Age-dependent effects of calcitriol and tacalcitol on the differentiation of Th17 lymphocytes with the participation of osteopontin in murine mammary gland cancer

SUMMARY

Studies on mammary gland cancer indicate that vitamin D_3 plays an important role in regulating the activity of Th17 lymphocytes in this type of cancer, but its action in this process is not clear. Th17 cell differentiation may also depend on the presence of osteopontin (OPN). The direct effect of OPN regulating Th17 differentiation results from the connection of OPN with its receptors on T cells. Calcitriol, via the genomic pathway, regulates the expression of OPN. Nevertheless, the role of OPN in the age-dependent effect of calcitriol and tacalcitol on the development of Th17 lymphocytes in mice bearing mammary gland cancer has not been fully explained so far.

This doctoral dissertation aimed to assess the effect of calcitriol and tacalcitol on the population of Th17 cells and the participation of OPN receptors in the differentiation process of these cells in mice bearing 4T1 and 67NR mammary gland cancer. In addition, the importance of menopausal status in these processes by including pre- (young) and postmenopausal (aged, ovariectomized) mouse models in the experiment was determined.

OPN-specific receptors - CD44, CD51 and CD29 were identified as the most modulated after the use of calcitriol and tacalcitol in mice bearing 4T1 and 67NR cancer. Blocking CD44 and CD51 led to stimulation of differentiation of Th17 lymphocytes isolated from young mice bearing 4T1 cells, treated with calcitriol and tacalcitol. The opposite effect was observed after blocking CD29. In the same model, weaker Th17 differentiation was also observed after blocking CD51 in cells from the control group compared to unblocked cells. The opposite effect was observed when blocking CD29. In the premenopausal 4T1 model, tacalcitol was shown to enhance metastasis and increase the percentage of Th17 lymphocytes in the lungs. In the postmenopausal mouse model, calcitriol and tacalcitol reduced the percentage of Treg cells in lymph nodes and

peripheral blood and the formation of metastases to the liver and lungs, while calcitriol alone increased the percentage of Th17 lymphocytes in the tumor. In the premenopausal 67NR cancer model, calcitriol and tacalcitol increased tumor angiogenesis, and tacalcitol also stimulated genes crucial to the differentiation of Th17 cells. In the postmenopausal model, tacalcitol reduced tumor angiogenesis and the Th17 population.

In summary, calcitriol and tacalcitol can exert both pro- and anti-tumor effects in mice, which correlate with the presence of immune cells (Th17 or Treg). The above results show that CD51, CD29 and CD44 receptors are key involved in calcitriol- or tacalcitol-dependent differentiation of Th17 lymphocytes.