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Research Article

Role 14-3-3 Protein in Regulation Some Cellular Processes

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Abstract: The aim of this study to review an overview of the current information on the structure of proteins 14-3-3 and their complexes, in addition to that it provides insights into the mechanisms of their functions. The 14-3-3 proteins are from families maintain regulatory molecules expressed in all eukaryotic cells. It was discovered before thirty years, it is attributes of 14-3-3 proteins are able to connect a large number of signalling proteins are functionally diverse, including kinases, phosphatases and transmembrane receptors. 14-3-3 proteins play an important role in a variety of vital regulatory processes, such as protein regulation, apoptotic cell death and cell cycle control. In this review, we discussed the structural basis of 14-3-3 proteins, common structural features of their complexes, Phosphorylation, Cell cycle and Apoptosis.

Keywords: 14-3-3 Protein, apoptosis, cell cycle, phosphorylation, structure

INTRODUCTION

The proteins of the 14-3-3 family description in 1967 for the first time in the process of systematic classification of the nerve tissue proteins (Moore *et al*., 1967). 14-3-3 has been translated proteins preferentially in neurons, but also expressed in a wide variety of cells and other tissues. Where these proteins were found in the 14th fraction of an ion-exchange column and at the fraction of the starch gel electrophoresis (Aitken, 2006). 14-3-3 proteins play diverse physiological roles and interact with a multitude of substrate proteins during normal development and adulthood (Mackintosh, 2004). For that continue these proteins to generate intense interest because of their roles in signal transduction pathways that control barriers in the cell cycle and activation of MAP kinase, apoptosis and gene expression programs. Historically, 14-3-3 proteins were identi¢ed as abundant polypeptides of unknown function in the brain (Moore *et al*., 1968) and later re-discovered as activators of tryptophan and tyrosine hydroxylase (Ichimura *et al*., 1988) and inhibitors of PKCs (Toker *et al*., 1990). Interest in 14-3-3 proteins grew when they were subsequently identi¢ed as molecules that co-associated with Raf and polyoma middle T antigen (Pallas *et al*., 1994) and as the molecules implicated in the DNA damage response of ¢ssion yeast (Ford *et al*., 1994). sca¡olding molecules (IRS-1, calmodulin, Grb2, poloma mid-T, p130Cas, CBL), proteins responsible cell cycle control are phosphatases Cdc25, Chk1, WEEL, P53 and the catalytic subunit of human telomerase, whereas, proteins that affect the control of transcriptional gene expression Since then, over 100 proteins have been found to interact with 14-3-3, including various proteins kinases (PKCs, Raf family members, receptor proteins, enzymes such as the tyrosine, tryptophan hydroxylase and cytoskeletal proteins, small G-proteins and their regulators (Zhai *et al*., 2001), as box TATA binding protein TBP and TFIIB, family members forkhead and proteins involved in the control of apoptosis (BAD, A20 and the p75NTR associated cell death executor NADE) (Tzivion and Avruch, 2002).

14-3-3 proteins are a family of phospho-Ser/Thr binding proteins that are prevalent in eukaryotes which stimulated by various protein kinases, one of the ways involving translational modification affecting the structure and characteristics of many proteins (Sluchanko and Gusev, 2010). Accompanied by the transfer of a phosphate group to the significant changes that affect the structure and characteristics of the functional activity of proteins phosphorylated. Over 300 14-3-3 interacting proteins have been identified until now. The members of the 14-3-3 family was participated in the organization of apoptosis of cell, cell cycle, proliferation, transcription, replication and organization of cytoskeleton. According to data recently published that 14-3-3 proteins play a significant role in neurodegenerative diseases and carcinogenesis (Foote and Zhou, 2012). This is prompting to increased interest to investigate the structure and properties of proteins 14-3-3.

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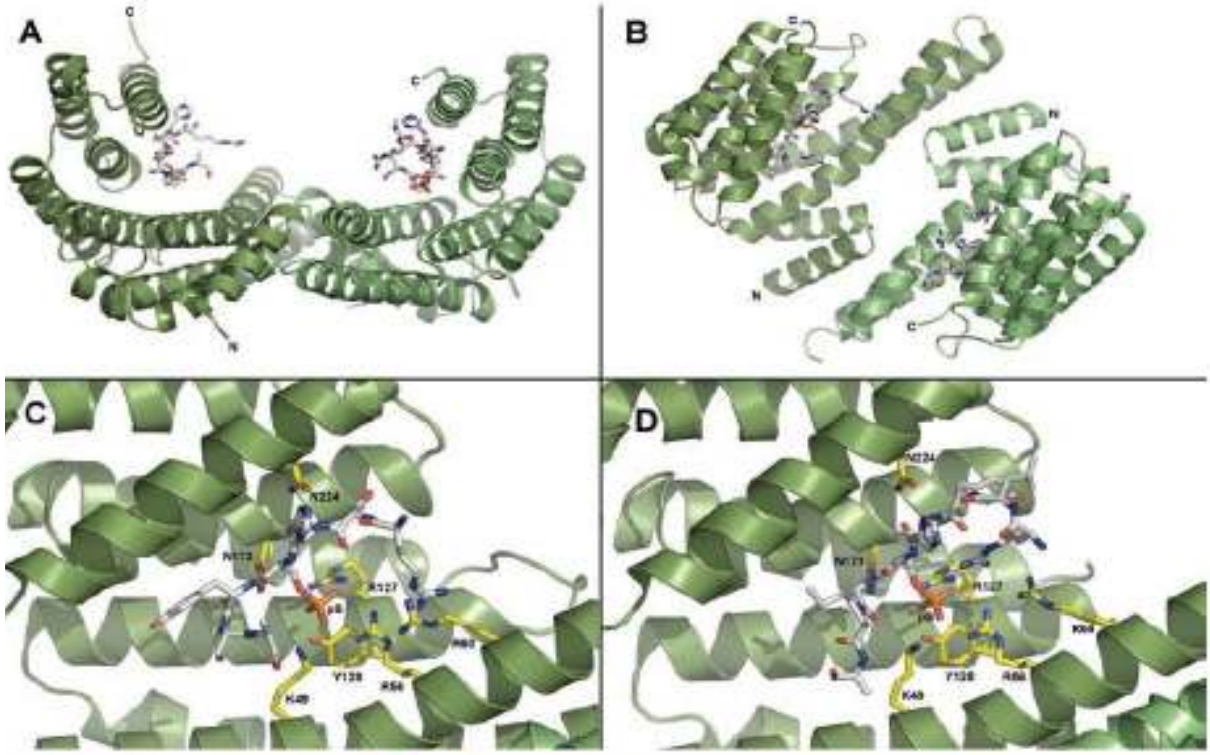

Fig. 1: Crystal structure of the 14-3-3ζ protein (human- isoform with bound phosphopeptides containing optimal 14-3-3 binding motif); (A and B) Two orthogonal views of 14-3-3ζ dimer (ribbon representation) with bound phosphopeptide (stick representation); (C) A detailed view of the phosphopeptide ARSHpSYPA bound to 14-3-3ζ; (D) A detailed view of the phosphopeptide RLYHpSLPA bound to 14-3-3ζ (Rittinger *et al*., 1999)

In this review, we will focus to give an overview on summarizing some of the biochemical, structural and genetic recent data that will help to elucidate the molecular basis of 14-3-3 function and the role of this protein in regulating phosphorylation, cell cycle and apoptosis cell death. Then comment on some of the outstanding questions that need to be addressed.

Structure and function of 14-3-3 proteins: The 14-3-3 proteins are a family of regulatory proteins, found in the all eukaryotes (Fu *et al*., 2000). 14-3-3 proteins serve as molecular scaffolds by modification the conformation of its binding partners (Hermeking and Benzinger, 2006). During the formation of a functional from a wide variety of binding partners, 14-3-3 proteins are participate, in many biologically important processes, including regulation of the cell cycle, control of metabolism, apoptosis, control of gene transcription and the sub cellular localization of their substrates to enhance a particular signal or sequester and inhibit a particular pathway (Ichimura *et al*., 2013). The name of this protein, "14-3-3", originates from the rinse and the migration pattern on two-dimensional chromatography DEAE cellulose and starch gel electrophoresis. Since the initial discovery of 14-3-3 proteins, members of this protein family have also been given other names, e.g., BAP-1, Bilardo, Exo1, Leonardo, Stratifin etc., when they have been rediscovered due to their involvement in many regulatory processes. The 14-3-3 proteins are highly conserved over a wide range of eukaryotic species and many organisms express multiple isoforms. While lower eukaryotes, for example, yeast, containing only two genes 14-3-3, either eukaryotes Supreme possess up to 15 gene from 14-3-3 genes. For instance, in mammals seven isoforms (β, ε, η, γ, τ, ζ and σ) have been identified to date. With exception of mammalian sigma isoform, all 14-3-3 proteins can form both homo- and heterodimers (sigma isoform preferentially forms homodimers) (Wilker *et al*., 2005). Initial structural studies confirmed a dimeric nature of 14-3-3 proteins and revealed that each monomer consists of nine antiparallel α-helices (Xiao *et al*., 1995) (Fig. 1A and B). A large 40 Å wide deep channel located in the center of a cup-shaped 14-3-3 protein dimer contains two amphipathic grooves. Crystal structures of phosphopeptide-bound 14-3-3 complexes demonstrated that pS (or pT) -containing segments (pS and pT denotes phosphoserine and phosphothreonine, respectively) are bound within amphipathic grooves at either edge of the central channel of the 14-3-3 dimer and adopt an extended main chain conformation (Fig. 1) (Petosa *et al*., 1998). The phosphate group of phosphoserine (or phosphothreonine) is coordinated by salt bridges to the side chains of the R56, R127 and

K49 and a hydrogen bond to the hydroxyl group of Y128 (Fig 1C and D). The proline residue in the phosphopeptide adopts a cis-conformation, producing a sharp change in chain direction and allowing the remaining portions of the peptide to exit the binding cleft (Rittinger *et al*., 1999). The whole molecule of the 14-3-3 dimer is very rigid likely as a result of extensive interactions between helices. The most flexible region is the C-terminal segment which is also the most variable region among 14-3-3 isoforms. The highly conserved regions map of the interior surface of the central channel. The dimeric nature of 14-3-3 proteins seem to be very important for their functions. Many binding partners of 14-3-3 proteins possess more than one 14-3-3 binding motif and the presence of two binding grooves within the 14-3-3 dimer might enable simultaneous binding of two phosphorylated motifs and thus more efficient ligand binding (Yaffe, 2002; Shen *et al*., 2003). A synthetic peptide containing two 14-3-3 binding motif binds with 30 times higher percentages compared phosphorylated peptide containing only one of its ability to bind phosphoserine or contain phosphothreonine peptide motifs (Johnson *et al*., 2010).

14-3-3 regulatory proteins: The majority of protein isoforms 14-3-3, with the exception of mammalian σ isoform, expressed in the presence of all the tissues and they associate with the convergence of similar objectives. Thus, the binding properties of proteins from 14-3-3 seems to be regulated by post-translational modifications and/or binding of cofactors (Athwal *et al*., 1998; Wurtele *et al*., 2003). From various post-translational modifications the phosphorylation of 14-3-3 isoforms on specific residues is now a well established mechanism of 14- 3-3 regulation. Phosphorylation sites are not conserved among 14-3-3 isoforms thus this post-translational modification can enable selective isoform regulation. 14-3-3 protein isoforms are phosphoryted at four sites by a number of Ser/Thr kinases that are known to be involved in cell signaling and regulation (Wilker and Yaffe, 2004). Two sites are located at the dimer interface (Ser58 and Ser63 in human 14-3-3ζ numbering) and it has been shown that phosphorylation of Ser58 promotes the formation of 14-3-3 monomers (Powell *et al*., 2003; Woodcock *et al*., 2003). Monomerization of otherwise dimeric 14-3-3 proteins might have a profound effect on their function. The other two sites (Ser184 and Ser/Thr232) are located in the perimeter of the ligand binding groove and phosphorylation of both these sites have been shown to reduce ligand binding (Obsilova *et al*., 2004; Tsuruta *et al*., 2004). Phosphorylation site Ser/Thr232 is located within the C-terminal segment, a region that is believed to be elastic. On the structure of this part of the molecule 14-3-3 is unknown because it cannot be seen in any of the available 14-3-3 crystal structures presumably due to a disorder (Obsil *et al*., 2001). Several reports indicated that the C-terminal segment is involved in the regulation of ligand binding (Liu *et al*., 1995). Phosphorylation site Ser/Thr232 is present in the C terminal segment of vertebrate ζ and τ isoforms only and can be phosphorylated both in vitro and in vivo by casein kinase Iα. It has also been shown that in human embryonic kidney 293 cells 14-3-3ζ is phosphorylated exclusively at Thr232 (Dubois *et al*., 1997a). Since in these cells only non-phosphorylated 14-3-3ζ binds to Raf-1 kinase (Rommel *et al*., 1996), it has been concluded that in vivo phosphorylation at Thr232 inhibits interaction between 14-3-3ζ and Raf-1 kinase. Some studies found the conformational changes of 14-3-3ζ C-terminal stretching caused by phosphopeptide binding and phosphorylation at Thr232 (Silhan *et al*., 2004). Time-resolved fluorescence measurements revealed that the phosphopeptide binding changes the conformation and increases the flexibility of 14-3-3ζ C-terminal stretch, proving that this region is directly concerned in ligand binding. The Förster Resonance Energy Transfer (FRET) measurements between Trp residue inserted into the C-terminal segment and a dansyl group (attached at two different cysteine residues) pointed out that without ligand, the C-terminal segment occupies the ligand binding groove of the 14-3-3 protein. Upon the phosphopeptide binding the C-terminal segment is displaced from the ligand binding groove and its flexibility increases. Phosphorylation of 14-3-3ζ at Thr232 changed the structure of the C-terminal segment and resulted in inhibition of phosphopeptide binding (Obsilova *et al*., 2004; Silhan *et al*., 2004). The precise mechanism of this inhibition is still unknown, but it is possible to speculate that phosphorylation-induced conformational change could affect interactions between the C-terminal segment and the ligand binding groove thus making its displacement from the groove more difficult.

Regulation of 14-3-3 by Phosphorylation: Phosphorylation is the first post-translational modification and affects nearly one-third of all proteins in the cell (Gough and Foley, 2010). And can regulate the function14-3-3 in a number of different ways. First, it can be accomplished by regulating the changes in content 14-3-3. It was found that over expression of 14-3-3 is accompa- Nied by increase in total activity Raf-1 and reduction in protein kinase C activity (Fu *et al*., 2000). This can lead to the evolution of oncological diseases and is associated with the serious damage DNA by the p53-dependent induction of 14-3-3s synthesis. Second, certain isoforms of 14-3-3 are caspase substrates hydrolyzed protein is limited to some isoforms of 14-3-3 leads to the liberation of proteins proapoptotic (Bad and Bax), which led to the initiation of apoptosis (Won *et al*., 2003). Third, 14-3-3 is subject to the changes after the various transport. For example, acetylation of Lys residues of 14-3-3 involved in pillar binding may significantly affect the protein-protein interactions (Choudhary *et al*., 2009). It also contains proteins 14-3-3 on a number of locations phosphorylated by various protein kinases for example,

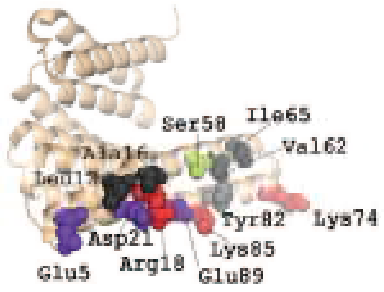

Fig. 2: Site interaction monomers of 14-3-3; The structure of the monomer 14-3-3 spirals as beige; Show remnants without charge to participate in the dimerization in black and gray; An Ser58 to participate in the organization of dimerization in green; Show remnants participate in the formation of salt bridges between 14-3-3 monomers in red (positively charged) and violet (negatively charged) (Sluchanko *et al*., 2008)

Protein kinase SDK1 (Megidish *et al*., 1998), protein kinase A (PKA) activated by sphingosine (Ma *et al*., 2005), some isoforms of protein kinase C, protein kinase B (PKB/Akt), Bcr (The product of an oncogene protein Breakpoint cluster region) (Clokie *et al*., 2005) and a isoform of casein kinase I (CKI) which phosphorylate with Ser58, Ser63, Ser184 and Thr232 of 14-3-3. It is well known that phosphorylation affects the structure and properties of 14-3-3, despite efforts to answer the question how it affects phosphorylation 14-3-3 performance remains elusive. It is also accepted that the range Ser63 phosphorylation is low, it is not very important (Dubois *et al*., 1997b). However, the phosphorylation of Ser58, Ser184 and Thr232 they effectively *in vivo* (Ahmed *et al*., 2008). Therefore, the analysis of the phosphorylation sites are of great importance. And not all of the isoforms of 14-3-3 contain Ser or Thr in similar sites. Thus, Ser58 of 14-3-3 is phosphorylated by a number of various protein kinases both in vitro and in vivo. Nevertheless, there is no agreement on the question of how Ser58 phosphorylation of the structure and properties of 14-3-3. It was found that PKA or MAPKAP2 stimulating kinase phosphorylation of Ser58 14-3-3Z or mutation S58E/D simulation leads to phosphorylation and accumulation of dimer dissociation 14-3-3 monomers. So, it was supposed that phosphorylation of Ser58 located at the intersubunit contact (Fig. 2) It plays an important role in regulating of the oligomeric state of 14-3-3. The investigation revealed the mutant S58E point simulation phosphorylation that the replacement of Ser by Glu by leads to dimer dissociation, reduces thermostability and increases the chances of exposure to the protein 14-3-3Z. These changes are more obvious, especially in the low concentration of the protein and may indicate that phosphorylation of Ser58 raises dimer dissociation of 14-3-3. Phosphorylation of Ser58 pays not only dissociation of the dimer 14-3-3 but it also reduces the interaction of 14-3-3 with the p53 transcriptional factor (Sunayama *et al*., 2005). It also found that the phosphorylation of Thr232 located at the C terminal of 14-3-3 reduces protein interaction with different substrates. Due to the fact that the C-terminal end could overburden 14-3-3 inner channel and in this way to interact with the locations responsible for the binding of protein substrates (Nikolai *et al*., 2012). Thus, we conclude that phosphorylation affects the physical and chemical characteristics of 14-3-3 and may be participate in regulating the interaction of 14-3-3 with different protein objectives. It is worth pointing out that interaction of 14-3-3 with substrates protein regulates mostly through phosphorylation of protein targets. Therefore, can identify the specific sites of protein phosphorylation targets 14-3-3 and the formation of a narrow site interaction with protein substrates 14-3-3.

Role of 14-3-3 proteins in regulating cell cycle: 14-3-3 proteins regulating the cell cycle by controlling the distribution of nuclear and cytoplasmic signals of molecules that interact with it. 14-3-3 proteins have vital functions during cell divisions without hindrance and several mechanisms to involve associations 14-3-3 Legend ensure that the division is not activated untimely before the completion of DNA doubling in interphase (Brunet *et al*., 2004). Also 14-3-3 proteins regulate the cell cycle through a checkpoint kinase 1 (Chk1) (Jiang *et al*., 2003) and phosphorylation of cell division cycle 25 phosphatases (CDC25 s) (Forrest and Gabrielli, 2001) and cyclin-dependent kinase 1 (CDK1) (Samuel *et al*., 2001). CDC25 are the main target for regulation 14-3-3. CDC25 activate CDKs by dephosphorylation, which thereby stimulating cell cycle progression. CDC25 involved at different stages of the cell cycle. CDC25A involved in organizing the G1/S transition, while the accumulation of phosphorylated (an inactive) forms of CDK s, which are not able to participate in the initiation of recurrence (Sancar *et al*., 2004).

In addition mitogen-activated protein kinase kinase kinase 7 (TAK1), which may be involved in the phosphorylation of CDC25B and CDC25C. Different isotypes of 14-3-3 proteins prevent phosphorylated CDC25s, maybe that results in the maintaining the CDC25s in the cytoplasm and prevent access of CDKs to the catalytic site of CDC25s (Bulavin *et al*., 2003). Also, CDK1 is organized by 14-3-3 proteins directly through 14-3-3 via or sigma Wee1. Active Wee1 prevents Cdk1 by Tyr15 phosphorylation. Wee1 may be stimulated by 14-3-3 alpha/beta and 14-3-3 delta/zeta isotypes. In addition, Wee1 phosphorylation by protein kinase B (AKT) on Ser-642 may be maintained into cytoplasm by 14-3-3 eta. It turns out that some of the proteins isotypes of 14-3-3 (14-3-3 gamma, 14-3-3 tau, 14-3-3 epsilon and 14-3-3 sigma) (Mhawech, 2005) may activate p53. Ionizing radiation caused by dephosphorylation of p53 on Ser-376 is essential for this process.

Role of 14-3-3 in Apoptosis: Apoptosis is a form of programmed cell death that eliminates the individual cells within the organism, while maintaining the overall structure of the surrounding tissue. And also plays a critical role in the normal development and pathophysiology of a variety of diseases. The role of 14-3-3 in apoptosis has been indicate by several reports that 14-3-3 protein binding partners interacting with the target begins to events that support cell survival, therefore mediate an essential anti-apoptotic signal (Masters *et al*., 2002). Some studies have indicated that 14-3-3 proteins bind family members Bcl-2, Bcl-XL/Bc1-2-associated death promoter (BAD) and BCL 2 associated protein X (BAX), thus inhibiting their activities proapoptotic (Zha *et al*., 1996). In addition, overexpression of 14-3-3 block cell death initiated by the promoters of death, such as apoptosis signal regulating kinase 1 (ASK1) (Zhang *et al*., 1999). Also, 14-3-3 protein reaction with a members of the family of the forkhead transcription factors and protein box forkhead (Fox03a), nuclear translocation and blocks transcription of genes death (Brunet *et al*., 1999). Therefore, prevent apoptosis through 14-3-3 based cooperation with ASK1, BAD and Fox03a suggests that 14-3-3 has the function of key anti- apoptotic cells. Moreover, the expression of a peptide that prevents 14-3-3 cooperation with the binding proteins enhances apoptosis and reduces the usefulness in many cancer cell lines (Cao *et al*., 2010). The use of 14-3-3 antisense RNA molecules in cancer cell lines more the sensitivity of the stress -induced apoptosis (Neal *et al*., 2009). Additionally, the results of cell treatment with 2-methoxyestradiol decrease 14-3-3 expression that promotes cell activation and prevents the growth of cells (Kumar *et al*., 2003). The comprehensive analysis of 14-3-3 binding proteins in undisputed cells and compared with those subject to stimulate apoptosis and suggests new cell functions for 14-3-3 proteins. Taking into consideration the facts that 14-3-3 association protein with binding partners paid cell survival signal. And this is of great importance for the analysis of the role of protein in the 14-3-3 mechanism which controls in cell fate, for instance autophagy, cancer, diabetes, Parkinson's disease and other neurological disorders (Kim *et al*., 2011; Mercedes, 2012; Shimada *et al*., 2013).

CONCLUSION

In recent years significant progress has been made in discovering targets of the 14-3-3 family of proteins, Thus, we can conclude that the proteins of the 14-3-3 isoforms play various roles in the regulation of many cellular proteins. While they activate or stabilize some proteins and inactivate others, for many proteins 14-3-3 isoforms play an organizing role as a "scaffold" molecules. During the formation of a functional from a wide range of targets, 14-3-3 isoforms are participates in several processes, including regulation of the cell cycle metabolic control, apoptosis, phosphorylation and control of gene transcription. Due to the multitude of 14-3-3 binding partners and physiological activities, a specific definition of their cellular role or function is difficult. Recent studies have confirmed significant progress towards clarifying the functions of 14-3-3 proteins and proteomics approaches has allowed us to improve the understanding of the interactions with other proteins 14-3-3. However, much yet remains to be discovered. The mechanisms of 14-3-3 protein action is now known to be complex and their better understanding will require the crystal structure of additional 14-3-3 targets, both free and in complex with 14-3-3 proteins. Future research may explain how specific 14-3-3 isoforms regulate distinct proteins involved in cell cycle regulation and may inspire therapeutic inhibition of these interactions.

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