The influence of non-coding RNAs on breast cancer stem cell metabolism and survival

Summary

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Supervisor:	Prof. Dr. Martin Pichler
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Background:

Breast cancer is the most common diagnosed human cancer in women worldwide. Surgery of the primary tumor in combination with neoadjuvant/adjuvant medical treatment is the treatment of choice in localized stages with the aim of curative chances. Although several patients are cured by this treatment modality, some of them develop metastatic disease or are already diagnosed with primary metastatic breast cancer. Metastatic breast cancer is an incurable disease in all patients. In general, breast cancer is very heterogeneous in terms of underlying genetics and biology, treatment strategy and patients clinical outcome. In clinical routine, breast cancer is subdivided in three main subtypes based on the receptor profile of estrogen, progesterone and Her2/neu receptor. A lack of these three receptors on cancer cells leads to the diagnosis of “triple negative breast”. Triple negative breast cancer accounts for about 10-15% of all breast cancer cases. However, this subtype is frequently found in young women, has an aggressive biology, poor prognosis and due to a lack of identified molecular targets, cytotoxic chemotherapy is the mainstay of therapeutic intervention. For more than three decades, malfunctions of protein-coding oncogenes and tumor suppressors genes have been considered as the genetic causes of tumorigenesis. More recent development is molecular biology proved without doubts that cancer is a complex genetic disease involving structural and expression abnormalities of both coding and non-coding RNAs. Non-coding RNAs are defined as trancripts that fullfill their function without translation to a respective protein. Recently, the idea that long non-coding RNAs are involved in human tumorigenesis was proven.

Hypothesis and Objectives:

The central hypothesis of this PhD thesis is to determine the role of short and long non-coding RNAs in triple negative breast cancer biology and tumor metabolism and by doing so, discover novel therapeutic vulnerabilities to tackle this deadly disease.

Methodology:

Based on a plenty of pre-liminary data genome-wide expression data derived from a 3-dimensional growth cancer stem cell model system – a system commonly referred to cancer stem cell features – the student will determine the biological function of a selected number of promising non-coding RNA candidates with a special focus on tumor metabolism (glucose, glutaminolysis) and cancer stem cell biology. In this aim, he/she will apply techniques of gain and loss of function (SiRNA, shRNA, lentiviral overexpression techniques, molecular cloning, CRISPR/Cas9) and cellular assays (proliferation, apoptosis, autophagy, senescence, migration/invasion, stem cell self-renewal) in vitro and in vivo (mouse models). Second, long non-coding RNA relevant in breast cancer biology will be further tested for molecular interaction partners with a special focus on druggable proteins/signaling pathways. The methods used in this aim will comprise traditional techniques in molecular biology (qRT-PCR, Western blot) and more focused techniques on RNA-Protein interaction (RIP, pull-down assays, CHIP). Last but not least, we will test in international collaborative efforts with leading cancer centers in the US RNA-therapeutics in combinatorial approaches with metabolic drugs for their therapeutic potential using mouse models.

References:

1. Rigoutsos I, Lee SK, Nam SY, Anfossi S, Pasculli B, Pichler M, Jing Y, Rodriguez-Aguayo C, Telonis AG, Rossi S, Ivan C, Catela Ivkovic T, Fabris L, Clark PM, Ling H, Shimizu M, Redis RS, Shah MY, Zhang X, Okugawa Y, Jung EJ, Tsirigos A, Huang L, Ferdin J, Gafà R, Spizzo R, Nicoloso MS, Paranjape AN, Shariati M, Tiron

A, Yeh JJ, Teruel-Montoya R, Xiao L, Melo SA, Menter D, Jiang ZQ, Flores ER, Negrini M, Goel A, Bar-Eli M, Mani SA, Liu CG, Lopez-Berestein G, Berindan-Neagoe I, Esteller M, Kopetz S, Lanza G, Calin GA. N-BLR, a primate-specific non-coding transcript leads to colorectal cancer invasion and migration. Genome Biol. 2017 May 24;18(1):98. doi: 10.1186/s13059-017-1224-0

2. Stiegelbauer V, Vychytilova-Faltejskova P, Karbiener M, Pehserl AM, Reicher A, Resel M, Heitzer E, Ivan C, Bullock M, Ling H, Deutsch A, Wulf-Goldenberg A, Adiprasito JB, Stoeger H, Haybaeck J, Svoboda M, Stotz M, Hoefler G, Slaby O, Calin GA, Gerger A, Pichler M. miR-196b-5p Regulates Colorectal Cancer Cell Migration and Metastases through Interaction with HOXB7 and GALNT5. Clin Cancer Res. 2017 Sep 1;23(17):5255-5266. doi: 10.1158/1078-0432.CCR-17-0023
3. Pichler M, Stiegelbauer V, Vychytilova-Faltejskova P, Ivan C, Ling H, Winter E, Zhang X, Goblirsch M, Wulf-Goldenberg A, Ohtsuka M, Haybaeck J, Svoboda M, Okugawa Y, Gerger A, Hoefler G, Goel A, Slaby O, Calin GA. Genome-Wide miRNA Analysis Identifies miR-188-3p as a Novel Prognostic Marker and Molecular Factor Involved in Colorectal Carcinogenesis. Clin Cancer Res. 2017 Mar 1;23(5):1323-1333. doi: 10.1158/1078-0432.CCR-16-0497.