Components of the PI3K-Akt Signaling Pathway and Their Role With Molecular Motors

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Abstract

The PI3K-Akt pathway is a signaling cascade known to be involved in regulating cell death. Previous studies have shown that inhibition of this pathway leads to increased neuronal cell death. Since disruption of transport can lead to neuronal death, here we tested the hypothesis that axonal transport defects activate cell death via PI3K-Akt pathways. One prediction of this hypothesis is that components of the PI3K-Akt pathway are transported within axons. Using Drosophila we evaluated interactions between proteins in the PI3K-Akt pathway and the molecular motors kinesin and dynein, which power axonal transport on microtubules. When Akt or PI3K were over expressed in the presence of a 50% reduction in kinesin motors, transport defects were observed. Over expression of Akt or PI3K in the presence of a 50% reduction in dynein motors gave similar results. Larvae expressing 14-3-3Zeta loss of function mutations showed transport defects in the presence of a 50% reduction in kinesin. 14-3-3Zeta loss-of-function larvae with 50% reduced dynein also showed transport defects. Collectively our data suggests that the proteins in the PI3K-Akt pathway may genetically interact with both kinesin and dynein motors. Perhaps perturbations in axonal transport may lead to the inhibition of the PI3K-Akt pathway, activating neuronal cell death and neurodegeneration.

The PI3K-Akt Pathway Inhibits Apoptosis

A

B

C

PI3K Interacts With Kinesin and Dynein

Quantitative analysis reveals that the number of axonal blockages is significant in larvae over expressing PI3K in the presence of either reduced kinesin or reduced dynein. All values are compared to wildtype (YW) N=5 larvae

Akt Interacts With Kinesin and Dynein

Quantitative analysis shows that larvae heterozygous for 14-3-3Zeta loss of function mutations show transport defects in the presence of 50% Kinesin or 50% Dynein. Larvae heterozygous for a partial ([07103], A) or complete ([12BL], D) loss of function of 14-3-3Zeta do not show axonal transport defects. In the presence of 50% kinesin both mutants show transport defects (B,E), Similarly in the presence of 50% dynein both mutants show transport defects (C,F). These results suggest that 14-3-3Zeta genetically interacts with both kinesin and dynein.

Future Directions

Do other proteins in the PI3K-Akt pathway interact with kinesin and dynein?

Do axonal transport defects cause inhibition of the PI3K-Akt pathway or activating neuronal cell death?

Acknowledgements

Future work will be supported by the Honors College Research and Creative Activity Fund. We would like to thank all members of the Gunawardena Lab.