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REVIEW

## Integrate Omics Data and Molecular Dynamics Simulations toward Better Understanding of Human 14-3-3 Interactomes and Better Drugs for Cancer Therapy

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#### ABSTRACT

The 14-3-3 protein family is among the most extensively studied, yet still largely mysterious protein families in mammals to date. As they are well recognized for their roles in apoptosis, cell cycle regulation, and proliferation in healthy cells, aberrant 14-3-3 expression has unsurprisingly emerged as instrumental in the development of many cancers and in prognosis. Interestingly, while the seven known 14-3-3 isoforms in humans have many similar functions across cell types, evidence of isoform-specific functions and localization has been observed in both healthy and diseased cells. The strikingly high similarity among 14-3-3 isoforms has made it difficult to delineate isoform-specific functions and for isoform-specific targeting. Here, we review our knowledge of 14-3-3 interactome(s) generated by high-throughput techniques, bioinformatics, structural genomics and chemical genomics and point out that integrating the information with molecular dynamics (MD) simulations may bring us new opportunity to the design of isoform-specific inhibitors, which can not only be used as powerful research tools for delineating distinct interactomes of individual 14-3-3 isoforms, but also can serve as potential new anti-cancer drugs that selectively target aberrant 14-3-3 isoform.

KEYWORDS: Interactome; Chemical genomics; Structural genomics; Molecular dynamics simulation

### **INTRODUCTION**

First discovered by nervous system protein analysis through ion-exchange chromatography and gel electrophoresis, the 14-3-3 proteins were so named as a description of the enriched fraction number (Moore and Perez, 1968). Later 14-3-3 protein family was observed in almost all eukaryotic organisms from yeast to plants to humans, although the number of isoforms varies greatly among species. In humans, there are seven known 14-3-3 proteins:  $\beta$  (identical to  $\alpha$  when phosphorylated),  $\gamma$ ,  $\varepsilon$ ,  $\eta$ ,  $\zeta$  (identical to  $\delta$  when phosphorylated),  $\theta$ , and  $\sigma$ . Although they are not the results of alternative splicing,

\* Corresponding author. Tel: +1 317 274 7645, fax: +1 317 274 1560. *E-mail address:* jliu2@iu.edu (J.-Y. Liu). the seven human isoforms have highly similar primary sequences (Fig. 1). Not only is each isoform coded by a different gene, but also the gene for each isoform is located on a different chromosome. Due to their widespread presence in multiple subcellular locations and involvement in various signaling pathways, misregulated 14-3-3 expression can contribute to, or be the cause of, many diseases such as neurological diseases and cancers (Fu et al., 2000a; Zhao et al., 2011b). Thus, work to elucidate the involvement of 14-3-3 proteins in both diseases has been pursued for decades (Berg et al., 2003; Mhawech, 2005). In this review, we summarize the currently known functions of the human 14-3-3 isoforms and their contributions to cancers. We touch on their unique properties and omics studies using high-throughput genomics, as well as structural and chemical genomics.

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	H1	H2	H3		H4	
14-3-3γ	-MVDREQLVQKARLAEQA	ERYDDMAAAMKNVTELNE	PLSNEERNLLSVAYKNVVGARR	SSWRVISSIEQKTSADGN	EKKIEMVRAYREKIEKELEAVCQD	99
14-3-3n	-MGDREQLLQRARLAEQA	ERYDDMASAMKAVTELNE	PLSNEDRNLLSVAYKNVVGARR	SSWRVISSIEQKTMADGN	EKKLEKVKAYREKIEKELETVCND	99
$14-3-3\beta/\alpha$	MTMDKSELVQKAKLAEQA	ERYDDMAAAMKAVTEQGH	IELSNEERNLLSVAY KNVVGARR	SSWRVISSIEQKTERN	EKKQQMGKEYREKIEAELQDICND	98
14-3-3ζ/δ	MDKNELVQKAKLAEQA	ERYDDMAACMKSVTEQGA	<b>AELSNEERNLLSVAY KNVVGARR</b>	SSWRVVSSIEQKTEGA	EKKQQMAREYREKIETELRDICND	96
14-3-30	MEKTELIQKAKLAEQA	ERYDDMATCMKAVTEQGA	ELSNEERNLLSVAY KNVVGGRR	SAWRVISSIEQKTDTS	DKKLQLIKDYREKVESELRSICTT	96
14–3–3σ	MERASLIQKAKLAEQA	ERYEDMAAFMKGAVEKGE	ELSCEERNLLSVAYKNVVGGQR	AAWRVLSSIEQKSNEEGS	EEKGPEVREYREKVETELQGVCDT	98
14–3–3ε	-MDDREDLVYQAKLAEQA	ERYDEMVESMKKVAGMDV	ELTVEERNLLSVAY KNVIGARR	ASWRIISSIEQKEENKGGI	EDKLKMIREYRQMVETELKLICCD	99
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		H5	H6	]	H7 H8	
14–3–3γ	VLSLLDNYLIKNCSETQY	ESKVFYLKMKGDYYRYLA	EVATGEKRATVVES SEKAYSEA	HEISKEHMQPTHPIRLGL	ALNYSVFYYEIQNAPEQACHLAKT	199
14-3-3η	VLSLLDKFLIKNCNDFQY	ESKVFYLKMKGDYYRYLA	EVASGEKKNSVVEA SEAAYKEA	FEISKEQMQPTHPIRLGL	ALNFSVFYYEIQNAPEQACLLAKQ	199
14-3-3β/α	VLELLDKYLIPNATQP	ESKVFYLKMKGDYFRYLS	EVASGDNKQTTVSN SQQAYQEA	FEISKKEMQPTHPIRLGL	ALNFSVFYYEILNSPEKACSLAKT	196
14–3–3ζ/δ	VLSLLEKFLIPNASQA	ESKVFYLKMKGDYYRYLA	EVAAGDDKKGIVDQ SQQAYQEA	FEISKKEMQPTHPIRLGL	ALNFSVFYYEILNSPEKACSLAKT	194
14-3-30	VLELLDKYLIANATNP	ESKVFYLKMKGDYFRYLA	EVACGDDRKQTIDN SQGAYQEA	FDISKKEMQPTHPIRLGL	ALNFSVFYYEILNNPELACTLAKT	194
14-3-3σ	VLGLLDSHLIKEAGDA	ESRVFYLKMKGDYYRYLA	EVATGDDKKRIIDS ARSAYQEA	MDISKKEMPPTNPIRLGL	ALNFSVFHYEIANSPEEAISLAKT	196
14–3–3ε	ILDVLDKHLIPAANTG	ESKVFYYKMKGDYHRYLA	EFATGNDRKEAAEN SLVAYKAA	SDIAMTELPPTHPIRLGL	ALNFSVFYYEILNSPDRACRLAKA	197
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		Н9				
14 2 20				247		
$14 - 3 - 3\gamma$				247		
$14-3-36/\alpha$	AFDEAIAELDTLNEESYK	DSTLIMOLLRDNLTLWTS	ENOGDEG-DAGEG-EN	246		
14-3-3ζ/δ	AFDEAIAELDTLSEESYK	DSTLIMOLLRDNLTLWTS	DTOGDEA-EAGEGGEN	245		
14-3-30	AFDEAIAELDTLNEDSYK	DSTLIMQLLRDNLTLWTS	DSAGEEC-DAAEGAEN	245		
$14 - 3 - 3\sigma$	TFDEAMADLHTLSEDSYK	DSTLIMQLLRDNLTLWTA	ADNAGEEGGEAPQEPQS	248		
14-3-3ε	AFDDAIAELDTLSEESYK	DSTLIMQLERDNETLWTS	DMQGDGEEQNKEALQDVEDENQ	255		
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Fig. 1. Multiple sequence alignment of all seven human 14-3-3 isoforms by Clustal 2.1. Asterisks indicate identical residues across all seven isoforms. Positions of helices 1–9 are indicated by solid bars on the top.

Here, we borrow the term "interactome" and refer to "14-3-3 interactome(s)" as the whole set of proteins that directly interact with 14-3-3 proteins or certain 14-3-3 isoform. We suggest the integration of these data through the study of the energetics and dynamics of 14-3-3 proteins could be an approach to generate isoform-specific 14-3-3 inhibitors, which not only have potential for drug development with regards to cancer treatment, but also can be used as a powerful research tool to study different 14-3-3 isoforms.

#### GENERAL CELLULAR FUNCTIONS OF 14-3-3 PROTEINS AND THEIR CLINICAL IMPLICATIONS IN CANCER

The 14-3-3 protein family has a vast range of activity in eukaryotic cells, including functions in signaling pathways for cell cycle control, proliferation, and apoptosis (Messaritou et al., 2010). To overcome functional redundancy and compensate from different family members by classical genetics study for overall 14-3-3 protein function, Nguyen et al. (2004) performed functional knock-out (FKO) studies using a chemical genetics approach. Activity of all isoforms of 14-3-3 was antagonized simultaneously upon activation of caged phosphopeptides through exposure to UV-A. Not only was cell death significantly increased in U20S cells in response to phosphopeptide activation, but also the rate at which cells undergoing division reached mitosis was significantly accelerated. These observations, coupled with the noted decrease in the fraction of non-dividing cells in stable G1 phase, imply a modulatory role of 14-3-3 proteins in the entrance to the mitotic stage of cell division (Clapp et al., 2012). In 2001, Masters and Fu observed that elimination of 14-3-3/Raf-1 interaction through use of the pan isoform 14-3-3 antagonist, difopein, resulted in death of HEK293 cells (Masters and Fu, 2001). This apoptotic response appears to be the consequence of lost signal transduction between pro-survival kinases, such as protein kinase C, phosphatidylinositol 3-kinase, and MAPKKK1, and apoptotic proteins, such as Bad, in the COS-7 cell line (Masters and Fu, 2001). Use of difopein on glioma cell line U251 also generated an apoptotic response as suggested by DNA ladder marker experiments. Decreased levels of pro-survival factor Bcl-2 mRNA and increased levels of pro-apoptotic factor Bax mRNA upon cell transfection with difopein-containing plasmid further indicate the importance of 14-3-3 in pro-survival signal transduction process (Yang et al., 2009). These observations paint 14-3-3 proteins as signal integrators: the connection between phosphorylation by kinases such as PKC and decreased apoptotic protein activity.

To trace their individual functions, knockdown/knockout or overexpression of individual 14-3-3 isoforms, especially in the context of cancer, has been extensively investigated. For example, the  $\sigma$  isoform appears to provoke cellular migration through forming a complex with cytoskeletal components and allowing them to be readily available during migration (Boudreau et al., 2013). In the absence of 14-3-3 $\zeta$  expression, the activity of both the c-Jun N-terminal kinase (JNK) and p38/MAPK pathways appear to be involved in the negative regulation of hepatoma cell proliferation (Choi et al., 2011). When HepG2 liver hepatocellular carcinoma cells were transfected with siRNA against 14-3-3 $\zeta$ , the amount of cell Download English Version:

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