Editorial

T-cell responses to small cell lung cancer: the immune system and the tumor are two sides of the same coin

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Reliable prediction of the success of treatment of small cell lung cancer (SCLC) patients with immune checkpoint inhibitors (ICIs) would improve the treatment of these patients enormously. Balbach *et al.* studied the T-cell receptor (TCR) repertoire in SCLC patients with the aim to link TCR diversity to clinical outcomes. They studied 14 patients of which 5 with chemotherapy followed by treatment with ICIs (1). The study was motivated by the finding that in non-small cell lung cancer (NSCLC) TCR repertoire diversity of peripheral T-cells is a positive predictor of the success of treatment with ICIs (2). Other data already showed that TCR diversity of tumor infiltrating lymphocytes are predictive for better clinical outcomes in cancer patient treated with or without immunotherapy (3).

Balbach *et al.* did not find a correlation between TCR repertoire diversity and clinical outcomes. But this should not be the end of the story, particularly since immunotherapy may finally be an effective treatment of SCLC.

SCLC is a very aggressive form of cancer due to resistance to chemotherapy and subsequent rapid spreading of metastatic disseminations. SCLC represents about 15% of all lung cancer cases and annually kills about 250,000 people, worldwide. At the initial diagnosis metastatic lesions are already present in about two thirds of the patients. Most patients respond well to initial chemotherapy, but after the development of metastatic lesions patients die at a median of 10 to 12 months after diagnosis. Over many decades survival rates have not improved and by U.S. law it is a 'recalcitrant cancer'. During the past years, considerable progress has been made in the treatment of other tumor types by the introduction of immunotherapy. This was successful since tumor cells often contain mutated proteins which are recognized by cytotoxic T cells as foreign, leading to the death of the tumor cells. The tumor environment inhibits the T-cells, but this can be overcome by ICIs. SCLC is no exception in that it has many mutations and clinical trials for SCLC showed some effects, but improved overall survival (OS) were limited to just a few months (4). However, results differ between subtypes of SCLC. Histologically and genetically SCLC is homogeneous and until recently SCLC was approached as a single disease entity with a 'one-size-fits-all' treatment. Recent insights, both from human data and mouse models showed that there are various subtypes of SCLC, based on the presence of transcription factors (5-7).

Within a single tumor multiple subtypes may exist, and conversion between subtypes of SCLC occurs. Importantly, these subtypes differ in response to therapy (8) and survival

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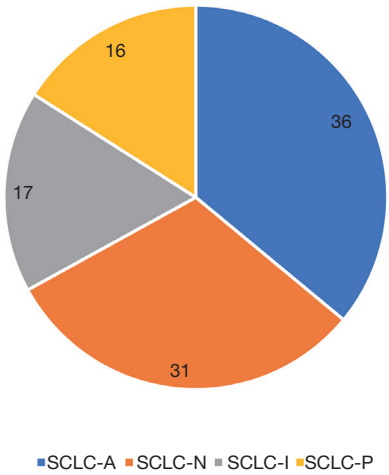

Figure 1 Transcriptional subtypes of SCLC. Data from (8). The distribution is approximate, dependent on the selection of SCLC samples. SCLC, small cell lung cancer.

rates (9). *Figure 1* gives a summary of subtypes found in SCLC cell lines and tumors. The shown subdivision is based on the dominance of transcription factors: ASCL, NEUROD1, POU2F3 in SCLC-A, SCLC-N and SCLC-P, respectively and the absence of a dominant factor in SCLC-I. The first three groups have a neuroendocrine phenotype. They express the biomarkers chromogranin, synaptophysin and NCAM (CD56). At the same time, they are restricted in the expression and presentation of antigens mediated by major histocompatibility complex (MHC) class I molecules, making them resistant to immunotherapy. The SCLC-I subclass lost it neuroendocrine properties. It is less sensitive to chemotherapy, but regained the capability to synthesize MHC 1, process protein antigens, and present the resulting peptides on the cell surface bound to MHC 1. This makes them sensitive to immunotherapy (8). The implication of this finding is that, to make predictions on the success of ICI treatment not only the T-cells but also the tumor cells should be characterized.

What are important considerations for a new program to identify patients that may benefit from ICI treatment?

(I) Start with determining the tumor subtype. Is it 'hot', that means SCLC-I or does it belong to one of the other 'cold' subtypes that are unable to process and present tumor antigens? In the latter case it is unlikely that ICI treatment will have added value.

(II) Carry out the TCR typing. Alternatively, a more direct approach can be chosen, e.g., *ex vivo* killing of tumor cells by T-cells (10).

(III) Consider to use epigenetic drugs to make 'cold' tumors 'hot'. This work is still in a pioneering phase, but initial results indicate that this is in principle possible (11).

Additional considerations are: the need to investigate larger numbers of patients. With the present numbers there is a chance to miss 'hot' tumors. Another unknown is whether the analysis of peripheral T-cells is predictive for tumor infiltrating lymphocytes.

This program represents a considerable amount of work. I am not suggesting that Balbach *et al.* are obliged to carry this out. However, they made a start and hopefully discussions and further actions to improve the therapy of SCLC will follow.

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