Barzan A Sadiq, J Cell Sci Ther 2018, Volume: 9
DOI: 10.4172/2157-7013-C1-042

Essential role for PI3K alpha in prostate cancer growth, metabolism and tumorigenesis

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Globally, there is over a million new annual cases of prostate cancer. In approximately 70% of the cases, at least one copy of the tumor suppressor gene, phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*), is found to be lost at diagnosis. *PTEN* is a phosphatase that works in contrast to the class I PI3Ks (phosphoinositide 3-kinase). Class I PI3Ks are heterodimers composed of a catalytic subunit (p110α, p110β, p110δ, or p110γ), which lend their names to the different PI3K complexes, and a regulatory subunit (p85α, p85β, p84, or p101). These heterodimers are expressed differently and seem to assume specific roles in different cellular functions, both within different tissues and single cell types, and are able convey spatially restricted signals, by phosphorylating the $PI(4,5)P_2$ (phosphatidylinositol 4,5-bisphosphate) to produce $PI(3,4,5)P_3$ (phosphatidylinositol 3,4,5-trisphosphate) in the inner leaflet of plasma membrane. These lipids belong to a complex signaling network widely implicated in human pathophysiology. $PI(3,4,5)P_3$ activates vital downstream effector proteins, namely Akt, which is crucial for many cellular processes such as glucose metabolism, transcription, cell proliferation, cell migration, and apoptosis. The $PI(3,4,5)P_3$ pool is controlled by the dephosphorylating abilities of *PTEN*, to produce $PI(4,5)P_2$, and SHIP to produce $PI(3,4)P_2$, respectively. $PI(3,4)P_2$ is an important second messenger itself that can also activate Akt. The loss of *PTEN* causes unregulated PI3K/Akt signaling, which allow survival of prostate cancer cells and prevent apoptosis. We have utilized an established system to culture mouse prostate organoids from prostate progenitor cells to explore the role PI3K signaling in prostate growth, metabolism and tumorigenesis. The prostate-specific deletion of *PTEN* results in a significant reduction in the *PTEN* gene and protein expression in the mouse prostate tissue and cultured organoids. The animals display hyperplasic growth of epithelial cells, which develops into prostate intraepithelial neoplasia by 6-8 weeks, and eventually to adenocarcinoma by 4 months of age. Whilst, cultured organoids grow to a condensed yet sizable cell mass, in comparison to the wild type controls. This presented a good opportunity to study the PI3K signaling mechanisms of prostate cancer, and the tumor microenvironment in isolation. Our data indicates that there is a substantial increase in the accumulated levels of $PI(3,4,5)P_3$ and $PI(3,4)P_2$ lipids. This may offer a route in which these lipids play a role in the development and survival of prostatic cancerous cells. We show that this increased level of signaling is primarily driven by the PI3Kα isoform. We further report that the aberrant signaling is dependent on the pH level of the tumor microenvironment, as raising the pH of the organoids medium dramatically increases accumulation of $PI(3,4,5)P_3$ and $PI(3,4)P_2$, although the cause of this effect was unclear, we hypothesize the pH of the local environment may influence signaling via class I PI3Ks. Furthermore, the vast accumulation of $PI(3,4)P_2$ -seen suggest that *PTEN* may also negatively regulate the $PI(3,4)P_2$ signal, in addition to that of $PI(3,4,5)P_3$. Our findings further our knowledge in understanding the mechanisms of this disease and contribute to the development of more targeted treatments.

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