Acidic microenvironment promotes PDAC cells' selection inducing more aggressive cancer cells: role of Store-Operated Ca^{2+} signals

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Introduction

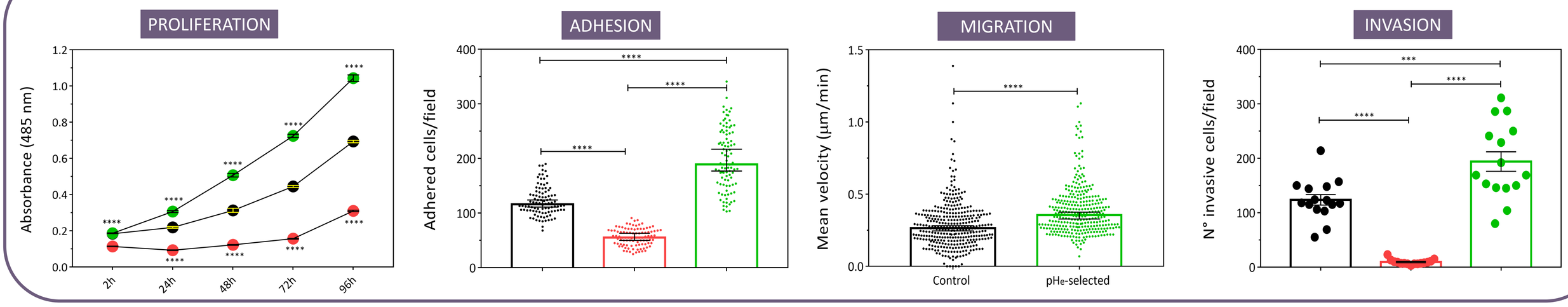
Pancreatic ductal adenocarcinoma (PDAC) is characterized by a poor prognosis and by a particular acidic microenvironment, that may play a key role in promoting its progression by selecting aggressive cancer cells. Alterations in Ca^{2+} signals are known to be involved in cancer progression and pH-sensitive Ca^{2+}-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 pH_e in the context of PDAC progression and its interplay with intracellular Ca^{2+} signals, with a focus on ORAI1, one of the major components of Store-Operated Calcium Entry mechanism and Ca^{2+} oscillations, in order to evaluate the hypothesis of PDAC acidic microenvironment and Ca^{2+} signaling working in synergy to induce and/or select most aggressive cancer phenotypes.

PDAC cell models

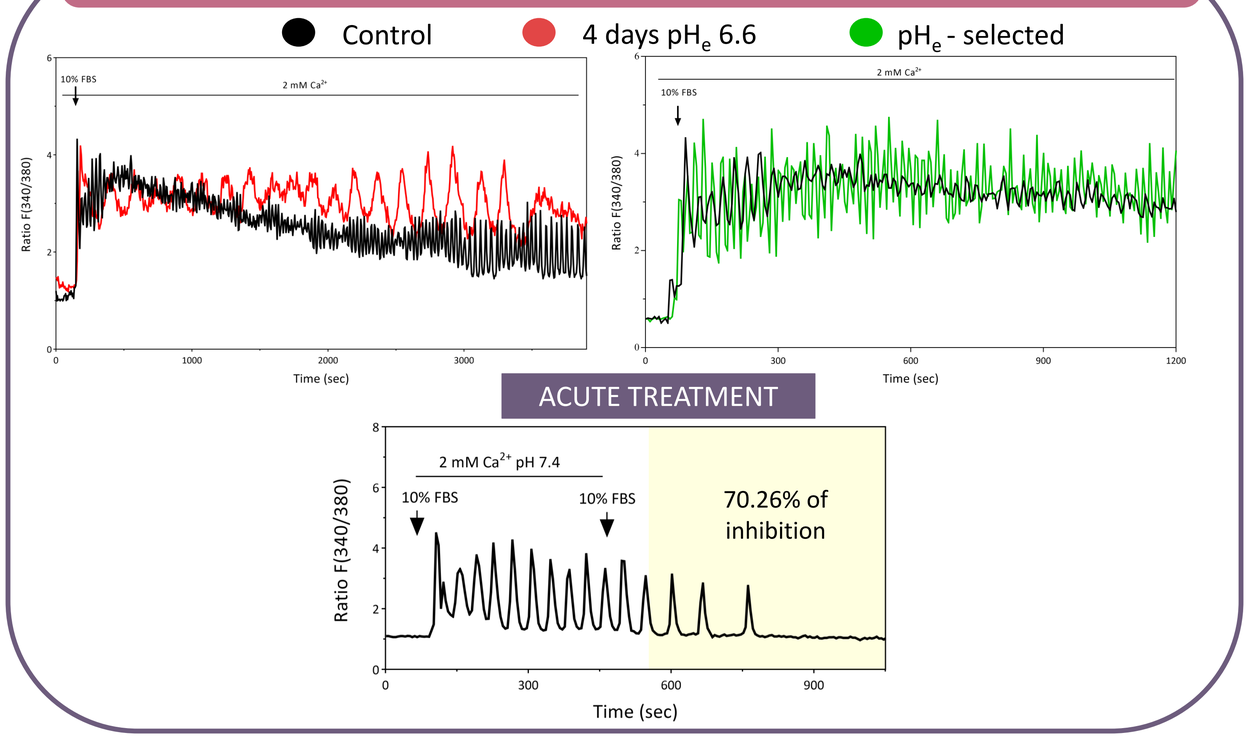
Control · 4 days pH_e 6.6 · pH_e - selected

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

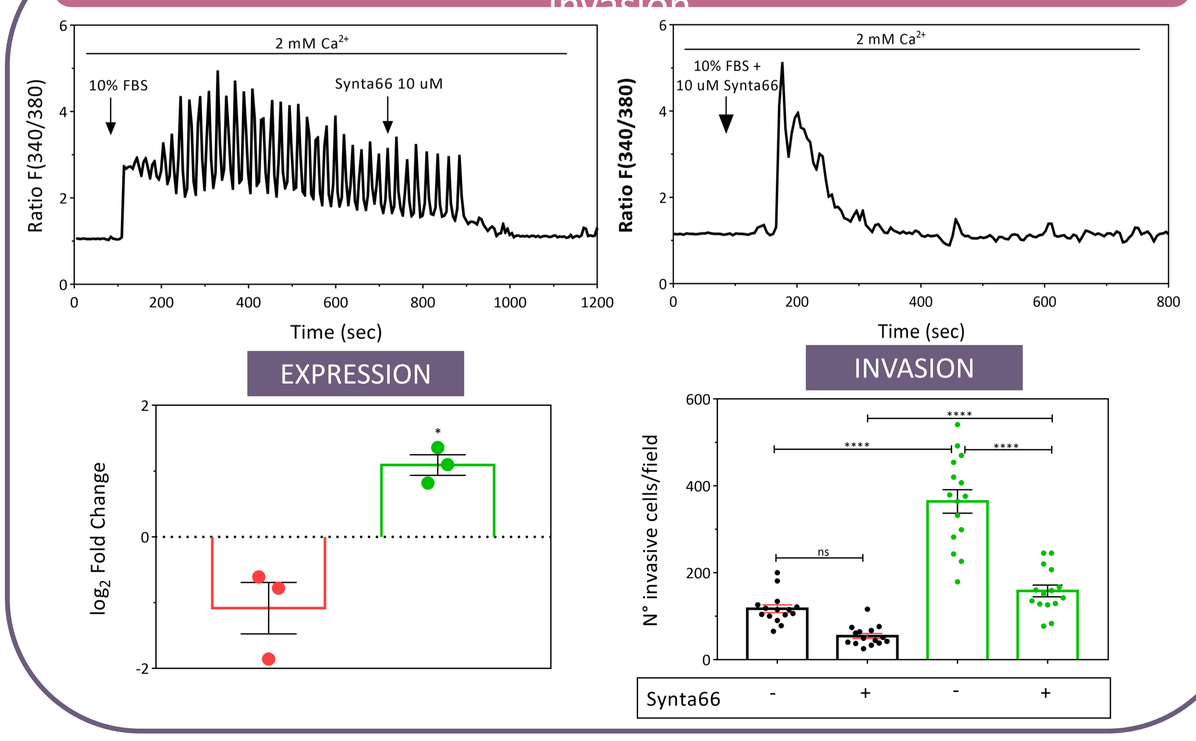
1. Effect of acidic pH_e on PANC-1 cells outcomes



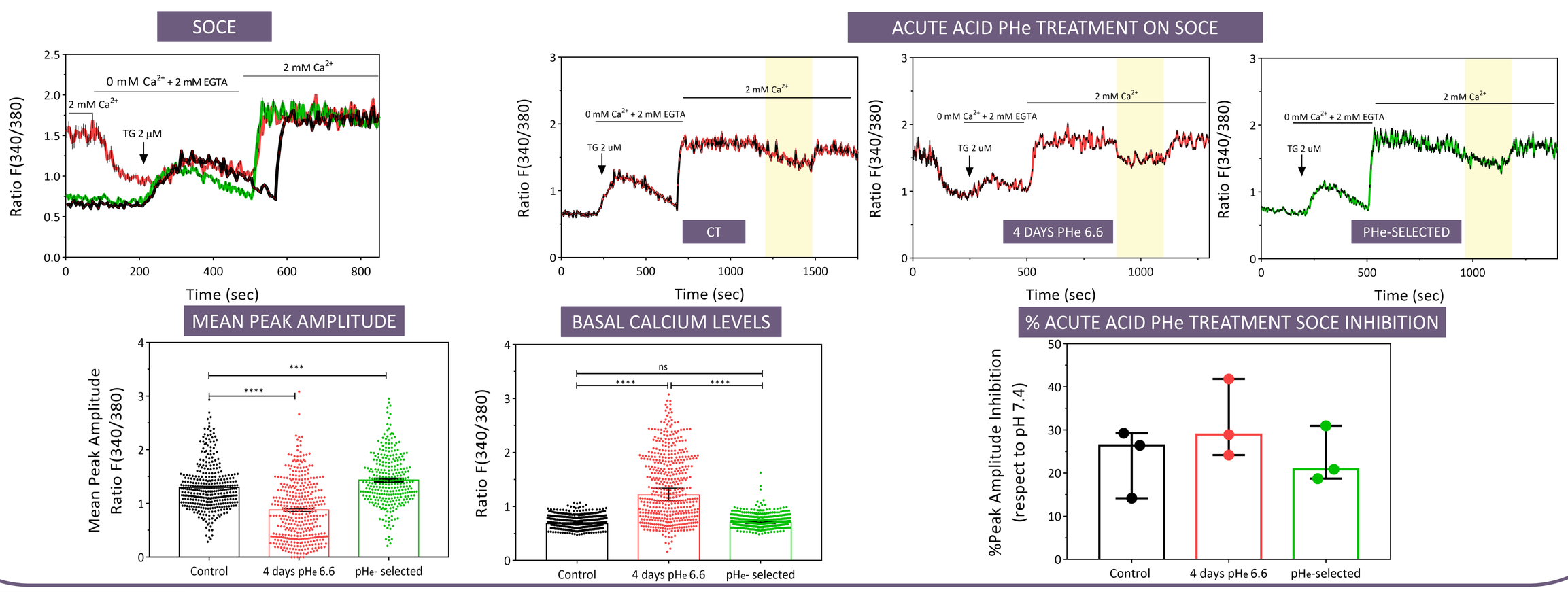
2. Effect of low pH_e on FBS-induced Ca^{2+} oscillations



3. SOCE dependency of Ca^{2+} oscillations and role of ORAI1 in invasion



4. Effect of low pH_e on calcium basal levels and TG-induced Store Operated Ca^{2+} Entry



Conclusion

Low pH_e exposition decreases SOCE and slows Ca^{2+} oscillations, promoting cancer cells death, selecting more aggressive cancer cell phenotypes; in turn low pH_e selection induces an increase in PDAC cell proliferation, adhesion, migration rate and invasion, correlated with an increase in SOCE-mediated Ca^{2+} oscillations frequencies due to upregulation of ORAI1 channels.

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