MAGEA3/6 TUMOUR ANTIGENS REGULATE GLYCOLYTIC PROTEIN HEXOKINASE TO ENHANCE PANCREATIC CANCER CELL SURVIVAL UNDER METABOLIC STRESS

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Melanoma antigen proteins (MAGEs) were the first tumor antigens identified over four decades ago. Despite the significant interest they have garnered as potential targets for cancer immunotherapy, a successful therapeutic approach remains elusive due to various side effects and limited efficacy. To better understand these challenges, we investigate their normal biological functions and how these are hijacked in cancer. Our data suggest that members of the MAGEA gene subfamily play a crucial protective role in male fertility and germ cell health, as they are typically expressed only in the testes. They appear to support spermatogenesis under various stress conditions, including nutrient deficiency. Here, we investigated the role of MAGEA3/6 in pancreatic cancer as they are detected in 10% of pancreatic cancers and their expression correlates with poor prognosis, aggressive tumor phenotype, and decreased survival. We hypothesized that pancreatic cancer cells hijack the normal protective role of MAGE-A3/6 to fuel unrestrained proliferation under nutrient stress.

To study the function of highly homologous MAGEA3 and MAGEA6 in pancreatic cancer cells, we utilized MIA PaCa-2 cells known for high rates of glucose consumption. We generated MAGEA6-expressing MIA PaCa-2 cell lines, which were subsequently exposed to different metabolic stressors such as glutamine depletion and glycolysis inhibition using 2-deoxy-D-glucose (2DG) treatment. The effects of MAGEA6 expression on viability and metabolism of MIA PaCa-2 cells were then studied using Western blotting, RNA sequencing, metabolic assays, and immunofluorescence (IF) staining with the MitoTracker, LysoTracker, and LysoTOX probes to label mitochondria, lysosomes, and the accumulated intracellular neutral lipids, respectively.

We found that, in comparison to control GFP-expressing cells, MAGEA6-expressing MIA PaCa-2 cells demonstrate increased resistance to glycolysis inhibition by 2DG but are more vulnerable to glutamine depletion, suggesting MAGEA6 role in the metabolic plasticity of pancreatic cancer cells. Further, we found that MAGEA6 expression promoted ATP production and oxidative phosphorylation of MIA PaCa-2 cells, particularly in response to 2DG. These findings were confirmed with the increased mitochondrial IF staining intensity in the MAGEA6-expressing MIA PaCa-2 cells. Furthermore, MAGEA6-expressing MIA PaCa-2 cells also had an increased number of but smaller lipid droplets. To understand the underlying molecular mechanism, we analyzed the expression of 2DG target enzyme hexokinase and other glycolysis proteins, including phosphofructokinase, lactate dehydrogenase A, pyruvate dehydrogenase, and numerous others. Our findings suggest that in pancreatic cancer MAGEA6 regulates glycolysis and oxidative phosphorylation to confer growth advantage under nutrient stress. This suggests that patients with MAGEA6-positive tumors may potentially benefit from a combination of chemotherapy with therapy targeting metabolic pathways.

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