Establishment and characterization of patient-derived malignant pleural mesothelioma cell lines and the development of novel therapeutic options using a high-throughput repurposing drug screen

Alexander Laure

Malignant pleural mesothelioma has a very poor prognosis: 50% of the patients die within 12 months after starting first-line treatment and no improvement in survival has been reached with second-line treatment. Hence, robust preclinical models to develop new therapeutic strategies are urgently needed for these patients. To date, limited data on screening for new treatment options using high-throughput approaches are available for MPM performed on highly passaged commercial cell lines. The use of these cell lines has to be questioned, as they do not closely resemble the originating tumor anymore.

To understand the reliability of preclinical models for MPM studies, we have performed whole transcriptome and whole exome analysis of fresh frozen MPM tumors and compared them to cell lines generated from these tumors as well as commercial cell lines. The established patient-derived cell lines were used to develop a robust cell viability assay for a high throughput repurposing drug screen, using a set of 6'500 chemical compounds including FDA-approved drugs and candidates in clinical development.

The sequencing results identified that patient-derived cell lines correlate to a high degree with their originating tumor. Using patient-derived cell lines, 11 promising compounds were identified in the high throughput drug screen to be repurposed in MPM. To validate the viability inhibiting potential of these drugs, 21 additional MPM cell lines were screened and revealed Regorafenib, Rigosertib, and NSC663284 as the most potent candidates.

These results are of major relevance for the scientific community regarding using cell lines as an appropriate model, resembling the pathway of interest. We could demonstrate that a robust high-throughput drug repurposing screen can be an effective tool to find new treatment candidates for MPM. Further, we show that low cGAS expression at baseline is favourable for PFS in MPM patients. This may provide new insights to predict the response to chemotherapy of MPM patients and to the pro-tumorigenic role of high cGAS levels in these patients.

Jury:

Prof. Dr. Alessandra Curioni-Fontecedro (thesis supervisor)

Prof. Dr. Olivier Michielin (external co-examiner)

Prof. Dr. Curzio Ruegg (internal co-examiner)

Prof. Dr. Jens Volker Stein (president of the jury)