Acidic microenvironment promotes PDAC cells’ selection inducing more aggressive cancer cells: role of Store-Operated Ca²⁺ signals

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a poor prognosis and by a particular acidic microenvironment, that may play a key role in promoting its progression by selecting aggressive cancer cells. Alterations in Ca²⁺ signals are known to be involved in cancer progression and pH-sensitive Ca²⁺-permeable channels sense microenvironmental cues and transduce signals to activate intracellular downstream pathways involved in PDAC progression.

The aim of this work is to study the effects of acidic pHₖ in the context of PDAC progression and its interplay with intracellular Ca²⁺ signals, with a focus on ORAI1, one of the major components of Store-Operated Calcium Entry mechanism and Ca²⁺ oscillations, in order to evaluate the hypothesis of PDAC acidic microenvironment and Ca²⁺ signaling working in synergy to induce and/or select most aggressive cancer phenotypes.

PDAC cell models

To study the role of acidic pHₖ in PDAC hallmarks and its interplay with Ca²⁺ signals, PANC-1 cells were selected for 1 month in pHₖ 6.6 prior recovery to pHₖ 7.4 for 2 weeks, while early stages of selection were studied exposing PANC-1 cells to pHₖ 6.6 for 4 days.

1. Effect of acidic pHₖ on PANC-1 cells outcomes

2. Effect of low pHₖ on FBS-induced Ca²⁺ oscillations

3. SOCE dependency of Ca²⁺ oscillations and role of ORAI1 in invasion

4. Effect of low pHₖ on calcium basal levels and TG-induced Store Operated Ca²⁺ Entry

Conclusion

Low pHₖ exposition decreases SOCE and slows Ca²⁺ oscillations, promoting cancer cells death, selecting more aggressive cancer cell phenotypes; in turn low pHₖ selection induces an increase in PDAC cell proliferation, adhesion, migration rate and invasion, correlated with an increase in SOCE-mediated Ca²⁺ oscillations frequencies due to upregulation of ORAI1 channels.

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