Temat "Analiza roli cyklicznego RNA MALAT1 w przerzutach raka piersi do mózgu"

Temat badawczy realizowany będzie pod kierownictwem dr hab. Agnieszki Bronisz (promotor główny) i dr Jakuba Godlewskiego (promotor dodatkowy) w ramach konkursu OPUS pt. "Kontrola dojrzewania microRNAome i jej zastosowanie w celowanej terapii nowotworowych komórek macierzystych" nr rej. 2020/39/B/NZ5/02893.

ABSTRACT: Breast cancer was the most commonly diagnosed cancer in 2020 worldwide (over 2.2 million cases; 11,7% of total cancer cases). At the same time, 380,000 deaths were recorded as a result of breast cancer, and the figure is estimated to reach 550,000 by 2030. Thus, breast cancer is a first-tier healthcare problem and the increasing number of cases as well as high mortality underlines the urgent need to develop new therapeutic approaches. The treatment of breast cancer subtype known as basal-like still constitutes a great challenge for modern medicine. Importantly, this subtype frequently metastasizes to distant locations, including the brain. Overall, breast-to-brain metastatic (BTB met) cancer is associated with poor prognosis and high mortality with a median survival of only 4-6 months despite aggressive chemotherapeutic treatment. Thus, the quest for new therapeutic targets in BTB met cancer is of critical importance. A large body of evidence suggests that non-coding RNAs are involved in the global regulation of cellular phenotypes, including in cancer cells, and these RNAs were shown to participate in breast cancer initiation, progression, and metastasis. Numerous classes of functional non-coding RNAs have been found, including microRNAs, long noncoding RNAs, and, recently, circular RNAs. Our team showed that the circular form of MALAT1 (denoted as circ2082) is responsible for the loss of microRNAome in glioblastoma stem cells, acting through nuclear DICER retention, and thereby boosting their tumorigenic potential. DICER is a crucial enzymatic complex involved in the processing of pre-microRNAs into mature microRNAs in the cytoplasm, therefore, its nuclear retention disrupts microRNAome homeostasis. MicroRNAs play a key role in the regulation of proliferation, differentiation, as well as apoptosis, while their dysregulation promotes cancer progression, metastasis and induces treatment resistance. Additionally, our team's study showed the de-regulation of single microRNA sensitizes glioblastoma cells to conventional therapy. Thus targeting microRNAs, or in this case - elements regulating microRNAome composition may affect the broad range of cellular processes, leading to a more benign setup and sensitization to chemotherapy. In a set of pilot experiments, we detected concurrent de-regulation of the microRNAome and high expression of circ2082 in patient-derived BTB met cells. Taking into account the preliminary data and previous publications of our team on glioblastoma, we hypothesize that circ2082 participate in molding the phenotype and molecular landscape of BTB met cancer. Our concept is to characterize BTB met cell lines and identify the mechanism of microRNAome deregulation which could contribute to the identification of the bona fide therapeutic target. A crucial element in achieving this goal is the "know your enemy" approach. The presence of the stem cell population is the main limitation of the therapy, due to their chemoresistance, therefore, determining the balance between stemness/differentiation in BTB met cells is essential to understand their nature and susceptibility to treatment. Preliminary studies have also shown the deregulation of microRNAome composition; thus, we aim to determine the mechanism of this phenomenon scrutinizing the role of circ2082 upregulated in these cells. Finally, we will evaluate the effect of circ2082 knockdown on response to chemotherapy. In summary, this proposal is designed to provide crucial missing information on BTB met cancer that remains a formidable challenge to modern medicine and science.

WYMAGANIA:

- doświadczenie w metodach biologii komórki (hodowla pierwotych komórek nowotworowych, testy na przeżywalność, klonalność, migracje, lekooporność) i biologii molekularnej (izolacja RNA, qPCR),
- doświadczenie w modelach nowotworowych in vitro i in vivo (praca ze zwierzętami)
- Bardzo dobra znajomość angielskiego (w stopniu umożliwiającym prezentacje wyników, pisanie publikacji i projektów badawczych