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Multifaceted Roles of 14-3-3 Proteins in Biological Processes: From Insect Physiology to Human Diseases

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

14-3-3 proteins are ubiquitous-sticky functional regulatory molecules entails for exerting an array of biological phenomenal processes across eukaryotes, including insects. They mainly execute their role by binding with specific targets of phospho-proteins, resulting multitude cross-talks among the

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signaling pathways crucial in transcendental cellular homeostasis. This particular factual review will be focused on underscores the underlying mechanism with multifaceted roles of 14-3-3 proteins in insect physiology with special emphasis on metamorphosis, early growth and developmental process in particular reproductive biology of the insect. Another facet of discussion is to unravel the arms race of strategic defense mechanism of insect against the challenged microbial pathogens would explain the unprecedented significant role in transcendental evolution of class insect. Unarguably intriguing quests are still appeared to be enigmatic in the insect crust to decipher the existence of orthologs functioning as like human patho-physiology situation gearing up of cancer progression, neurogenerative disorder and cardio-based insults. All together, these factual insights shed light on the scope of 14-3-3 proteins in myriad ways in normal and therapeutic strategy in control of the insect damage on the part of the plant and by developing a consortium of microbial flora against the insect pest is need of the hour for the researcher.

Keywords: Phosphorylated protein; insect metamorphosis; microbial pathogens; signal transduction; cell signaling.

1. INTRODUCTION

"14-3-3 proteins play phenomenal roles in myriad of biological processes, including insect resistance through phagocytosis mechanism" [1]. 14-3-3 proteins specifically act through adoptor-docking mechanism and sequester an interactome with phospho-proteins at cytosol of the cell. Since, 14-3-3 proteins are known to form complex with target proteins such as protein kinases, phosphatases, transcription factors and degradative pathway proteins by the virtue of catalytic and regulatory mechanisms of signal transduction process within the cells [2,3]. 14-3-3 protein families are distinct with their homology about 97% in the nucleic acid content, number of protein isoforms and exhibited a greater degree of functional significance in across the species of eukaryotes. Intriguingly, notwithstanding to homology, the *14-3-3* gene coding sequences derived from different chromosomes have been indicated to regulate the various cellular process through homo or hetero-dimerization in cohort manner between and betwixt them. Each 14-3-3 proteins, known to upregulate or distinctive expression has been observed among them, for instance 14-3-3β and γ in breast cancer in human, quite a few in the dimer form are known to exist in the different context plant existence in the ecosystem and taken into the context of insects Additionally, in species like *Tenebrio molitor* (Darkling beetle) and *Aedes aegypti* (Mosquito), 14-3-3ζ genes play important roles in host defense against bacteria and fungi [4,5]. Moreover, the 14-3-3ζ genes of *Drosophila melanogaster* Meigen (Diptera: Drosophilidae) not only required for neuronal differentiation and signal transduction, but also developmental and immune response [6].

2. ANCESTRAL DIVERSITY OF 14-3-3 PROTEINS

The 14-3-3 proteins are a family of conserved regulatory molecules sharing 50% similarity at amino acid level that are expressed differentially with distinct functional roles in all eukaryotic cells. Because of their amazing dimerizing property found to gear up multitude signalling pathways, preferentially docking kinases, phosphatases, and transmembrane receptors with higher magnitude. In general, Michal yaffe had revealed more than 200 proteins are known to interact with 14-3-3 proteins through proteome atlas. In most mammals, seven genes encode seven distinct 14-3-3 proteins. These genes are YWHAB, YWHAE, YWHAH, YWHAG, SFN, YWHAQ, and YWHAZ [7]. On contemporary, kingdom plantae, has a repository of 13-15 gene encoding 14-3-3 proteins and however primitive eukaryote like fungi has quenched only two isoforms of 14-3-3 proteins. In a far reaching manner of adoptation, class insecta has evolving growing chain of 14-3-3 protein isoforms. In rice (*Oryza sativa*), the GF14e gene, which encodes a 14-3-3 protein, is induced during effector-triggered immunity (ETI) associated with pathogens such as *Xanthomonas oryzae* pv. *oryzae* (Xoo). All together take away messages from growing knowledge of molecular array technologies are advancing towards in determining as biomarkers in the higher eukaryotes [8].

3. SPATIO-TEMPORAL EXPRESSION OF 14-3-3 PROTEINS IN GROWTH AND DEVELOPMENTAL STAGES OF ORGANISMS

The cellular dynamics has been well attributed by the mediator proteins at cytosolic level through

protein binding mechanism in the eukaryotic system. This phenomenon of cellular dynamics is significantly contributed by 14-3-3 proteins as their sticky-catalytic domains are indispensably involved in interaction with phosphoprotein targets. Presumably, due to the growing body of deregulated processes within the cell has necessitated to evolvement led to in arise of an array 14-3-3 proteins. The facet of derivation of variant types in insect has been well established through genomic and proteome tools. For instance, genomic variants of 14-3-3ζ in *Musca domestica*, has differentially regulated at post-transcriptional and translational level at different developmental and tissue-specific expression. Further, 14-3-3ζ could be used as biomarker in clinical challenge [9]. On the other hand, in case of *Bombyx mori,* has been revealed that notably 476 expressed sequence tags (ESTs) are homology to the 14-3-3ζ variant and global expression in all tissue types under probed [10].

Surprisingly one less of seven, 14-3-3σ contrasting isoform among 14-3-3 protein has manifested significant role as novel tumor suppressor in mammalian orthologs. Albeit by virtue of its facet molecular chaperonic activity, has less appreciated in insects due to lack of significant molecular studies indicating rigorous resurgent findings are need to be curetted [11,12]. "14-3-3ε is expressed uniformly throughout the oocyte with some peripheral accumulation, and absent in the interior of the egg cytoplasm in mouse" [13]. Further these highlights of studies have indicated to explore in more about significant functional roles of 14-3-3 protein roles in insect growth and developmental processes.

4. A ROLE FOR 14-3-3 PROTEINS IN CELLULAR DEVELOPMENT AND HOMEOSTASIS

Based on the growing body of knowledge and factual insights gained from studies on 14-3-3 proteins from mammalian to plant counter parts have poised and promoted us to uncover by reviewing the findings in the class of insecta. There are evidential supportive data was available in case of metamorphosis, wherein the involvement of 14-3-3 proteins are known to participate in the regulation of ecdysone hormone signalling pathway. 14-3-3 proteins will activate the ecdysone- responsive genes through the transcription factors mediation by regulating the transition stage of larval to adult stages of the insects [14]. In line with metamorphosis, there is exigency in targeting 14-3-3 proteins involved in ecdysone mediated transition of insect pest survival and quite a few strategic target studies in pipe line herein.

Metamorphosis: 14-3-3 proteins are involved in coordinating the complex process of metamorphosis in insects, which involves dramatic morphological and physiological changes from larval to adult stages. One example is the regulation of ecdysone signalling, a hormone critical for insect development and metamorphosis. 14-3-3 proteins can interact with components of the ecdysone signalling pathway, modulating the transcriptional activity of ecdysone-responsive genes and thus influencing developmental transitions [14].

Growth: 14-3-3 proteins are pivotal role in regulating cellular growth and activation of related proteins are involved in the growth processes of higher mammalian counterparts at the progenitor level. There is a niece piece of mechanistic cues are manifested by 14-3-3 proteins by activating the target of rapamycin (TOR) phosphor-protein at the downstream of the pathway. Upon modulation, further signals will transduce to nutrient sensing and growth components by their regulating homeostasis of insect [15]. These preliminary studies with 14-3-3 proteins in the insect growth and development will further prompted us in navigating the other cross-complexes involved thereby it also enhance the information related to specific target identification in the control of insect pests challenging against the crop species.

Reproduction: 14-3-3 proteins are acidic, ubiquitous, highly conserved, homologous protein family known to regulate in various metabolic process including reproductive processes via cell cycle, signal transduction, apoptosis, autophagy and development. mechanisms ranging from mammals to plants. Each Isoforms of 14-3-3 proteins are encoded by distinct chromosomes, have tissue-specific, developmental stage specific as well as isoform specific function at prelude or aftermath. For instance, *Drosophila melanogaster*, 14-3-3 proteins have been shown to interact with protein network of germ cell development and meiotic event further eluding the progression of spermatogenesis by formation of proper gamete formation [16].

5. MOLECULAR WIRING NET WORK OF 14-3-3 PROTEINS ARE INDISPENSIBLE IN CELLULAR HOMEOSTASIS OF THE INSECT SYSTEM

14-3-3 proteins, due to their isoform variability and ubiquitous expression in the cytosolic region lead to the cross-talk with multiple signalling pathways in the metabolic processes of the insect further regulates the growth, survival and apoptosis by their respective signals. By their virtue of inheritance pattern, each monomer of 14-3-3 proteins containing nine α-helix are held together to form an amphipathic groove by leading homo or heterodimerization of 14-3-3 proteins. Further the downstream, 14-3-3 proteins are known to exert their influence by way of binding with phospho-protein containing tethered serine or threonine residues in the target proteins will lead to activation of multiple signalling pathways through phosphorylation-dependent manner [17]. These signalling cascades mediated by 14-3-3 protein will be acting as molecular switches in the cytosol in triggering constant response or induced by external stimuli by regulating the catalytic activity, protein sequestration, and/or predictability of binding partner. Keeping in view the factual insights, in insect *Tenebrio molitor*, upon infection with *Escherichia coli* on larval haemocytes analysis revealed that there was a remarkable expression of the transcripts level about three folds14-3-3ε transcript exhibits a notable three-fold increase in expression. In contrast abrogation of T_m14-3-3ε results in significantly reduced survival rates when larvae are infected with *E. Coli* [18].

Reading 14-3-3 protein hub with wiring network: In *Drosophila melanogaster*, 14-3-3 proteins interact with several key regulators of cell cycle progression, such as Cdc25 phosphatase and Wee1 kinase. These interactions influence the activity of these proteins, thereby controlling cell cycle transitions during development [19]. Another example involves the interaction between 14-3-3 proteins and components of the insulin signalling pathway in insects. 14-3-3 proteins can bind to phosphorylated insulin receptor substrate (IRS) proteins, modulating their downstream signalling and affecting processes such as growth and metabolism. Additionally, 14-3-3 proteins interact with transcription factors involved in regulating gene expression during insect development. For instance, in *Bombyx mori*, 14-3-3 proteins bind to the transcription factor BmFTZ-F1, modulating its transcriptional activity and influencing the expression of genes essential for metamorphosis [10].

6. A ROLE FOR 14-3-3 PROTEINS IN NORMAL AND PATHO-PHYSIOLOGICAL CONDITIONS

Cancer: 14-3-3 proteins are involved in cell cycle regulation, apoptosis, and signalling pathways that are frequently dysregulated in cancer. They interact with numerous oncogenic proteins and tumour suppressors, influencing cancer progression and metastasis. For instance, 14-3-3 sigma (σ) is implicated in breast cancer progression by regulating cell proliferation and apoptosis [20].

Neurodegenerative disorders: In diseases like Alzheimer's and Parkinson's, 14-3-3 proteins play roles in protein aggregation and clearance mechanisms. They interact with tau and alpha-synuclein proteins, which are associated with neurodegeneration. Alpha-synuclein and 14-3-3 proteins are implicated in the pathogenesis of various neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis (ALS), among others. They play significant roles in the underlying mechanisms and progression of these conditions. Dysregulation of 14-3-3 interactions can contribute to the accumulation of toxic protein aggregates [21].

Metabolic disorders: Serotonin N-acetyltransferase (also known as aralkylamine N-acetyltransferase or AANAT) is an enzyme that plays a crucial role in the production of melatonin, a hormone that regulates the sleep-wake cycle in animals, including humans. AANAT interacts with 14-3-3z, suggesting AANAT evolved to recruit 14-3-3 for phosphorylation-dependent regulation. This binding modulates AANAT's substrate binding sites, enhancing enzymatic activity at low serotonin concentrations, crucial during nightly serotonin decreases. The complex formation potentially adapts enzymatic function to fluctuating substrate levels, suggesting a regulatory role distinct from static mutations. The structure supports dual-protein binding within the 14-3-3 dimer, a model relevant for understanding complex formation in other protein interactions [22].

Infectious diseases: During infections, 14-3-3 proteins can interact with viral proteins and modulate host immune responses. They influence viral replication and pathogenicity in diseases caused by viruses like HIV and influenza. The isoforms of 14-3-3 proteins, like β, θ, ε, γ, η, and ζ, were found to interact with single-stranded RNA viruses (ssRNA) such as the influenza A virus (IAV), measles virus, human respiratory syncytial virus, human immunodeficiency virus (HIV), La Crosse virus, and double-stranded DNA (dsDNA) viruses like herpes simplex virus type I, human herpes 4, hepatitis B virus (HBV), Nipah virus, Hendra virus and Murid herpesvirus [23].

Cardiovascular diseases: 14-3-3 proteins are involved in regulating endothelial function, vascular smooth muscle contraction, cardiac hypertrophy, and apoptosis in cardiomyocytes. They interact with key signalling molecules and ion channels involved in cardiovascular homeostasis and disease pathogenesis [24]. In the context of cardiovascular disorders, 14-3-3 proteins are involved in regulating endothelial function, vascular smooth muscle contraction, and cardiac re-modelling processes. Dysregulation of these proteins can contribute to hypertension and heart failure. The wide distribution of potential 14-3-3 targets and the resurging interest in metabolic pathway control in diseases like cancer, diabetes, obesity and cardiovascular disease [25].

7. CONCLUSION

14-3-3 proteins represent pivotal regulators across a broad spectrum of biological processes in both insects and other eukaryotes. Their ability to interact with diverse phosphorylated target proteins underscores their role as versatile modulators of signal transduction pathways critical for cellular function and development. In insects, these proteins are integral to key physiological processes such as metamorphosis, growth regulation, and reproductive functions. Their involvement in host defense mechanisms highlights their evolutionary significance in combating microbial pathogens. Beyond insect biology, 14-3-3 proteins play crucial roles in disease contexts, including cancer progression, neuro-degenerative disorders, infectious diseases, and cardiovascular conditions in humans. Their interactions with various cellular components influence disease pathogenesis, making them potential targets for therapeutic interventions. Continued research into the intricate regulatory mechanisms of 14-3-3 proteins promise to uncover new insights into their roles in health and disease, offering opportunities for innovative treatments and disease management strategies.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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