contributors** All authors contributed equally.

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