Na⁺ leak governs pacemaking activity of cancer cells required for the metastatic disease development


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Purpose: Deregulated ionic homeostasis has been observed in various pathologies, including tumourigenesis (Prevarskaya et al., 2010). Importantly, elevated total tissue Na⁺ concentration was even proposed as a highly specific in vivo indicator of malignant lesions in cancer patients (Ouwerkerk et al., 2007). Indeed, altered Na⁺ homeostasis was already implemented in prostate tumourigenesis (Yildirim et al., 2012). Therefore, we investigated possible link between prostate cancer and Na⁺ influx provided by the recently discovered Na⁺ leak channel NALCN.

Experimental Design: Tissue biopsies from prostate cancer patients with different stages of disease development were studied due to the immunohistochemical analysis. In vitro cell culture assays were performed on prostate cancer cell lines with various metastatic potential: LNCaP, C4-2, DU 145, PC-3 and PC-3M. NALCN expression was altered due to the applications of siRNA, shRNA and plasmid overexpression, and was verified due to qRT-PCR and immunoblotting techniques. Effects of NALCN alteration were investigated due to Ca²⁺ and Na⁺ imaging techniques. For in vivo studies prostate cancer cells were injected orthotopically (directly into prostate) and intratibially.

Results: NALCN is overexpressed in human prostate cancer tissues. Interestingly, NALCN expression was detected only in highly aggressive prostate cancer cell lines, but not in the cells with weak metastatic potential. Accordingly, NALCN was not involved in cell cycle, viability, apoptosis and proliferation, but significantly affected motility, migration and invasiveness of the prostate cancer cells. We showed that Na⁺ leak provided by NALCN exhibited important role in maintaining Ca²⁺ oscillations, which are required for invadopodia initiation and for secretion of the extracellular degrading enzymes leading to prostate cancer cell invasion, and subsequent metastasis. Finally, in vivo studies confirmed that NALCN downregulation significantly constrained prostate tumour growth, its metastatic spread and bone tissue destruction.
Conclusion: Overall, our data provide evidence on NALCN contribution to the increased metastatic potential of human prostate cancer cells *in vitro* and *in vivo*. Therefore, NALCN could provide new perspective molecular target for the disease suppression, in particular at its advanced stages.

References: