INVESTIGATING MECHANISMS OF TUMOR DEVELOPMENT USING 4T1 CANCER MODEL IN THE VIEW OF CANCER IMMUNITY AND ENERGY METABOLISM

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ABSTRACT

Cancer treatment faces a number of challenges ranging from low efficacy to failure to benefit all cancer patients. Understanding cancer development and discovery of better cancer drugs are now urgent matters. Tumors grow at a fast rate primarily due to their ability to evade the immune surveillance. However, mechanisms by which tumors evade immune surveillance remain incompletely understood. Previously murine mammary tumor (4T1) cells were reported to secrete soluble factor(s) that suppress secretion of interferon gamma (IFN-γ). One of these factors was identified to be macrophage colony-stimulating factor (M-CSF), a cytokine that regulates survival, proliferation, and differentiation of macrophages and monocytes. To date, the immunosuppressive activity of M-CSF is not well understood. In this study, activity of recombinant murine M-CSF using splenocytes from 4T1 tumor-bearing mice was evaluated. Reduced levels of IFN-γ in the presence of M-CSF were observed in a dose-dependent manner indicating suppressive activity of M-CSF. M-CSF reduces the secretion of IFN-γ without affecting its intracellular protein expression. The activity was dependent on the length of days after tumor inoculation as no activity was observed using splenocytes from one-week tumor-bearing mice, which correlates with an increase in myeloid cells in the spleen. The suppressive activity of M-CSF is thus mediated by the emerging myeloid cells during tumor progression. Studies using CT26 colon cancer cells failed to identify a specific immunosuppressive factor in the CT26 conditioned media. However, activity in some of the fractionated samples showed that, indeed, there are suppressive factors that are secreted and better methods may enhance their isolation and identification.

Cancer cells are characterized by altered metabolic activities including high rate of glycolysis and reduced mitochondrial respiration. These alterations have attracted great attention and are explored as potential therapeutic targets. Exploiting the altered metabolism in cancer cells, this study investigated the activity of bongkrekic acid (BKA), an adenine nucleotide translocase (ANT) inhibitor, on tumor cells as a potential anticancer agent. BKA was shown to reduce the viability of cancer cells with no effect on normal cells. Reduced viability was associated with reduced ATP and NADH levels in 4T1 cells with no effect on NIH3T3 cells. Blockade of ANT resulted in reduced ATP in the cells and caused cells to rely solely on glycolysis. Tumor cells are more sensitive to BKA since they have a higher rate of glucose consumption compared with normal cells. Combining BKA with a glycolysis inhibitor such as 2-deoxyglucose (2-DG) enhanced the cytotoxic effect of BKA in 4T1 cells.

This study has identified tumor-derived M-CSF as a significant contributor of immune suppression. Strategies to block M-CSF activity in tumor cases may help reduce tumor-induced immune suppression, and consequently enhance tumor immune responses. On the other hand, BKA was shown to specifically reduce viability of tumor cells and its activity was enhanced in combination with glycolysis inhibitor. These results suggest that BKA is a potential anticancer agent. Taken together, enhancing tumor immune response by blocking tumor-mediated suppressive mechanisms combined with effective anti-cancer agents may be a more efficient way to eradicate cancer and enhance the survival rate of cancer patients.