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Inflammatory-mediated Co-regulation of Voltage-gated Sodium Channels and Na,K-ATPase and its Effect on Metastasis in Breast Cancer

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Voltage-gated sodium channels (VGSCs) and Na,K-ATPase are two targets implicated in the metastatic progression in cancer. Both are upregulated in a variety of aggressive cancers and have been shown to correlate with invasiveness *in vitro* and metastasis *in vivo*. Despite their potentially significant role in cancerous progression, however, little is known as to what drives their overexpression in cancer cells, how they contribute to a metastatic phenotype, or whether these proteins that have complementary activity on sodium ions are co-regulated in cancer. This study provides evidence of inflammatory regulation of VGSCs and Na,K-ATPase in the metastatic breast cancer cell line, MDA-MB-231. Acute administration of TNF α increases RNA for clinically relevant VGSC (Nav1.5) and Na,K-ATPase (α1 and α3) subtypes by approximately 1.2-2 fold. The inflammatory effect on Na,K-ATPase is dependent on the expression and ion-transporting function of Nav1.5, while the inflammatory effect on Nav1.5 is independent of Na,K-ATPase expression. However, the results of siRNA knockdown and ion-blocking drug studies suggest a more complex regulatory intermingling of these two transporters. TNF α challenge also affects the protein localization and overall expression levels of VGSCs and Na,K-ATPase in MDA-MB-231 cells, and drives aggressive behavior of the cells *in vitro*. These inflammatory effects can be disrupted by addition of VGSC or Na,K-ATPase blocking drugs. In total, these studies demonstrate inflammatory regulation of VGSCs and Na,K-ATPase in metastatic breast cancer cells at the RNA and protein levels, as well as a sophisticated co-regulation of the two transporters at the RNA level. The results may help elucidate the complex factors that drive VGSC and Na,K-ATPase expression in metastatic cancer cells and their effect on cancerous behavior.

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