3-D prostasphere (PS) culture. Similar to estradiol-17β (E_2), 5 nM IGF-1 treatment increased the number of PS as well as long-term BrdU-retaining prostate stem cells. Conversely, knockdown of IGF-1R by siRNA decreased both parameters and consistently increased PS ERβ expression. Together these findings suggest that IGF-1R activation may drive prostate stem cell amplification through suppression of ERβ. Further studies revealed that E_2 (10 nM) exposure induced IGF-1R phosphorylation while IGF-1R knockdown inhibited the non-genomic E_2-induced pAkt and pERK confirming the cross-talk between these two signaling pathways. IGF-1R knockdown decreased PHLDA1, a known IGF-1 target gene, inhibited E_2-induced ERα phosphorylation, suggesting a positive interaction between IGF-1R and ERα. In summary, the present results document robust crosstalk between estrogen and IGF-1 signaling which together regulate their downstream signal molecules including pAKT/pERK and PHLDA1. We propose that these pathways coordinately modulate prostate stem and progenitor cell numbers to effectively maintain glandular homeostasis. Supported by NIH/NCI award R01 CA172220; scholarship by FAPESP grant#2014/10965-6.

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CROSS-TALK BETWEEN ESTROGEN RECEPTORS AND INSULIN-LIKE GROWTH FACTOR TYPE-1 RECEPTOR MODULATES HUMAN PROSTATE STEM/PROGENITOR CELL AMPLIFICATION

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We previously demonstrated that estrogen regulates human prostate stem/progenitor cell amplification by directly targeting estrogen receptors (ERs); ERα stimulates whereas ERβ suppresses stem cell self-renewal. In addition to ERα and ERβ, we find that human prostate stem/progenitor cells express robust level of IGF-1R. Since ER actions can be modified by IGF-1R through ligand-independent ER phosphorylation, we herein sought to characterize potential cross-talk between estrogen and IGF-1 signaling pathways in regulating human prostate stem/progenitor cell amplification. Human prostate stem/progenitor cells were isolated from normal primary prostate epithelial cells (PrEC) using