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Possibilities of PIP4K activity in *Schmidtea mediterranea* model

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Abstract— Phsophatidylinositol-5-phosphate-4-kinase (PIP4K) are stress regulated lipid kinase that utilise PIP5P as a substrate to generate PI(4,5)P2 product. Previous studies concluded the expression of PIP4K in different model organisms and the impact of dysregulated PIP4K activity causesdelayed growth, improper vesicle transport, less weight gain andmislocalisation of protein. In this review, we will analyse the possibilities of PIP4K activity in planaria and hypothesize on the chances of PIP4K related studies for future direction.

Keywords— PIP4K, Lipid Kinase, ***Schmidtea mediterranea,*** PIP5P

1. PLANARIANS

Planarians (*Schmidtea mediterranea*) could regenerate their complete bodies from a single excised segment (Samantha Herath, et al, 2020). This capability to regenerate enables them to proliferate asexually by fission, a mechanism that causes the body to split in a plane perpendicular to the anterior posterior axis (J. B. Best, et al, 1969). The torn-apart bits regenerate and re-pattern themselves to produce a whole animal. The size of the animal as well as environmental conditions influence the induction of this process (J. Baguna, et al, 1989). Although its biomechanics of this mechanism are well established, the molecular signalling pathways that trigger and regulate it demand more investigation.

PLANARIAN BIOLOGY

Planarians belongs to the Platyhelminthes phylum and order Tricladida (triclads) whichare free living flatworms (C. M. Child, 1911). They are found in freshwater, marine and terrestrial habitats. Flatworms of the Triclad family are bilateral, triploblastic, and acoelomate (Isao Hori, et al, 1998). The region between organ systems is loaded with connective tissue named mesenchyme or parenchyma. Planarians do not have a circulatory system, thus oxygen and nutrients are transferred by absorption along the body wall and diffusion via digestive system (Y Asano, et al, 1998). A muscular pharynx located ventrally permits food and waste to be exchanged with the environment. The nervous system comprised of ventral nerve cords that expand at the anterior region to form the brain, also known as the cerebral ganglia. The primary sensory system includes a pair of eyes and auricular grooves, which are also located in the head region (Kyle Alan Gurley, et al, 2008). The animal's reproductive states varies according on the strain, ranging from asexual to sexual to alternating between the two ways. Planarians are hermaphrodites which cross-fertilize during copulation (Miquel Vila-Farré, et al, 2018). The asexual strains of the animals also exhibit a cryptic dynamic form of segmentation, known as fission planes, which correlates with the size of the animal and number of subsequent fission progeny (Arnold, et al, 2019).

PLANARIA AS A MODEL ORGANISM

Planarian are triploblastic organisms constitute of ectoderm, mesoderm and endoderm. They exhibit bilateral symmetry, encephalization, and the capability to sense stimuli. However they are recognised mostly for the incredible regenerative property. The capacity to regenerate a whole organism from a fragment is due to the abundancy of pluripotent adult stem cells (neoblasts) present within them (Peter W. Reddien et al, 2004). Planarians are potential model organisms for understanding complicated biological processes often found in metazoans due to their receptiveness to molecular genetic approaches (Peter W. Reddien, et al, 2004) (N. J. Oviedo, et al, 2008).

REGENERATIVE CAPABILITIES OF PLANARIANS

Planarians are recognised for their remarkable capacity to regenerate entire organ systems. Planaria regenerate complete precisely proportioned individuals from each piece if it is sliced into multiple disproportionate fragments (Francesc Cebrià, et al, 2018). Due to their intrinsic mechanism of continually renewing all organismal cell types from pluripotent stem cells, these animals have the ability to minimize their size when starved (Jaume Baguñà and Romero, 1981). Neoblasts are planarians' sole pluripotent stem cells, and they're in charge of regeneration, asexual reproduction, growth, and homeostasis (Phillip A. Newmark, et al, 2002) (Felix Brinkmann, et al, 2018). These stem cells are found throughout the mesenchyme, not just within tissues. Before terminal differentiation, neoblasts must differentiate to mesenchyme to particular target tissues (Alejandro Sánchez Alvarado, et al, 2002).

ROLE OF PHOSPHATIDYLINOSITOL SIGNALLING

The phosphatidylinositol (PI) consist of glycerophospholipid accompanied by myoinositol head group (six hydroxyl groups

in a cyclic alcohol). Through a phosphodiester bond, at the position 1 of myo-inositol, the hydroxyl group is esterified to the sn-3 hydroxyl group of phosphatidic acid (PA) in PI. The synthesis of phosphorylated metabolic products allows phosphatidylinositol to act as signalling molecules (Di Paolo and De Camilli, 2006). Seven phosphatidylinositol are being produced; one trisphosphate PI(3,4,5)P3, three bisphosphates [PI(3,5)P2, PI(4,5)P2 and PI(3,4)P2] and three monophosphates [PI5P, PI3P and PI4P]. Past research on the phosphatidylinositol signalling in different model organisms to comprehend the molecular basis of defective phenotype. These in vivo findings were crucial in establishing the relevance of phosphatidylinositol metabolism, implemented the important role of phosphatidylinositol-4,5-bis phosphate [PI(4,5)P2] hydrolysis in regulating a physiological process in a living beings (Balakrishnan et al., 2015). The phosphodiester link between the PI(4,5)P2 of glycerol backbone and the inositol head group is hydrolyzed by PLC enzymes, resulting inDAG and inositol-1,4,5-triphosphate (IP3) production (Balakrishnan et al., 2015).

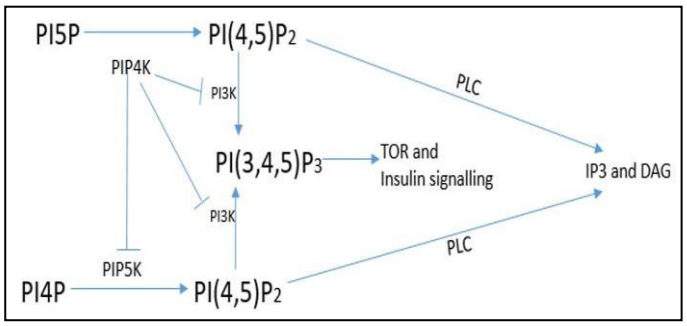

Figure 1-Signalling pathway of generation of phosphatidylinositol metabolic products.

PIP4K is encoded by a single gene in invertebrate models such as *Drosophila* and *Caenorhabditis elegans*, but three genes in mammalian genomes codes for phosphatidylinositol 5 phosphate-4 kinase protein isoforms. Each gene plays role in biological function: PIP4K2C, PIP4K2A and PIP4K2B. PIP4K enzymes and its substrate phosphatidylinositol 5 phosphate (PI5P) were considered to affect a variety of subcellular functions, including nuclear function (Fiume et al., 2015), membrane transport (Ramel et al., 2011; Boal et al., 2015; Kamalesh et al., 2017), *m*ammalian *T*arget *o*f *R*apamycin (mTOR) signalling (Gupta et al., 2013) and autophagy (Vicinanza et al., 2015). Drosophila PIP4K (dPIP4K) caused into null allele with dPIP4K^{29} resulted into elevated level of PI5P substrate (Gupta et al., 2013). In the dPIP4K^{29}, salivary glands cells showed delayed growth and development with a decrease mTOR activity (Gupta et al., 2013). Also, drosophila with knockout PIP4K, resulted into mislocalisation of Rh1 protein in the cytoplasm, associated with unregulated clathrin mediated endocytosis mechanism resulted into visual complication (Kamalesh et al., 2017).

In peripheral blood cells, the expression level of PIP4K2A (PIP4K isoform in humans) is high; PIP4K2B highly abundant in muscle tissue and PIP4K2C identified in kidney (Divecha et al., 1995; Castellino et al., 1997; Clarke et al., 2008). Similarly, the localisation of PIP4K enzyme in different model organism's tissue differs. These prevail the idea of PIP4K activity in different tissues of the same organism will differ due to fluctuations in PIP4K expression. And the downstream signalling outcome might also be altered.

Previous studies also investigated that PIP4K might regulate the functionally PI(4,5)P2 and play role in PIP4K mediated PI(4,5)P2 synthesis (Hinchliffe et al., 1996; Rozenvayn and Flaumenhaft et al., 2001). Also, the role of PIP4K in other pathway acting as a cross-talk signalling mediator has not been well established. Even few more questions are unanswered. Why do cells adopt two separate mechanisms to synthesisPI(4,5)P2?Does PI5P conduct any significant cell signalling functions? Role of PIP4K in planarian regeneration model?

Exploration of PIP4K activity in planarian model organisms is not well established. Although it would be interesting to find out the key concept behind the PIP4K activity in planaria. As planaria is considered as one of the standard model for regeneration and previous experiment explored the single cell RNA sequencing of planaria and proven the expression of PIP4K gene in planaria.

2. CONCLUSION-

Past experiments have concluded the role of PIP4K in the growth of an organism, crucial for vision, transport of vesicles, weight gain, pupariation, etc. But the role of PIP4K in planarian model regarding regeneration, sensory defects or growth is unexplored. There might be possibilities that those unknown concept related to PIP4K which has been addressed in previous studies could be answered through planarian model. In spite of the regeneration property in planaria, disease like cancer to be observe in planaria is very unlikely. Such a well control and resistance against cancer could be related to PIP4K activity (PIP4K activity controls the growth as proven in past studies). Many possibilities related to PIP4K activity in planaria are unresolved and further future studies have been opened for it.

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