ABSTRACT

Breast cancer is the most common cancer among women. A high degree of molecular and morphological heterogeneity is associated with malignancy and prognosis of the tumor, where genome and proteome analysis of cancer cells are the basis of treatment. In addition, in recent years studies have shown that tumor microenvironment in breast cancer is closely related to tumor progression and the interactions between tumor cells and microenvironment affects angiogenesis, tumor growth, metastasis, drug resistance and immune response. Sialylated glycans on cell membranes play a significant role in the process of biological recognition, and their interactions with specific immunoreceptors of the Siglec family are one of the regulatory mechanisms of immunosurveillance. The interaction between Siglec receptors and the sialome of cancer cells result in suppression or activation of the immune system and may be crucial in tumor progression. The paired Siglec-5/14 receptors share structural homology of the extracellular domain and affinity for the same ligands, but demonstrate different intracellular signal transduction pathways which induce opposite immune response. Selective modulators of estrogen receptors, including tamoxifen, are the basis of treatment for estrogen-dependent breast cancers. Furthermore, in vitro studies and clinical observations have shown that tamoxifen affects the activity of the immune system. This is important due to the immunogenic potential of cancer cells and their interactions with the components of the microenvironment.

The aim of the study was to evaluate the effect of tamoxifen on the activity of the immune system cells on the example of monocytes and the involvement of paired Siglec-5/14 receptors in the process of immune surveillance in a cellular in-vitro breast cancer model.

In order to imitate tumor microenvironment, the study was based on co-cultures of THP-1 monocytes with estrogen-dependent MCF-7 breast cancer cells and estrogen-independent MDA-MB-231 breast cancer cells. As a result of tamoxifen exposure at a dose of 10 μM, a decrease in growth and migration potential of MCF-7 cells were observed. No cytotoxic effect was observed in MDA-MB-231 cell culture. In addition, tamoxifen induced the immunomodulatory effect, which was expressed by an increase in production of pro-inflammatory cytokines and a simultaneous change of THP-1 monocytes phenotype cultured in the presence of MCF-7 or MDA-MB-231 cells. The presented changes in the analyzed cells showed an increase in expression of paired Siglec-5/14 receptors. Exposure to tamoxifen also modulated the transcriptional activity of the Siglec-5 and Siglec-14 receptor genes and modulated associated signaling molecules PTPN6, PTPN11 and DAP12 in THP-1 monocytes in all studied cell models. Moreover, tamoxifen increased the binding of the Siglec-5 and Siglec-14 fusion proteins in the studied breast cancer cells, which suggests changes in the sialylation pattern of the cells membrane.

The results presented in this study suggest that tamoxifen regulates immune surveillance by promoting the pro-inflammatory immunophenotype of monocytes in breast cancers unrelated to their estrogen dependence. Changes in the expression of paired Siglec receptors may be a regulatory mechanism of genetically conditioned immune response and participate in a tamoxifen-dependent immunomodulation of the tumor microenvironment. The analysis of the Siglec receptors profile, especially the expression of paired Siglec-5/14 receptors, may be an important tool not only for predicting tumor progression, but also to verify therapeutic strategies and its impact on the breast cancer microenvironment.