

Molecular Mechanisms Mediating Brain Metastasis Colonization

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Master thesis in Experimental Biomedical Research

Cancer is a group of diseases characterized by abnormal and uncontrolled cell growth and the ability to start spreading into nearby tissues. Breast cancer arises from breast epithelial cells, and it is the most common type of cancer across women. The real issue related to cancer in general is the formation of metastasis. Metastasis are caused by tumour cells that disseminated into a distant organ and were able to colonize and grow into a new environment, resulting in the disruption of vital organs, which, in most cases, leads to death. Breast cancer generally metastasizes primarily to the liver, lungs, and bones. Moreover, metastasis to the brain is a frequent late form of breast cancer metastasis, occurring in about 20-25% of patients. It is also the most severe complication of metastatic breast cancer, leading to death within 4–6 months upon diagnosis. There is therefore an unmatched need to define novel therapeutic strategies for brain metastasis.

One novel models to investigate and validate cellular and molecular mechanisms mediating brain metastasis formation have been developed by Prof. Dr. Curzio Rüegg, Dr. Girieca Lorusso and Dr. Christof B. Wyss. Using this model, they uncovered two related molecular mechanisms of breast cancer brain metastasis. The first reported mechanism involved the gap junction molecule Cx31, which favours brain metastasis colonization and progression through multiple mediators including increased levels of laminin 5 expression. The second one focused on the transcriptional activation of NF- κ B and HIF-1 that creates a favourable environment for brain metastasis proliferation. These studies have identified the target FAK or Pdgfr that can be pharmacologically targeted to prevent progression of brain metastases in mice. The role of NF- κ B or FAK in controlling laminin 5 expression was not addressed.

Hence, the aim of this Master Project is to investigate the effects of FAK/NF- κ B axis inhibition upon both pharmacological (FAK) and genetic approaches (FAK and NF- κ B) on laminin 5 protein production and deposition in the brain. The study hypothesizes that FAK modulates laminin 5 and therefore, helping the development of a favourable niche for disseminated metastatic cells to colonize and proliferate into the brain.

Results show that pharmacological and genetic inhibition of FAK impinged on the expression of key genes playing a crucial role in brain metastasis formation and colonization. In particular, the production and deposit of laminin 5 was drastically decreased.

In conclusion, FAK can be considered to regulate laminin 5 production and deposition, therefore, favouring the formation of a favourable niche for brain metastasis colonization. These results support the notion of targeting FAK with small molecular kinase inhibitors to halt brain metastasis formation and progression in patients.

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