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Significance of K^+ Channel Function and Expression Regulation in Cancer Immunosuppressor Cells in the Tumor Microenvironment

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Summary

In the tumor microenvironment (TME), immunosuppressive cells such as tumor-associated macrophages (TAM), myeloid-derived suppressor cells, and regulatory T cells infiltrate the tumors and suppress the tumor immune surveillance system. Clinically, the density of infiltrating immunosuppressive cells is associated with high malignant grade and poor prognosis in cancer. Therefore, immunosuppressive cells forming TME networks are targets for cancer drug discovery strategies. The purpose of this study is to elucidate the potential of K^+ channel activators in immunosuppressive cells. In the present study, human acute monocytic leukemia cell line THP-1 was differentiated into M_0 macrophages by stimulation with PMA for 24 hr and then differentiated into TAM-like M_2 macrophages with IL-4/IL-13 supplemented medium for 72 hr. Gene expression was analyzed by real-time PCR, protein expression by Western blotting, and cytokine expression by ELISA. We examined the involvement of Ca^{2+}-activated K^+ channel $K_{Ca}3.1$ in THP-1-derived M_2 macrophages in expressing pro-tumorigenic cytokines. In THP-1-derived M_2 macrophages, the expression levels of IL-8 and IL-10 were significantly decreased by treatment with the selective $K_{Ca}3.1$ activator, SKA-121. Furthermore, under *in vitro* experimental conditions that mimic extracellular K^+ levels in the TME, IL-8 and IL-10 levels were both significantly elevated, and these increases were reversed by combined treatment with SKA-121. Respective treatments with ERK and JNK inhibitors significantly repressed IL-8 and IL-10 transcriptions, and treatment with SKA-121 significantly reduced the phosphorylation levels of ERK and JNK. These results suggest that the $K_{Ca}3.1$ activator may suppress IL-10-induced tumor immune surveillance escape and IL-8-induced tumorigenicity and metastasis by inhibiting their production from TAMs through ERK-CREB and JNK-c-Jun cascades.