

Correlation Between Syntaxin Isoform Localization and Loss of Polarity of PSA Secretion in Transformed and Non-Transformed Prostate Cell Lines

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Prostate specific antigen (PSA) is a serine protease that is normally secreted in the lumen of the prostate. Normal blood levels of PSA are low with values between 0-4 ng/ml. However, in the case of prostate cancer, blood levels can rise above 4 ng/ml. Therefore these elevated PSA levels in blood have been commonly used as a marker for detection of prostate cancer.

Relatively little is known about the mechanism of PSA secretion and how PSA is missorted in to the blood in the case of prostate cancer. In this study, we have addressed the question how cell transformation can alter the polarity of protein secretion.

We have focused on syntaxin proteins, a subset of SNARE proteins that may be involved in docking and fusion of secretory granules containing PSA. There are several forms of syntaxins in epithelial cells and it was shown that syntaxin 3 is located at the apical membrane and syntaxin 4 is located at the basolateral membrane. Therefore, syntaxin 3 and 4 are likely candidates in mediating specificity in polarized secretion.

We have used two cell model systems. In the first model we used MDCK (Madin Darby canine kidney cells), a widely used model for epithelium, that were transfected with a inducible raf-kinase construct in which cellular transformation can be induced upon raf activation.

In this case we determined polarity of gp80 secretion, which under normal conditions 90% is secreted apically. We found that raf activation caused a loss in polarized secretion of gp80 and apical secretion was in this case 50%. We also observed a change in expression levels of syntaxin 3 and 4, and we detected some mislocalization of syntaxin 4.

In another model system, we tried to determine the polarity of PSA secretion in prostate epithelial cell lines. Since PSA expression is dependent on activation of the androgen receptor, RWPE-1 (normal prostate epithelial cells), RWPE-2 (transformed prostate epithelial cells), and LNCaP (prostate cancer cells) were treated with Mibolerone, a testosterone analog, to increase PSA expression. We observed a change of expression levels of syntaxin 2 and 3 between the normal, transformed and cancer cell lines. However, only minor changes were noted in the expression levels of PSA and no change in the polarity of PSA secretion.