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Fruit fly possesses phosphate-storing organelles: A Review

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ABSTRACT

Cell biology is constantly evolving, with a groundbreaking discovery by Charles Xu and his research team. They discovered a new organelle called PXo organelle, which regulates phosphate transport in fruit fly guts. Xu and his team observed that even with minimal phosphate, the gut cells grew rapidly. They also discovered that the PXo bodies, which have a spiral arrangement of cell membranes, help transport phosphate from the cytoplasm into the bodies, regulating the supply of phosphate for cellular functions. This discovery has significant implications for understanding development, behavior, and disease mechanisms in fruit fly models.

Keywords: Alzheimer's disease, Drosophila melanogaster, Reactive oxygen species, Single nucleotide polymorphism

INTRODUCTION

The field of cell biology continually unravels new discoveries that reshape our understanding of cellular structures and their functions.

One such groundbreaking finding is the discovery of a new organelle by Charles Xu and his research team. This

review aims to critically analyse literature surrounding Xu's discovery providing a comprehensive understanding of its importance and its potential implementations in the context of Drosophila melanogaster,a model organism widely utilized in biological research.[1]

Drosophila melanogaster,commonly known as fruit fly,has served as a valuable model organism for numerous biological investigations.Its short life cycle,remarkable physiological similarities to humans and well characterized genetics has made it a tool for understanding various biological processes.The study of Drosophila has contributed significantly to our understanding of development, behavior and disease mechanisms.

In conclusion this review will explore the key findings and implications of Charles Xu's discovery of new organelle within the context of drosophila.We will examine the experimental methods employed, the characteristics and functions of the newly identified organelle and its potential impact life cycle on drosophila.[2]

DISCOVERY : pxo organelle

While working on how phosphate absorption during digestion affects the tissue renewal in fruit flie's guts and providing the flies with drugs that inhibit phosphate absorption,Charles Xu and his colleagues noticed [3] :

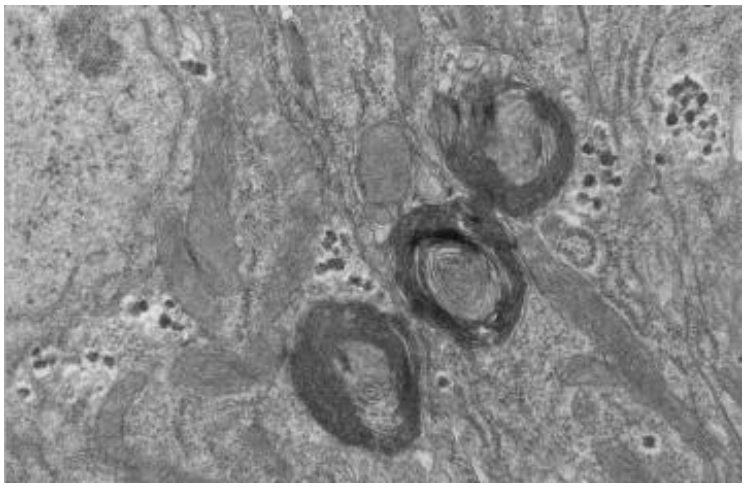
a) Even after having very little phosphate, the cells lining the gut multiplied rapidly.
b) The cells even multiplied after the researchers inhibited the action of PXo,a protein known to govern intracellular phosphate transport.

Now, in order understand the location and role of PXo protein further the researchers fused it to a fluorescent protein and with the help of a fluorescence microscope they observed that these proteins were located on certain oval shaped structures. They named these newfound structures "PXo bodies".[4]

Xu and his team tried to understand the architecture and structure of these PXo bodies further by electron microscopy and observed:

Whorls or spiral arrangement of the cell membrane of these bodies.

This arrangement helps the PXo protein that transport phosphate from the cytoplasm into the PXo bodies. Therefore, regulating the supply of phosphate available for cellular functions.



(Photo By: Charles (Chiwei) Xu)

Two examples of the newly discovered fruit fly organelles, known as PXo bodies, studded with PXo proteins (black dots) (By Kamal Nahas published May 12, 2023).

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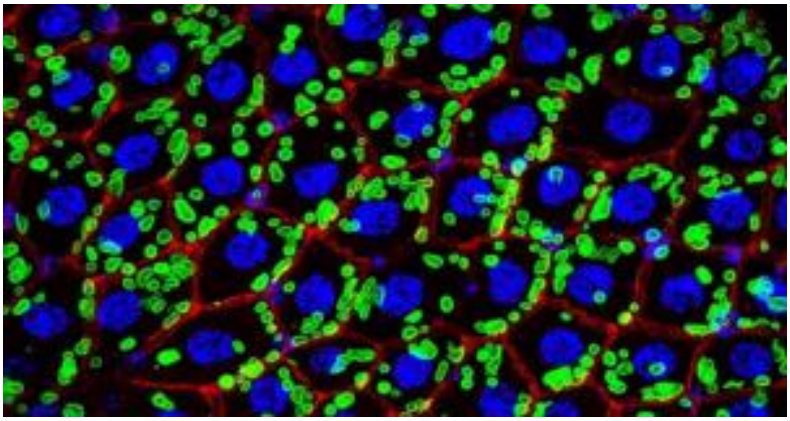
Certain other inferences were made out this chance discovery like the gut being a prominent tissue of nutrient absorption explaining why the PXo bodies are mainly present there, apart from this, many proteins have also been identified that interact with PXo with not known functions presently. [1]

The team tagged the PXo protein with a fluorescent marker to track it — and found it to be involved with mysterious structures inside the cell.[4]

A stained image of cells, with the PXo bodies appearing in green. Charles (Chiwei) Xu.



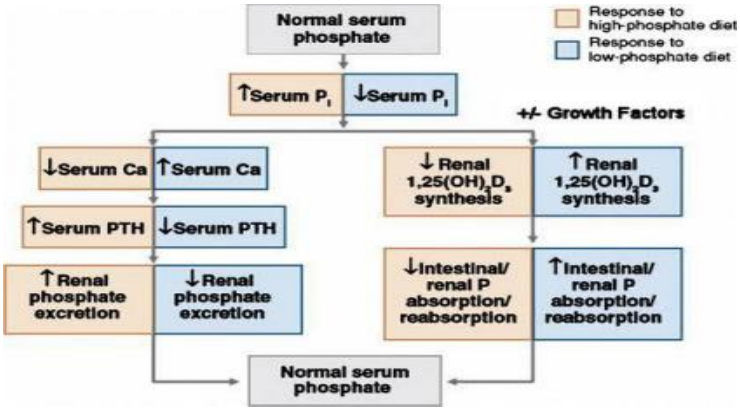
(**Photo By:** B. David Zarley May 14, 2023)

The organelles, called PXo bodies, act as reservoirs for an electrolyte phosphate essential to life.[4]

Implementation of Phosphate in Human Body

Conventionally vacuoles are the organelle for the storage of phosphate. Normal concentration of phosphate in blood plasma is 3-4.5 mg /do [5]. concentration below 3 is considered as hypophosphatemia. The symptoms involve muscular weakness, tooth decay and late baby teeth etc. The concentration above 4.5 mg/dl is considered as hyperphosphatemia. It can cause arteriosclerosis, producing systolic hypertension, widened pulse pressure, and subsequent left ventricular hypertrophy by the deposition of calcium-phosphate complexes throughout our body[6]. Phosphate is absorbed in the gut, stored in bones and eliminated by the kidneys. Phosphate is responsible for metabolic reactions such as ammoniagenesis and glycolysis, important component of our genome and cellular structures like lipid bilayer [7]. In context with drosophila, it is known that drosophila's larvaldevelopment is dependent on the phosphate concentration in the medium. If the fruit flies are cultured in high phosphate medium it shows inverse effect on life span. When the phosphate concentration is increased in hemolymph of the fruit flies it is considered that the malpighian tubules are impaired [8][9].

Homeostasis of phosphate



The interaction between parathyroid hormone and vitamin D– endocrine system in the regulation of phosphorus homeostasis.

(Shaikh, A., Berndt, T. & Kumar, R. Regulation of phosphate homeostasis by the phosphatonins and other novel mediators. Pediatr Nephrol23, 1203–1210 (2008).)

Phosphorus is a vitally important mineral plays a crucial role in all kinds of biological processes. It is a mostabundant anion in human body cover 1% of total body weight. Therefore, maintenance of phosphate is important for several metabolic functions and of cell membranes,generation of ATP,and urinary acid base buffer.Body phosphate is maintained by the profound coordination of gut, bones and kidneys. [10][11]

Phosphate is absorbed by the gut from the food we intake and stored in bones, which will act as a reservoir for up to 90 % of total body phosphate as hydroxyapatite crystal.

The main regulators which have been known till now includes parathyroid hormone, calcitriol which is an active form of vitamin D, and phosphatonins which are long peptide chains in which FIBROBLAST GROWTH FACTOR 23 is most essential.[10][11]

In humans already existing organelles and organs are responsible for phosphate regulation and homeostasis but in prokaryotes like bacteria yeast and in plants a specific organelle is responsible and discovered for the first time in animal cell drosophila a new specific organelle has been found for phosphate metabolism and homeostasis known as PXO.

Drosophila as a model organism

Drosophila has been used as a model organism in many diseases some of them are:

DROSOPHILA IN CHEMOTHERAPY

The severity of the toxic effect of chemotherapy is highly variable among different individuals which are likely based on genetic variation. The toxic side effect of chemotherapy can be predicted by simple DNA tests, which could be revolutionary in the field of cancer treatment. Polymorphism affects toxicity in humans; therefore, we use drosophila. As a model, the offspring of drosophila are being used followed by the exposure to carboplatin, gemcitabine, and mitomycin C, for the identification of naturally occurring DNA variants which help in the prediction of toxicity. Drosophila Synthetic Population Resource (DSPR) is being used as a panel for recombinant interbred lines. These recombinant interbred lines are derived from the multi potent advance intercross, which is helpful in identifying qualitative trait loci (QTL), which ultimately has an effect on chemotoxicity. No quantitative trait loci are being identified for mitomycin whereas two QTL are identified each for carboplatin and gemcitabine toxicity. The first QTL is linked with fly orthologs of priori human carboplatin candidate gene ABCC2 and MSH2. The second QTL is linked with fly orthologs of human gemcitabine candidate genes RRM2 and RRM2B. The third QTL carboplatin is linked with post human orthologs from solute carrier family 7A, INPPHA&B and NALCN. The fourth, a gemcitabine QTL, also impacts the methotrexate toxicity which is linked with human orthologs GPX4. Mapping of QTL is helpful in explaining a considerable fraction of variations in toxicity, yet the QTL peak is not being explained by individual SNP's and transposable elements in the candidate gene regions. Furthermore, the estimation of founder haplotype effect is constant with time with the gene harbouring several segregating functional alleles. Though very little evidence is being found for non-synonymous SNP's explaining mapped QTL. Thus, it could be concluded that regulatory genes are responsible for the standing variations in toxicity. [12]

Drosophila in Parkinson's Disease

Parkinson's disease is characterized as a chronic and progressive neurodegenerative ailment that impacts the central nervous system, resulting in challenges related to movement. Among neurodegenerative disorders, it ranks as the

second most widespread, second only to Alzheimer's disease. The hallmark symptoms of Parkinson's disease include a resting tremor, slowed movement (bradykinesia), muscle stiffness (rigidity), and problems with balance (postural instability). In addition to these motor symptoms, individuals with Parkinson's may also experience changes in mood and disruptions in sleep patterns. These symptoms manifest as a consequence of the specific loss of dopaminergic neurons within a region called the substantia nigra pars compacta. This depletion results in a reduction of dopamine levels within the striatum. Furthermore, emerging research suggests that mitochondrial dysfunction and increased oxidative stress are significant contributors to the development of Parkinson's disease.

Current treatment approaches for Parkinson's disease primarily rely on the replenishment of dopamine through the administration of dopamine precursors, dopamine agonists, and inhibitors of dopamine metabolism. Although these treatments can provide relief from Parkinson's symptoms, they are insufficient in effectively slowing down or halting the progression of the disease. As a result, there is a need for novel therapeutic strategies to address Parkinson's disease. At present, simpler organisms like Drosophila (fruit flies) have proven to be valuable models for studying the genetic factors and pathways involved in various disorders. Drosophila shares biological pathways similar to humans, making it an ideal organism for experimentation due to its experimental tractability and the availability of sophisticated genetic tools and assays. Researchers have developed several Drosophila models for familial Parkinson's disease. One of these models involves the inactivation of the DJ-1β gene, which is the Drosophila counterpart of the human DJ-1 gene. In this particular model, scientists have noted motor dysfunction, reduced lifespan, elevated levels of reactive oxygen species (ROS), and enhanced susceptibility to toxins that induce oxidative stress in DJ-1β mutants.

Furthermore, researchers have demonstrated that these flies respond to pharmacological interventions, as some of their phenotypes can be modified by antioxidant supplementation. Hence, to identify potential new drugs for Parkinson's disease treatment, the same DJ-1ß gene mutation in Drosophila was utilized as a sensitized genetic background. A modifier screen was conducted using 23 compounds possessing antioxidant, anti-inflammatory, or neuroprotective properties.[13]

Drosophila in Alzheimer's Disease

Alzheimer's disease is a neurodegenerative condition characterized by a gradual decline in memory function, accompanied by histological changes such as the loss of neurons and the formation of neurofibrillary tangles and senile plaques. The build-up of amyloid-β (Aβ) peptide, specifically Aβ42, which is the major component of senile plaques, has been suggested as the primary event in the development of Alzheimer's disease. Researchers utilized a Drosophila model to compare and examine the specific pathological functions of Aβ40 and Aβ42. In Drosophila, the protein complex responsible for β-secretase activity is highly conserved, while α-secretase activity is either absent or minimal. While Drosophila does have an analogous protein resembling APP called APPL, the Aβ domain in Drosophila is not conserved. Notably, behavioral deficits observed in a null mutation of APPL were rescued by introducing a human APP transgene. Drosophila has been extensively utilized to investigate the physiological functions of APP and APPL in processes such as synaptogenesis, axonal transport, and apoptosis. In order to investigate the molecular mechanisms involved in the development of Alzheimer's disease, researchers evaluated the impacts of Aβ40 and Aβ42 in the Drosophila brain by employing the GAL4-UAS system. This approach allowed for separate analysis and identification of specific roles played by Aβ40 and Aβ42 in progressive learning impairments and neurodegeneration.

In this study, researchers discovered that the accumulation of Aβ40 or Aβ42 peptides in the Drosophila brain resulted in a progressive decline in learning abilities. However, only Aβ42 prompted the formation of diffuse amyloid deposits, impaired locomotor function, neurodegeneration, and premature death. Interestingly, the onset of learning impairments caused by Aβ42 preceded degeneration in the flies, mirroring findings in AD mouse models and patients. This suggests that neuronal dysfunction and neurodegeneration may involve distinct mechanisms.

Notably, the majority of amyloid deposits in the Aβ42 flies were diffuse rather than mature plaques with clear amyloid fibrils. The absence of mature plaques did not seem necessary for the development of pathological symptoms in the Aβ42 flies. Neurodegeneration was observed in the Aβ42 flies without mature plaques or neurofibrillary tangles (NFTs), indicating that prefibrillar oligomers or protofibrils may contribute to cell death. Similar dissociation between neurodegeneration and the formation of inclusion bodies or NFTs has been observed in other studies. The study also found a weak correlation between cognitive defects and amyloid deposits in AD patients, similar to the observations in Aβ40 flies that exhibited learning impairments without amyloid deposits. Putative oligomeric forms of both Aβ40 and Aβ42 were detected in the fly brains, although their specific pathological roles remain uncertain.[14]

DISCUSSION

The research team is fully engaged in conducting an experiment aimed at demonstrating the effects of inorganic phosphate starvation on the digestive epithelium of the Drosophila (fruit fly) midgut. They discovered that this form of starvation triggers hyper proliferation, as well as enterocyte differentiation within the digestive epithelium. The researchers hypothesise that this response may be a survival mechanism employed by the flies to produce an increased number of enterocytes capable of absorbing phosphate, which is crucial for cellular functioning.

Furthermore, the team made an intriguing observation that during phosphate depletion, the expression of a specific gene called PXo (CG10483) was significantly reduced. Intrigued by the potential role of the PXo protein, the researchers designed a series of interrogation experiments. To investigate its function, they inhibited the expression of PXo or completely removed the gene from the flies' genetic makeup. Remarkably, the outcome was identical to the effects observed when inducing inorganic phosphate starvation. These findings strongly suggest that PXo plays a critical role in the transport of phosphate within the organism.

Like any well-conducted research, the conclusion of this study highlights the need for further investigation. In order to fully comprehend the significance and implications of the findings, future research endeavours will be necessary. These subsequent investigations should focus on mapping out the complete range of functions and interactions associated with this newly discovered organelle. Additionally, it would be beneficial to explore whether PXo bodies are present in other organisms, thereby expanding our understanding of their prevalence and potential significance across different life forms. By conducting such investigations, scientists can deepen their understanding of the underlying mechanisms involved and potentially uncover broader implications for cellular biology and phosphate metabolism.

CONCLUSION

The PXo organelle, which Charles Xu and his research team found, controls the transfer of phosphate in the bellies of fruit flies. The organelle helps move phosphate from the cytoplasm into the gut cells, controlling the amount of phosphate available for cellular processes. The organelle features a spiral arrangement of cell membranes. This finding has important ramifications for our understanding of fruit fly model growth, behavior, and disease pathways.

ABBREVIATION

- AD : Alzheimer’s disease
- APP : Amyloid precursor protein
- DSPR : Drosophila synthesis population resources
- FRUIT FLY : Drosophila melanogaster
- NFT’s : Neurofibrillary tangles
- QTL : Quantitative trait loci
- ROS : Reactive oxygen species

- SNP : Single nucleotide polymorphism

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