

Inhibitors of Vacuolar ATPase Proton Pumps Inhibit Human Prostate Cancer Cell Invasion and Prostate-Specific Antigen Expression and Secretion

- Vacuolar ATPases (V-ATPases) comprise specialized and ubiquitously distributed pumps that acidify intracellular compartments and energize membranes.
- The role of V-ATPases in prostate cancer (PCa), was studied by inhibiting V-ATPase pumps in androgen-dependent (LNCaP) and androgen-independent (C4-2B) cells of a human PCa progression model.
- Treatment with nanomolar concentrations of the V-ATPase inhibitors bafilomycin A (Baf.A) or concanamycin A (Conc.A) reduced the *in vitro* invasion in both cell types by 80%, regardless that V-ATPase was prominent at the plasma membrane of C4-2B cells and only traces were detected in the low-metastatic LNCaP parental cells.
- The V-ATPase inhibitors, additionally, interfered with the AR-PSA axis under conditions that reduced invasion. Bafilomycin A significantly reduced steady-state and R1881-induced PSA mRNA expression and secretion in the LNCaP cells which are androgen-dependent, but not in the C4-2B cells which are androgen ablation-resistant. In the C4-2B cells, an increased susceptibility to V-ATPase inhibitors was detected after longer treatments, as proliferation was reduced and reversibility of bafilomycin-induced responses impaired.
- ***These findings make V-ATPases attractive targets against early and advanced PCa tumors.***



Cancer Cell Biology

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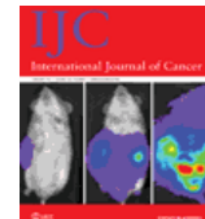
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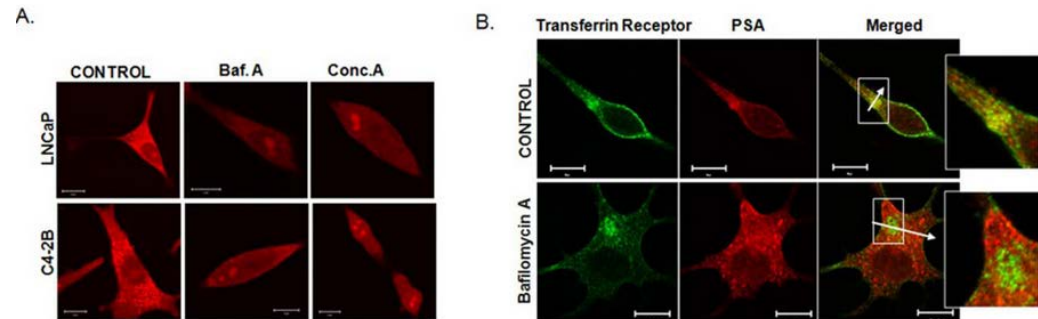
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Effect of V-ATPase inhibitors on endosomal acidification and trafficking
 (A) V-ATPase inhibitors disturb endosomal and lysosomal acidification. Cells were treated with 10 nM Baf.A or Conc.A for 24 h, incubated with 1 μ M acridine orange, and analyzed by confocal microscopy. (B) Transferrin Receptor recycling to the plasma membrane is reduced by Baf