Role of the Amyloid Precursor Protein in the cellular phosphoinositide metabolism through its interaction with the PIKfyve complex

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Role of the Amyloid Precursor Protein in the cellular phosphoinositide metabolism through its interaction with the PIKfyve complex

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Research Abstract

While the role of the Amyloid Precursor Protein APP in Alzheimer’s disease is well established, its normal role in organisms is ill defined. As most proteins that fulfill complex functions do so in concert with other proteins that they physically bind (so-called interaction partners), knowing binding partners can give valuable insights into protein function. We have established a large number of binding partners of APP, among them a protein complex consisting of the subunits

PIKfyve, Vac14 and Fig4. These three proteins are well known to regulate the levels of an important signalling lipid, phosphatidylinositol-3,5-bisphosphate (PI3,5P2). Interestingly, loss of Vac14 or Fig4 lead to profound neurodegeneration in mice as well as humans. The fact that both APP and the PIKfyve complex are implicated in neurodegeneration and the fact that they bind each other is novel and surprising. This suggests that both participate in the same cellular process. We suggest that APP is a regulator of PI3,5P2 via its binding of the PIKfyve complex. We now need to test whether this hypothesis is correct.

We will test this idea using the genetic model organism C. elegans. In this simple organism there are genes that are highly similar to human APP, PIKfyve, Vac14 and Fig4. The powerful advantage of using C. elegans is the availability of numerous mutants. We have obtained mutants in which APP, PIKfyve and Vac14 are defective. We will characterise the consequences of these defects in animals in terms of appearance of the animals, their behavior and the integrity of their neuronal system. In the next step, through crossing the APP mutants with PIKfyve or Vac14 animals we can combine the mutations in one animal. This then allows to compare the consequences of the double mutants with the single mutants and allows to deduce whether genes act in concert to fulfill a biological function (termed a genetic interaction). We predict that the double mutants will have a strongly enhanced phenotypecompared to the single mutants. This type of phenotypic enhancement is only observed when several genes are functionally connected. This type of approach provides invaluable information that cannot be obtained by any other approach.

We will also analyse the levels of the signalling lipid PI3,5P2 that appears to be of key importance for the integrity of the central nervous system. Correlating the levels of this with the characteristics of the animals (appearance, behavior etc.) will allow us to understand what role APP and the PIKfyve complex play in its regulation.

Our work suggests that the transmembrane receptor (APP) is able to module the production of PI3,5P2 by a direct interaction with the PIKfyve complex. Loss of function of the PIKfyve complex is known to lead to neurodegeneration in mammals. Our work for the very first time links APP with PI3,5P2 regulation and thus may provide an entirely novel and unexpected mechanism how loss or aberrant processing of APP can instigate neurodegeneration.

Further information available at:

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