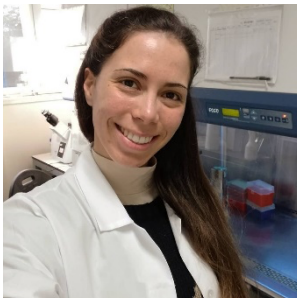
COLORECTAL CANCER-LIVER AXIS ON CHIP TO STUDY METASTASIS PROCESSES



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The metastatic process remains one of the important reasons for cancer-related death. Many solid tumors, including Colorectal cancer (CRC), metastasize to the hepatic level due to the anatomical localization concerning the portal circulation as well as tumor permissive microenvironmental properties. In addition, it is widely accepted that cancer progression and metastatic process are influenced by several phenomena that take place in the tumor microenvironment (TME), such as the ECM remodeling, activation of the host cells and, epithelial-mesenchymal transition (EMT) processes, supporting cell growth, invasion and colonization from the primary tumor site to another organ target. Since most of the patients still have poor prognoses after metastasis, the need to understand the mechanisms underlying liver metastases is mandatory to improve the drug development and screening.

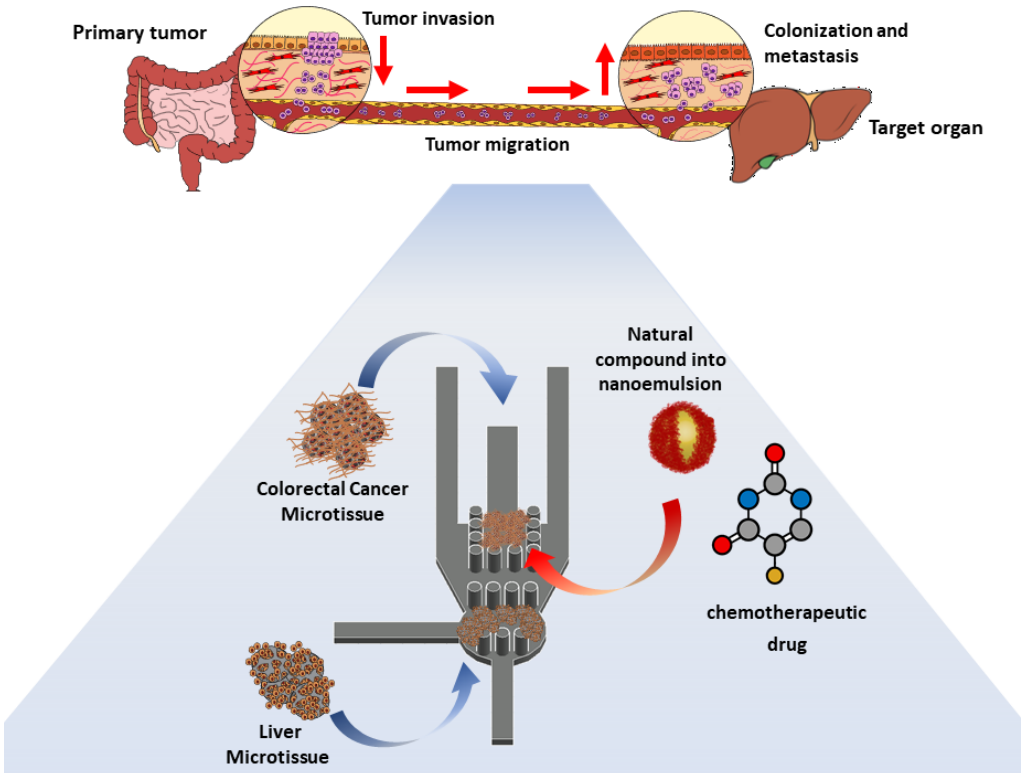
As recognized, current animal and 2D in vitro models used in cancer research poorly mimic human cancer physiology. We have previously demonstrated that 3D organotypic tumor models can help to understand the complex mechanisms underpinning cancer progression, reproducing the morphological changes of epithelial cells and stromal activation in the EMT process in long time. Recently, in vitro 3D models, such as multi-organ-on-a-chip, have become a potential tool to reproduce the cross-talk between primary tumor and the distant metastatic niche formation in secondary site of human body. However, these models don't recapitulate the complexity of tumor microenvironment and the metastatic cascade that occurs in native tissue, due to the use of exogenously produced ECM.

In this direction, the main purpose of my P.h.D. was to exploit the multi-organ-on-a-chip technology to faithfully reproduce in vitro the "spontaneous formation of micro-metastases" on chip , by integrating a human colorectal cancer model into a custom made microfluidic device to investigate the migration of metastatic cells from primary to target tissue as well as the role of TME in cancer progression and metastasis process. In addition, this multi-compartmentalized microfluidic device was able to investigate the bidirectional crosstalk between primary tumor and target organ in terms of paracrine stimuli that play a key role in the metastatic processes. This device can be used as a suitable platform for several applications, such as drug and/or natural compounds testing and high-throughput screening with the aim to improve the efficiency in translating new treatment options to clinical success.

The first year of the PhD was primarily focused on the production and characterization of 3D human Colorectal cancer microtissues co-culture (CRC-µTPs) obtained by seeding intestinal myo-fibroblasts and colon-rectal cancer cells on porous biodegradable gelatin microbeads in dynamic conditions. In these conditions the epithelial cells grown on mesenchymal cells that are induced to continuously synthesize and assemble their own ECM. Then, a 3D human hepatic model was also developed by using spinner flask dynamic culture.

The second year of the PhD was focused on the production of colon-liver axis biochip in which was analyzed the spontaneous formation of micro-metastases from CRC-µTPs to liver microtissue. To this aim a compartmentalized microfluidic device was designed and fabricated in order to host the two organs. In this perspective, CRC µTPs and Liver µTPs were perfused in microfluidic platform in order to investigate and detect the chemoattractant agents that promote the preferential route of the cancer cell migration from primary tumor tissue (Colorectal cancer) to target organ (Liver).

Then, in the third and final year of this PhD research work, the hCRLM-on-a-chip will be validate and used as platform for drug and or natural compounds testing and high-throughput screening to investigate their actions and effects on the cancer progression and metastasis process. In this direction, preliminary chemotherapeutic drug was tested on 2D cell culture models in order to select the best concentration to translate these treatments on a microfluidic platform. In addition, natural compound encapsulated into nanoemulsion will tested in order to reduce the cytotoxic effect or to improve the efficacy of conventional chemotherapeutical agents as widely reported Furthermore, these compounds will be used to analyze the prevention of hepatotoxicity into the hCRLM-on-a-chip.



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