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Functional Influence of 14-3-3 (YWHA) Proteins in Mammals

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Abstract

The 14-3-3 (YWHA) proteins are homologous, ubiquitous, and conserved in most organisms ranging from plants to animals and play important roles in regulating key cellular events such as cell signaling, development, apoptosis, etc. These proteins consist of seven isoforms in mammals, termed under Greek alphabetization: beta (β), gamma (γ), epsilon (ε), eta (η), tau/theta (τ), sigma (σ), and zeta (ζ). Each of these isoforms can interact with a plethora of binding partners and has been shown to serve a distinct role in molecular crosstalk, biological processes, and disease susceptibility. Protein 14-3-3 isoforms are scaffolding proteins capable of forming homodimers and heterodimers in mammalian cells. The dimerizing abilities of these isoforms have helped the understanding of their importance in mammalian cells. This article provides a comprehensive review encapsulating the functional influence of the 14-3-3 isoforms in various species, cells, tissues, organs, developmental stages, and disease states within mammals.

Keywords: 14-3-3 proteins, 14-3-3 isoforms, YWHA, functions, mammals

Introduction

Functionality is an important factor in the understanding of mammalian organisms' physiology. There is an abundance of protein isoforms that affect the functionality of mammalian organisms across various species. The 14-3-3 (Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation protein) was initially discovered in brain tissues by Moore and Perez (Aitken, 2006). This family of proteins has been shown to constitute seven isoforms in mammals (Muslin et al., 1996). The seven 14-3-3 isoforms present in mammals have been classified under Greek alphabetization: 14-3- 3 beta(β), gamma(γ), epsilon(ε), eta(η), tau/theta(τ), sigma(σ), and zeta(ζ).

The structural overview of 14-3-3 indicates that these proteins are capable of forming homodimers and heterodimers, which can interact with a multitude of other proteins. The structure of these proteins plays an essential role in their function. Every monomer of 14-3-3 possesses a similar helical structure and produces a conserved, amphipathic, and concave groove which associates with target proteins, particularly through phosphoserine/phosphothreonine-containing motifs, that can influence cell division, apoptosis, and differentiation in mammalian species (Rittinger et al., 1999).

The highly conserved protein, 14-3-3, through its seven isoforms, regulates several cellular functions and processes. In this review, we will analyze the functional significance of each of the 14-3-3 isoforms within mammalian species, tissues, and developmental stages. We will highlight the roles of each isoform primarily in *Homo sapiens* (humans) and *Mus musculus* (mouse), in addition to other mammalian species. The functions in apoptosis, phosphorylation, cell cycle control, and binding of each isoform with other proteins/factors will also be discussed in this review. Protein 14-3-3 isoforms are associated with regulation of diverse diseases in *Homo sapiens*; these connections will be reviewed in greater depth.

Functions of 14-3-3 Proteins in Various Mammalian Species

The isoforms of 14-3-3 protein are homologous in nature. When comparing each of these isoforms amongst species, it is apparent that *Homo sapiens* and *Mus musculus* are comparable in terms of molecular function, biological processes, and canonical sequence. The similarity in 14-3-3 isoforms' function between *Homo sapiens and Mus musculus* can be attributed to the comparable synteny and homologous genes of mutuality in both species (Monaco et al., 2015). The seven mammalian isoforms of 14-3-3, viz. β, γ, ε, η, τ, σ (stratifin or SFN), and ζ, are all

found as scaffolding proteins and function as ligand binders using a phosphoserine or a phosphothreonine motif in both the featured species (Cornell & Toyo-Oka, 2017).

Protein 14-3-3β inhibits the transcription of osteogenesis and signaling pathway in *Homo sapiens* and *Mus musculus*. The 14-3-3β isoform is found in the cytoplasm of *Homo sapiens* and *Mus musculus* as homodimers and heterodimers. Ror2 is a protein receptor expressed in the featured species that are responsible for chemical signaling between cells; research has shown that the Ror2 receptor phosphorylates 14-3-3β (Liu et al., 2007). This phosphorylation has shown that the β isoform is a direct substrate to Ror2 which functions to prevent osteogenic differentiation of human Mesenchymal Stem Cells (hMSCs). In *Mus musculus*, it is seen that 14-3-3β behaves as an inhibitor of osteoblast number and action. Isoform 14-3-3β is a negative regulator of osteogenesis bound to TAZ (protein-coding gene) in both the featured species. This binding regulates cellular localization of osteogenic differentiation factors (Liu et al., 2007). Research indicates that the 14-3-3β isoform has been isolated in *Ovis aries* (sheep); it was determined that there were high levels of expression of the β isoform in the brain of the species which inhibit the protein kinase C (PKC) in the cell (Wheeler-Jones et al., 1996).

The 14-3-3γ isoform functions as a murine double minute X (MDMX)-regulator in the presence of UV radiation exposure in *Homo sapiens*. This isoform has been shown to activate p53 through the repression of MDMX function in *Homo sapiens* and *Mus musculus*. MDMX is an oncoprotein known for its ability to bind to the p53 tumor suppressor protein. This oncoprotein has been shown to bind to 14-3-3γ with a high affinity. Research has stated that Chk1 UV radiation exposure activates the interaction between 14-3-3γ and MDMX in vitro. The interaction between the isoform and MDMX had led to the understanding that the γ isoform performs to complete G1 arrest and p53 activation by binding to MDMX phosphorylated by

Chk1 (Jin et al., 2006). The 14-3-3γ isoform has also shown significant expression in the spinal fluid of *Bovinae* affected by prion disease (Chaudhri et al., 2003).

Protein 14-3-3ε allows the process of transcription to occur with Heat Shock Factor 1 (HSF1) from the nucleus to the cytoplasm in *Homo sapiens and Mus musculus*. The binding of HSF1 to 14-3-3ε occurs in the cytoplasm and functions to prevent transcription of HSF1. The HSF1 is a transcriptional factor present in mammalian cells that is critical in the development and stress response of an organism. Protein 14-3-3ε isoform associates to the regulatory domain of HSF1 and leads to the inhibition of HSF1. Research has indicated that the binding of ε to HSF1 inhibits its functions and prevents the transcription of proteins compulsory for folding and unfolding macromolecular structures during the featured species' developmental growth (Wang et al., 2003). The presence of 14-3-3ε has been confirmed in *Rattus norvegicus* (brown rat), the ε protein amplifies the activity of the EAG K+ channel (Hsu et al., 2012).

Protein isoforms 14-3-3η and 14-3-3τ perform identical functions in both species. These isoforms prevent the transcription of 3-Phosphoinositide-dependent protein kinase-1 (PDK1) phosphorylation in *Homo sapiens and Mus musculus*. Protein 14-3-3η and τ have identical interactions in mammalians. Research indicates that these isoforms prevent gene expression of PDK1 via the development of a complex. The PDK1 gene is an enzyme responsible for carbohydrate fuel homeostasis regulation in mammalians. The η and τ isoforms of 14-3-3 interact with PDK1 through protein-protein interaction, these are the only isoforms from the 14-3-3 protein family that, in vitro, bind to PDK1. However, it is seen that 14-3-3τ has a greater affinity to PDK1 than 14-3-3η. To indicate the function of 14-3-3η and τ in PDK1 inhibition, researchers transfected *Myr*-Akt protein with cDNA from 14-3-3η and τ and were able to determine that these isoforms repress PDK1 phosphorylation and its binding is essential in signal

transduction (Sato et al., 2002). Proteins 14-3-3η have also been identified in the brains of *Murinae* experiencing neurodegeneration (Baxter et al., 2002). Studies have shown that 14-3-3τ functions with upward regulation in *Rattus norvegicus* (brown rat) post hypoglossal nerve injury (Shimada et al., 2013).

The 14-3-3ζ isoform functions as a regulator and protein binder in both the species. The functions of the seven 14-3-3 isoforms in *Homo sapiens, Mus musculus,* and *Rattus norvegicus* are extensive and play a critical role in the regulation of several biological processes. Research has shown that the phosphorylation of 14-3-3ζ isoform in human embryonic kidney cells may be linked to its function of protein complex formation regulation and signal transduction. It has also been identified that the ζ isoform exhibits prolific phosphorylation at the Casein Kinase I site. The phosphorylation of 14-3-3ζ prevents interrelation with Raf proteins and other proteins essential for differentiation, cell survival, and cell growth in *Homo sapiens* and *Mus musculus* (Dubois et al., 1997). Protein 14-3-3ζ has also been shown to play a crucial role in cell signaling and cytoskeletal rearrangements of *Mus musculus* (Angrand et al., 2006).

Functions of 14-3-3 Proteins in Mammalian Cells, Tissues, and Organs

Each of the seven 14-3-3 isoforms have been studied and detected across various mammalian species. It has been determined that this protein family displays its greatest rate of expression in the brain; although it is found in all cell types. The 14-3-3ε isoform has shown high levels of expression in the testes, adipocytes, and lymphocytes of *Homo sapiens*. Studies have shown that each isoform functions vary depending on tissue presence. Protein 14-3-3γ is noted to be expressed in embryonic stem cells, skeletal muscle, and the heart of *Homo sapiens*. Research has determined that the ε and γ isoforms behave as negative regulators in Leydig cells during the

formation of androgen. Protein 14-3-3τ has been indicated to have an affinity for endothelial cells while 14-3-3σ has shown high specificity for T cells (Aghazadeh et al., 2015). The 14-3-3β isoform has shown expression in keratinocytes (Leffers et al., 1993). Protein 14-3-3η has been found in the joints of *Homo sapiens* and indicated to function as an up regulator of cytokines and enzymes (Carrier et al., 2016). The ζ isoform is known for its presence in the lungs of *Homo sapiens*, it has been inferred that the ζ isoform may be essential in its standard function (Qi et al., 2005). An intermediate filament protein, keratin 17 (K17) which is induced quickly in stratified epithelia that are wounded, interacts with 14-3-3σ, thereby regulating cell growth (Kim et al., 2006).

Functions of 14-3-3 Proteins in Mammalian Developmental Stages

The seven isoforms of the 14-3-3 proteins are essential in a multitude of developmental stages in mammals. Research has shown that these isoforms are crucial in the regulation of the cell cycle, metabolism, apoptosis, intracellular protein trafficking, and cell signaling. Each of these proteins interacts differently depending on which mammalian species in which they are present (Aghazadeh et al., 2015). Cell cycle in mitotic and meiotic cells as well as other cellular processes are governed by 14-3-3; multiple isoforms of 14-3-3 have been detected in various developmental stages of adult mouse ovaries, oocytes, and eggs (De, 2014; Santanu De, Shawn Davis, et al., 2012; De & Kline, 2013; Santanu De & Douglas Kline, 2014; Santanu De & Douglas Kline, 2014; De, Marcinkiewicz, et al., 2011; S. De et al., 2012; De, Villarreal, et al., 2011; Eisa et al., 2019) as well as testis and sperm (Eisa et al., 2020; Puri et al., 2011; Puri et al., 2008). Over 200 binding partners of 14-3-3 in mouse oocytes and eggs have been identified, a notable one of which is the M-phase inducer phosphatase 2 (CDC25B) (De & Kline, 2011; De,

Reese, et al., 2011; Santanu De, Angela Reese, et al., 2012a, 2012b; Detwiler et al., 2015). Reproduction in several other mammalian species and cell-types also is regulated by 14-3-3 proteins (De, 2020a). Furthermore, the 14-3-3 proteins underlie signaling and development in many non-mammalian species such as the fruit-fly or *Drosophila melanogaster* (De, 2020b), and are differentially expressed with species-specific, isoform-specific, tissue-specific, and developmental stage-specific localizations in most mammals (Neha Kumrah & Santanu De, 2020; Neha Kumrah & Santanu De, 2020).

The 14-3-3 Proteins in Regulating Diseases within Mammals

The seven isoforms of protein 14-3-3 have been linked to various forms of disease in mammals. Research indicates that these protein isoforms function in neurodegenerative and neuropsychiatric diseases. Bipolar disorder is a mental illness associated with depression and heightened mood fluctuations. Schizophrenia is also a psychiatric disorder that affects a person's mood, increases depressive and mania feelings, and leads to hallucinations. It has been noted that 14-3-3η single nucleotide polymorphisms have a significant presence in the 22q12-13 chromosomal region of individuals diagnosed with schizophrenia and bipolar disorder. Genetic and mRNA research has indicated that 14-3-3ε, and ζ isoforms play a role in the vulnerability of individuals with schizophrenia. Protein isoforms 14-3-3ε, σ, and ζ have shown decreased mRNA levels in the brains of individuals with bipolar disorder. Further information on this can be found within an article on 14-3-3 proteins in neurological disorders (Foote & Zhou, 2012).

The 14-3-3 proteins also show a presence in various forms of cancer. Studies have indicated that 14-3-3ζ is overly expressed in patients with breast, lung, and other cancers. This overexpression has been linked to the capability of 14-3-3ζ and other isoforms allowing

chemoresistance (Bergamaschi et al., 2011). Protein 14-3-3γ isoform has been indicated for its relation to prion disease in various species. *Bovine* systems have been shown to contain a substantial amount of 14-3-3γ in their spinal fluid. This isoform can be researched in greater depth to confirm its correlation with prion diseases (Chaudhri et al., 2003).

Protein 14-3-3σ inhibits tumor growth by positively regulating p53 and protecting it from ubiquitination and degradation mediated by mouse double minute 2 homolog (MDM2) (Yang et al., 2006; Yang et al., 2003). Caspase 8/10-associated RING (CARP) proteins are ligases that target p53 for degradation in mammalian cells. When the CARP2 protein interacts with 14-3-3σ it leads to the stabilization of MDM2. MDM2 is a protein present in *Homo sapiens* and *Mus musculus* that inhibits the process of transcription of the p53 tumor suppressor. Since 14-3-3σ functions to activate p53 in mammalian cells following DNA damage, caspase 8/10-associated 'really interesting new gene' or RING proteins 2 (CARP2) degrade this isoform to stabilize MDM2 (Yang et al., 2008).

Discussion

Supported by a wide range of research, numerous experimental evidences have determined that the 14-3-3 proteins are essential in the regulation of a multitude of mammalian species, cellular/physiological processes, and developmental stages (Barley & De, 2020). Each of the seven mammalian 14-3-3 isoforms exists as homodimers and heterodimers that bind to proteins necessary for cell differentiation and growth. Several research investigations on the significance of each of the isoforms have confirmed the presence, role, and disease-inducing factors associated with the isoform in several mammalian species. This review summarizes key functional impacts of these proteins in a wide variety of cells, tissues, organs, developmental

stages, and disorders within several mammalian species. Further studies on the isoform-specific functions of 14-3-3 will enhance the understanding of the centrality of these critical regulatory proteins in mammalian systems and may assist the diagnosis, prognosis, and/or treatment of relevant disorders.

References

Aghazadeh, Y., Zirkin, B. R., & Papadopoulos, V. (2015). Pharmacological regulation of the cholesterol transport machinery in steroidogenic cells of the testis. *Vitam Horm, 98*, 189-227. https://doi.org/10.1016/bs.vh.2014.12.006

Aitken, A. (2006). 14-3-3 proteins: a historic overview. *Semin Cancer Biol, 16*(3), 162-172. https://doi.org/10.1016/j.semcancer.2006.03.005

Angrand, P. O., Segura, I., Volkel, P., Ghidelli, S., Terry, R., Brajenovic, M., Vintersten, K., Klein, R., Superti-Furga, G., Drewes, G., Kuster, B., Bouwmeester, T., & Acker-Palmer, A. (2006). Transgenic mouse proteomics identifies new 14-3-3-associated proteins involved in cytoskeletal rearrangements and cell signaling. *Mol Cell Proteomics, 5*(12), 2211-2227. https://doi.org/10.1074/mcp.M600147-MCP200

Barley, E., & De, S. (2020). Functions of 14-3-3 proteins and their isoforms across various mammaliam species, cells, tissues, organs and developmental stages [Presentation]. https://nsuworks.nova.edu/trick/2020/events/12/ (Trick to the Treat of Internships and Research, Nova Southeastern University)

Baxter, H., Liu, W.-G., Forster, J., Aitken, A., & Fraser, J. (2002). Immunolocalisation of 14-3-3 isoforms in normal and scrapie-infected murine brain. *Neuroscience, 109*(1), 5-14. https://doi.org/https://doi.org/10.1016/S0306-4522(01)00492-4

Bergamaschi, A., Christensen, B. L., & Katzenellenbogen, B. S. (2011). Reversal of endocrine resistance in breast cancer: interrelationships among 14-3-3zeta, FOXM1, and a gene signature associated with mitosis. *Breast Cancer Res, 13*(3), R70. https://doi.org/10.1186/bcr2913

Carrier, N., Marotta, A., de Brum-Fernandes, A. J., Liang, P., Masetto, A., Menard, H. A., Maksymowych, W. P., & Boire, G. (2016). Serum levels of 14-3-3eta protein supplement C-reactive protein and rheumatoid arthritis-associated antibodies to predict clinical and radiographic outcomes in a prospective cohort of patients with recent-onset inflammatory polyarthritis. *Arthritis Res Ther, 18*, 37. https://doi.org/10.1186/s13075-016-0935-z

Chaudhri, M., Scarabel, M., & Aitken, A. (2003). Mammalian and yeast 14-3-3 isoforms form distinct patterns of dimers in vivo. *Biochemical and Biophysical Research Communications, 300*(3), 679-685. https://doi.org/https://doi.org/10.1016/S0006-291X(02)02902-9

Cornell, B., & Toyo-Oka, K. (2017). 14-3-3 Proteins in Brain Development: Neurogenesis, Neuronal Migration and Neuromorphogenesis. *Front Mol Neurosci, 10*, 318. https://doi.org/10.3389/fnmol.2017.00318

De, S. (2014). *Protein 14-3-3 (YWHA) isoforms and their roles in regulating mouse oocyte maturation* Kent State University]. Electronic Thesis or Dissertation. http://rave.ohiolink.edu/etdc/view?acc_num=kent1401803571

De, S. (2020a). The 14-3-3 (YWHA) Proteins in Mammalian Reproduction. *International Annals of Science, 10*(1), 52-59. https://doi.org/https://doi.org/10.21467/ias.10.1.52-59

De, S. (2020b). The 14-3-3 (YWHA) Proteins in Signalling and Development of the Fruit Fly, Drosophila melanogaster. *International Annals of Science, 9*(1), 80-85. https://doi.org/https://doi.org/10.21467/ias.9.1.80-85

De, S., Davis, S., Letwin, D., Mozena, C., & Kline, D. (2012). Protein 14-3-3 eta (YWHAH) is essential for normal meiotic spindle assembly during in vitro maturation of mouse oocytes [#1967]. *Mol Biol Cell, 23*. https://doi.org/10.1091/mbc.E12-10-0757

De, S., & Kline, D. (2011). Interactions of 14-3-3 proteins with CDC25B phosphatase in ovaries and oocytes of adult mice [Conference Presentation, 26th Annual Graduate Research Symposium, Kent State University]. https://nsuworks.nova.edu/cnso_bio_facpres/326

De, S., & Kline, D. (2013). Evidence for the requirement of 14-3-3eta (YWHAH) in meiotic spindle assembly during mouse oocyte maturation. *BMC Dev Biol, 13*(1), 10. https://doi.org/10.1186/1471-213X-13-10

De, S., & Kline, D. (2014). Erratum to: evidence for the requirement of 14-3-3eta (YWHAH) in meiotic spindle assembly during mouse oocyte maturation. *BMC Dev Biol, 14*(1), 20.

De, S., & Kline, D. (2014). The importance of 14-3-3 (YWHA) proteins in mammalian reproduction and fertility [Conference Presentation, 29th Annual Graduate Research Symposium, Kent State University]. https://nsuworks.nova.edu/cnso_bio_facpres/333

De, S., Marcinkiewicz, J., & Kline, D. (2011). Expression of 14-3-3 Protein Isoforms in Different Stages of Follicular Development in Adult Mouse Ovaries. *Biology of Reproduction, 85*(Suppl_1), 639. https://doi.org/10.1093/biolreprod/85.s1.639

De, S., Marcinkiewicz, J. L., Vijayaraghavan, S., & Kline, D. (2012). Expression of 14-3-3 protein isoforms in mouse oocytes, eggs and ovarian follicular development. *BMC Res Notes, 5*, 57. https://doi.org/10.1186/1756-0500-5-57

De, S., Reese, A., & Kline, D. (2011). Interactions of 14-3-3 protein isoforms with CDC25B phosphatase in mouse oocyte maturation [Conference Presentation, Duolink User Meeting]. https://nsuworks.nova.edu/cnso_bio_facpres/328

De, S., Reese, A., & Kline, D. (2012a). Duolink in situ proximity ligation assays reveal interactions of 14-3-3 protein isoforms with CDC25B phosphatase in mouse oocyte maturation [Conference Presentation, 27th Annual Graduate Research Symposium, Kent State University]. https://nsuworks.nova.edu/cnso_bio_facpres/332

De, S., Reese, A., & Kline, D. (2012b). Interactions of 14-3-3 (YWHA) protein isoforms with CDC25B phosphatase in mouse oocytes [#1571]. *Mol Biol Cell, 23*. https://doi.org/10.1091/mbc.E12-10-0757

De, S., Villarreal, B. F., Vijayaraghavan, S., & Kline, D. (2011). Identification of 14-3-3 Protein Isoforms and their Differential Subcellular Distribution in Mouse Oocytes and Eggs [#381]. *Mol Biol Cell, 22*. https://doi.org/10.1091/mbc.E11-08-0667

Detwiler, A. C., De, S., & Kline, D. (2015). Interactions of YWHA (14-3-3) protein isoforms with CDC25B phosphatase in regulating mouse oocyte maturation [Conference Presentation, 48th Annual Meeting of the Society for the Study of Reproduction]. https://nsuworks.nova.edu/cnso_bio_facpres/331

Dubois, T., Rommel, C., Howell, S., Steinhussen, U., Soneji, Y., Morrice, N., Moelling, K., & Aitken, A. (1997). 14-3-3 is phosphorylated by casein kinase I on residue 233. Phosphorylation at this site in vivo regulates Raf/14-3-3 interaction. *J Biol Chem, 272*(46), 28882-28888. https://doi.org/10.1074/jbc.272.46.28882

Eisa, A., Dey, S., Ignatious, A., Nofal, W., Hess, R. A., Kurokawa, M., Kline, D., & Vijayaraghavan, S. (2020). The protein YWHAE (14-3-3 epsilon) in spermatozoa is essential for male fertility. *Andrology*. https://doi.org/10.1111/andr.12865

Eisa, A. A., De, S., Detwiler, A., Gilker, E., Ignatious, A. C., Vijayaraghavan, S., & Kline, D. (2019). YWHA (14-3-3) protein isoforms and their interactions with CDC25B phosphatase in mouse oogenesis and oocyte maturation. *BMC Dev Biol*, *19*(1), 20. https://doi.org/10.1186/s12861-019-0200-1

Foote, M., & Zhou, Y. (2012). 14-3-3 proteins in neurological disorders. *Int J Biochem Mol Biol*, *3*(2), 152-164. https://www.ncbi.nlm.nih.gov/pubmed/22773956

Hsu, P. H., Miaw, S. C., Chuang, C. C., Chang, P. Y., Fu, S. J., Jow, G. M., Chiu, M. M., & Jeng, C. J. (2012). 14-3-3theta is a binding partner of rat Eag1 potassium channels. *PLOS ONE*, *7*(7), e41203. https://doi.org/10.1371/journal.pone.0041203

Jin, Y., Dai, M. S., Lu, S. Z., Xu, Y., Luo, Z., Zhao, Y., & Lu, H. (2006). 14-3-3gamma binds to MDMX that is phosphorylated by UV-activated Chk1, resulting in p53 activation. *EMBO J*, *25*(6), 1207-1218. https://doi.org/10.1038/sj.emboj.7601010

Kim, S., Wong, P., & Coulombe, P. A. (2006). A keratin cytoskeletal protein regulates protein synthesis and epithelial cell growth. *Nature*, *441*(7091), 362-365. https://doi.org/10.1038/nature04659

Kumrah, N., & De, S. (2020). Expression & Localization of the 14-3-3 Protein Family Within Mammals [Presentation]. https://nsuworks.nova.edu/trick/2020/events/11/ (Trick to the Treat of Internships and Research, Nova Southeastern University)

Kumrah, N., & De, S. (2020). Expression and Localization of the 14-3-3 (YWHA) Protein Family within Mammals. *Mako: NSU Undergraduate Student Journal, 2020*(2), Article 2. https://nsuworks.nova.edu/mako/vol2020/iss2/2

Leffers, H., Madsen, P., Rasmussen, H. H., Honore, B., Andersen, A. H., Walbum, E., Vandekerckhove, J., & Celis, J. E. (1993). Molecular cloning and expression of the transformation sensitive epithelial marker stratifin. A member of a protein family that has been involved in the protein kinase C signalling pathway. *J Mol Biol, 231*(4), 982-998. https://doi.org/10.1006/jmbi.1993.1346

Liu, Y., Ross, J. F., Bodine, P. V., & Billiard, J. (2007). Homodimerization of Ror2 tyrosine kinase receptor induces 14-3-3(beta) phosphorylation and promotes osteoblast differentiation and bone formation. *Mol Endocrinol, 21*(12), 3050-3061. https://doi.org/10.1210/me.2007-0323

Monaco, G., van Dam, S., Casal Novo Ribeiro, J. L., Larbi, A., & de Magalhaes, J. P. (2015). A comparison of human and mouse gene co-expression networks reveals conservation and divergence at the tissue, pathway and disease levels. *BMC Evol Biol, 15*, 259. https://doi.org/10.1186/s12862-015-0534-7

Muslin, A. J., Tanner, J. W., Allen, P. M., & Shaw, A. S. (1996). Interaction of 14-3-3 with signaling proteins is mediated by the recognition of phosphoserine. *Cell, 84*(6), 889-897. https://doi.org/https://doi.org/10.1016/S0092-8674(00)81067-3

Puri, P., Acker-Palmer, A., Stahler, R., Chen, Y., Kline, D., & Vijayaraghavan, S. (2011). Identification of testis 14-3-3 binding proteins by tandem affinity purification. *Spermatogenesis, 1*(4), 354-365. https://doi.org/10.4161/spmg.1.4.18902

Puri, P., Myers, K., Kline, D., & Vijayaraghavan, S. (2008). Proteomic analysis of bovine sperm YWHA binding partners identify proteins involved in signaling and metabolism. *Biology of Reproduction, 79*(6), 1183-1191. https://doi.org/10.1095/biolreprod.108.068734

Qi, W., Liu, X., Qiao, D., & Martinez, J. D. (2005). Isoform-specific expression of 14-3-3 proteins in human lung cancer tissues. *Int J Cancer, 113*(3), 359-363. https://doi.org/10.1002/ijc.20492

Rittinger, K., Budman, J., Xu, J., Volinia, S., Cantley, L. C., Smerdon, S. J., Gamblin, S. J., & Yaffe, M. B. (1999). Structural analysis of 14-3-3 phosphopeptide complexes identifies a dual role for the nuclear export signal of 14-3-3 in ligand binding. *Mol Cell, 4*(2), 153-166. https://doi.org/10.1016/s1097-2765(00)80363-9

Sato, S., Fujita, N., & Tsuruo, T. (2002). Regulation of kinase activity of 3-phosphoinositide-dependent protein kinase-1 by binding to 14-3-3. *J Biol Chem, 277*(42), 39360-39367. https://doi.org/10.1074/jbc.M205141200

Shimada, T., Fournier, A. E., & Yamagata, K. (2013). Neuroprotective function of 14-3-3 proteins in neurodegeneration. *BioMed Research International, 2013*. https://doi.org/10.1155/2013/564534

Wang, X., Grammatikakis, N., Siganou, A., & Calderwood, S. K. (2003). Regulation of molecular chaperone gene transcription involves the serine phosphorylation, 14-3-3 epsilon binding, and cytoplasmic sequestration of heat shock factor 1. *Mol Cell Biol, 23*(17), 6013-6026. https://doi.org/10.1128/mcb.23.17.6013-6026.2003

Wheeler-Jones, C. P., Learmonth, M. P., Martin, H., & Aitken, A. (1996). Identification of 14-3-3 proteins in human platelets: effects of synthetic peptides on protein kinase C activation. *Biochem J, 315 (Pt 1)*, 41-47. https://doi.org/10.1042/bj3150041

Yang, H., Zhao, R., & Lee, M. H. (2006). 14-3-3sigma, a p53 regulator, suppresses tumor growth of nasopharyngeal carcinoma. *Mol Cancer Ther*, *5*(2), 253-260. https://doi.org/10.1158/1535-7163.MCT-05-0395

Yang, H. Y., Wen, Y. Y., Chen, C. H., Lozano, G., & Lee, M. H. (2003). 14-3-3 sigma positively regulates p53 and suppresses tumor growth. *Mol Cell Biol*, *23*(20), 7096-7107. https://doi.org/10.1128/mcb.23.20.7096-7107.2003

Yang, W., Dicker, D. T., Chen, J., & El-Deiry, W. S. (2008). CARPs enhance p53 turnover by degrading 14-3-3sigma and stabilizing MDM2. *Cell Cycle*, *7*(5), 670-682. https://doi.org/10.4161/cc.7.5.5701