The search for new treatment strategies for malignant pleural mesothelioma

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Thesis Outline

My research has focused on a relative unknown tumor type: malignant pleural mesothelioma (MPM). Mesothelioma is an aggressive tumor of the mesothelial cells lining the pleura, peritoneum, pericardium and tunica vaginalis. Accounting for 70% of all cases, the most common form is MPM.

MPM is strongly associated with exposure to asbestos. Although the use of asbestos is banned in most developed countries, Russia, China, Brazil, and Kazakhstan continue to produce asbestos for the use in developing countries. Due to the latency period between exposure and presentation of the tumor, ranging from 20 to 50 years, the incidence of MPM has slightly increased over the last years. In 2015, the incidence in Europa was 3 cases per 100.000 persons.

Histologically, MPM is classified in three subtypes; epithelioid type (60% of the cases), sarcomatoid type (20% of the cases), and biphasic type (20% of the cases), the latter containing both epithelioid and sarcomatoid cells. Survival is associated with histological subtype, with epithelioid MPM having the best prognosis and sarcomatoid MPM the worst. The overall median survival is 12-15 months, when patients receive first-line chemotherapy. This first-line chemotherapy consists of a platinum-based combination with an anti-folate. Since the last 15 years, no further improvement in second-line therapy has been realized.

The poor prognosis of patients with MPM indicates the importance to find more effective treatments for this patient population. Therefore, this thesis focused on finding new treatment strategies for patients with MPM.

Chapter 1 gives an overview of the efforts made in testing new treatments in MPM (till 2016), both on the clinical as well as on the translational level.

Chapter 2 presents a method in which primary MPM cultures were chemically profiled to determine second-line treatment for patients. With this personalized treatment strategy we were able to predict individual patient responses to selected drugs. Based on chemical profiling, MPM could be subdivided in three groups, so called; responders, intermediate responders and non-responders.

This model together with cell line and mouse models, also identified a novel targetable pathway in MPM. In **Chapter 3**, an FGFR inhibitor-sensitive subgroup is identified by combining high-throughput drug screens, comprehensive molecular characterization and functional assays. BAP1 protein could serve as a potential biomarker to select patients for FGFR inhibitor treatment.

In **Chapter 4**, a different treatment strategy is tested. We show that the 5T4 antigen is expressed in MPM cells and internalized upon binding by specific antibodies. By targeting 5T4, with antibody-drug conjugates (ADC), high 5T4 expressing MPM cells were effectively killed, showing a promising novel strategy in the treatment of this tumor type.

Although the mutational load in MPM is intermediate, BAP1 is identified as one of the molecular targets in the treatment of MPM. **Chapter 5** describes the multiple interaction partners of BAP1 as well as proteins under influence of BAP1. The phenotypic effect of BAP1 is diverse, but pre-clinical data on inhibitors reversing these phenotypic effects is promising.

Finally, **Chapter 6** discusses how the different treatment strategies described in this thesis may ultimately contribute to improve survival outcome for patients with MPM. Furthermore, it discusses which other treatments are tested in patients with MPM and what would be necessary to improve survival outcome in this patient population.