Abstract

Colorectal cancer (CRC) is third the most common cancer in the world and the second most common cause of cancer deaths. One of the significant risk factors for developing colorectal cancer is obesity. Excess body weight not only increases the chance of developing CRC, but also accelerates its progression, increases patients' resistance to treatment and the risk of disease recurrence.

Obesity is considered as a global pandemic. It is defined as an abnormal and excessive accumulation of adipose tissue (AT). White adipose tissue, in addition to storing energy in the form of lipid droplets, is also a secretory organ. It releases molecules, that might act locally or peripherally on various cells. Under the excess calories, AT, which consists of various cellular elements (adipocytes, fibroblasts, immune system cells, etc.) and non-cellular elements (extracellular matrix, biologically active molecules), undergoes transformations. This remodeling involves an increase in the number and size of AT main cellular component - adipocytes.

Cancer cells are located in the niche, which consist of various cell types and is called tumor microenvironment (TME). The surroundings of CRC is rich with adipose tissue. Adipocytes localized in close anatomical proximity to cancer cells could by modified by tumor cells into cancer associated adipocytes (CAA), which support for example the proliferation, migration and invasion of malignant cells.

In the initial stage of this doctoral thesis, I analyzed the changes occurring in adipocytes in conditions simulating their fattening. For this purpose, the studied cells were treated with sodium salts of palmitic, oleic and linoleic acids. It was shown that fattened adipocytes were characterized by the presence of larger lipid droplets and increased expression of the main fatty acids (FA) transporters. However, no differences were observed in the levels of enzymes involved in selected elements of lipid, glucose and glutamate metabolism and activation of most of the signaling pathways studied.

Due to the significant influence of adipocytes on cancer progression, the majority of the work was devoted to examining the mutual impact of adipocytes and CRC cells. To achieve this goal, two research models were used. One of them was treating the cancer cells with conditioned medium collected from adipocytes and CAA, and the other was based on indirect co-culture using Transwell inserts. A number of studies were performed, focusing mainly on the analysis of proliferation, migration, selected aspects of metabolism and activation

of signaling pathways in CRC cells. On the other hand, differences between adipocytes and CAA obtained from co-culture with colon cancer cells were analyzed.

The results presented in this work indicate, that all tested colon cancer cells lines induced the transformation of adipocytes into CAA. It was associated with changes in phenotypic and morphological features. CAAs had reduced lipid content, expression of metabolism-related genes, activation of selected signaling pathways, and increased lactate and MMP2 protease secretion, compared with control adipocytes. On the other hand, CAAs promoted migration, proliferation, and accumulation of lipid droplets in CRC cells. Moreover, changes in the expression and production of the studied molecules related to the transport and metabolism of substrates important for the cellular metabolism were noted. In addition, the observed effect of the influence of indirect co-culture of adipocytes and CRC was noticeably greater than that noticed in the case of conditioned media from adipocyte and CAA on cancer cells.

In summary, the doctoral research showed that adipocytes cultured in the presence of fatty acids had larger lipid droplets and increased expression of the primary FA transporters. Additionally, this study proved the existence of a bidirectional interaction between adipocytes and CRC cells. Cancer cells contributed to the transformation of adipocytes into cancer-associated adipocytes. Under the influence of culture with CRC cells, decline of lipid content, a decrease in the expression of adipocyte markers and genes involved in lipid synthesis in CAA was observed. On the other hand, adipocytes and CAA contributed to the increase in the content of lipid droplets and changes in the expression of selected molecules related to metabolism in CRC. The obtained results indicate that it is worth expanding researches on this subject using a direct co-culture model. This will allow for a deeper understanding of the role of the tumor adipogenic niche in colorectal cancer progression, linking CRC with obesity.

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