V-ATPase as an effective therapeutic target for sarcomas

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A B S T R A C T

Malignant tumors show intense glycolysis and, as a consequence, high lactate production and proton efflux activity. We investigated proton dynamics in osteosarcoma, rhabdomyosarcoma, and chondrosarcoma, and evaluated the effects of esomeprazole as a therapeutic agent interfering with tumor acidic microenvironment. All sarcomas were able to survive in an acidic microenvironment (up to 5.9–6.0 pH) and abundant acidic lysosomes were found in all sarcoma subtypes. V-ATPase, a proton pump that acidifies intracellular compartments and transports protons across the plasma membrane, was detected in all cell types with a histotype-specific expression pattern.

Esomeprazole administration interfered with proton compartmentalization in acidic organelles and induced a significant dose-dependent toxicity. Among the different histotypes, rhabdomyosarcoma, expressing the highest levels of V-ATPase and whose lysosomes are most acidic, was mostly susceptible to ESOM treatment.