The role of Dlg5 in the progression of human prostate cancer

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Dlg5 has been reported to participate in cancer progression; however, its role in prostate cancer still remains poorly understood. Therefore, understanding the function of Dlg5 in prostate cancer development and progression will provide insight into potential therapeutic targets to treat prostate cancer.

In Chapter 1, the author found that Dlg5 is frequently downregulated in prostate cancer. Knockdown of endogenous Dlg5 markedly increased prostate cancer cell migration and invasion. The PI3K/Akt signaling pathway is required for cell migration induced by depletion of Dlg5. The present study shows, for the first time, that Dlg5 interacts with Girdin, an actin-binding protein and downstream target of Akt. Knockdown of Dlg5 resulted in increased phosphorylation of Girdin. Small interfering RNA directed against Girdin and wortmannin treatment, which was found to reduce Girdin phosphorylation, impaired the effect of Dlg5 depletion on cell migration. Taken together, the findings demonstrate that Dlg5 interacts with Girdin and inhibits its activity, thereby suppressing the migration of prostate cancer cells.

In Chapter 2, the region of Girdin responsible for binding with Dlg5 was determined. It was revealed that Dlg5 binds preferentially to the CT1 domain of Girdin, which has a binding site for Akt. These findings suggest that Dlg5 and Akt bind to the same region of Girdin, raising the possibility that Dlg5 competes with Akt for the binding site. This would explain how Dlg5 suppresses phosphorylation of Girdin.

In summary, this study provides evidence that Dlg5 plays an important role in prostate cancer progression. Based on these findings, I propose a model to explain how Dlg5 regulates prostate cancer cell migration (Fig. 1). In normal human prostate, Dlg5 is expressed at high

levels and suppresses cancer development by inhibiting cell migration. Dlg5 binds to Girdin and inhibits Akt-mediated Girdin phosphorylation. This phosphorylation seems to be crucial for cell migration. It is possible that Dlg5 competes with Akt for the same binding site on Girdin, thereby preventing the binding of Akt and Girdin. Further investigation is required to confirm this possibility. In prostate cancer, the expression of Dlg5 is downregulated, allowing Akt to phosphorylate Girdin efficiently. In conclusion, Dlg5 regulates migration of prostate cancer cells *via* modulation of the PI3K/Akt/Girdin signaling pathway, and may, therefore, act as a potential target in prostate cancer metastasis.

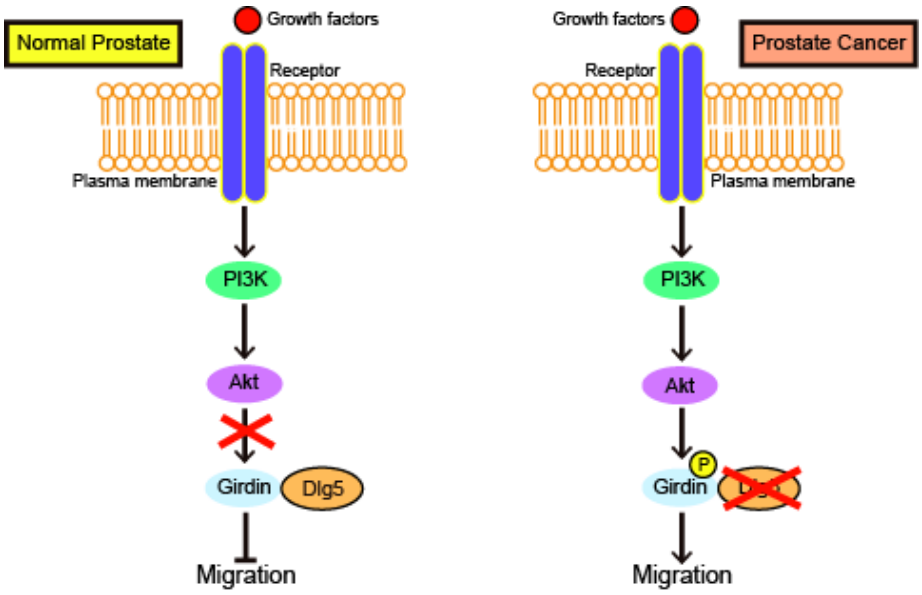

Figure 1: Proposed mechanism by which Dlg5 regulates prostate cancer cell migration