Molecular and cellular landscape of pulmonary and hepatic metastases of colorectal cancer with potential clinical implications

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Colorectal cancer (CRC) is one of the most frequently diagnosed cancers as well as the second cause of cancer-related mortality in both men and women. Localised disease is associated with a relatively good prognosis, yet, about a third of patients develop metastatic relapse at some point. Sadly, metastatic CRC (mCRC) patients demonstrate tremendously poor outcomes, with 5-year overall survival rate of only 14%. This is mainly due to excessively limited targeted therapeutic options for CRC, resulting from both lack of druggable targets and the presence of molecular alterations precluding any benefits from currently available therapies.

Liver is the most frequent site of distant CRC metastases, followed by lung and peritoneum. Of note, concurrent liver and lung metastases are diagnosed in 1 out of 5 of patients. Current knowledge of mCRC is limited to the molecular characterization of primary tumours and (to a much lesser extent) of liver metastases. The biology of pulmonary metastases of CRC remains vastly undiscovered. Overall, isolated lung metastases tend to have a slightly better prognosis than isolated liver metastases, while the involvement of both is associated with particularly poor outcomes. Yet, the mechanisms underlying metastasis formation at either site have not been determined. Thus, the understanding of molecular and cellular landscapes of CRC metastases is critical to successfully tailor therapeutic strategies against this heterogeneous disease.

The proposed project aims at comprehensive molecular and cellular characterization of CRC metastases in liver and lungs (both isolated and concurrent). To this end, metastatic tissue samples will be subjected to high-throughput transcriptome profiling. In parallel, the study cohort will undergo a thorough histological and immunohistochemical characterisation. Based on the generated data, various bioinformatics and biostatistics approaches will be employed to identify the site-specific molecular and cellular signatures of CRC dissemination to lung or liver.

To conclude, the project aims at providing the missing knowledge on the biology of mCRC and identifying potential systemic markers of metastatic disease. Apart from the benefits in the field of basic science, the results will possess considerable translational value, as they may provide novel rationales for precision oncology approaches.