European Journal of Cell Biology 96 (2017) 206–217

Contents lists available at ScienceDirect

European Journal of Cell Biology

journal homepage: www.elsevier.com/locate/ejcb

Review article

An account of fungal 14-3-3 proteins

Ravinder Kumar*

Department of Biosciences and Bioengineering, Indian Institute of Technology Bombay, Powai, Mumbai 400 076, Maharashtra, India

ARTICLE INFO

Article history:
Received 12 February 2017
Received in revised form 21 February 2017
Accepted 21 February 2017

Keywords:
Fungus
Bmh1/2
14-3-3
Proteomics
Cell cycle
Stress

ABSTRACT

14-3-3s are a group of relatively low molecular weight, acidic, dimeric, protein(s) conserved from single-celled yeast to multicellular vertebrates including humans. Despite lacking catalytic activity, these proteins have been shown to be involved in multiple cellular processes. Apart from their role in normal cellular physiology, recently these proteins have been implicated in various medical consequences. In this present review, fungal 14-3-3 protein localization, interactions, transcription, regulation, their role in the diverse cellular process including DNA duplication, cell cycle, protein trafficking or secretion, apoptosis, autophagy, cell viability under stress, gene expression, spindle positioning, role in carbon metabolism have been discussed. In the end, I also highlighted various roles of yeasts 14-3-3 proteins in tabular form. Thus this review with primary emphasis on yeast will help in appreciating the significance of 14-3-3 proteins in cell physiology.

1. Introduction

14-3-3s are a group of acidic, relatively low molecular weight (with mol. mass around 30 kDa) dimeric proteins conserved in all eukaryotic species studied so far (Moore and Perez, 1967; Aitken et al., 1991, 1992, 1995; Aitken, 1995; Ichimura et al., 1988; Nielsen 1991; Hirsch et al., 1992; Lu et al., 1992; Brandt et al., 1992; Martens et al., 1992; Swanson and Ganguly, 1992; van Heusden et al., 1992; van Heusden, 2009; van Heusden and Steensma, 2006; van Hemert et al., 2001; Knetsch et al., 1997; Owen et al., 2012). The number 14-3-3 originates from the fraction numbers of these proteins after DEAE-cellulose chromatography and the position after subsequent starch gel electrophoresis (Moore and Perez, 1967). First identified in brain tissue (Moore and Perez, 1967) their significance was first recognized upon identification of their role in neurotransmitter synthesis (Ichimura et al., 1987). Since then, these proteins have also being implicated in additional cellular processes including, DNA duplication, cell division, cell signaling (Morrison, 1994; Muslin et al., 1996), vesicular trafficking (Gelperin et al., 1995), apoptosis (Xing et al., 2000), regulation of gene expression (Parua et al., 2014), proteins aggregation (Xu et al., 2013). Though, these proteins lack enzymatic activity, through interaction with their interacting partner(s), 14-3-3 protein(s) participates in the regulation of numerous cellular processes, including neuronal development (Cheah et al., 2012), cell growth, and microbial infection. The ability of these proteins to modulate the stability, activity (Winge et al., 2008; Obsilova et al., 2014) and localization of their binding partners such as kinases, phosphatases, and membrane proteins (Mrowiec and Schwappach, 2006) implicate these proteins in almost all cellular processes of the eukaryotic cell. Apart from their role in normal cellular physiology (biological functions mentioned above), recently, these proteins were also found to be associated with several medical implications *viz* neurological Miller–Dieker and spinocerebellar ataxia type 1 diseases bovine spongiform encephalopathy (BSE) (Robey et al., 1998; Lee and Harrington, 1997), Alzheimer (Molly and Zhou, 2012), cancer (Zhang et al., 2015; Cao et al., 2015; Dowling et al., 2015), bacterial (Patel et al., 2006; Shandala et al., 2011), viral infection (Pei et al., 2011; Aoki et al., 2000; Bolton et al., 2008) and diabetes (Ramm et al., 2006; Xiang et al., 2002). Although 14-3–3s can function both as homo- or heterodimers (Yaffe et al., 1997), in budding yeast Bmh1/2 mainly functions as heterodimers (Chaudhri et al., 2003). Various cellular processes in which yeast 14-3-3 have been involved are shown in Fig. 1. It is important to mention that in recent past, more different functions of 14-3-3 have been reported in higher eukaryotes especially in mammals, but I will highlight only those which were reported in yeast or fungal systems except in few cases.

In this present review, I will brief the readers with various aspects of fungal 14-3-3 proteins including basic background, local-

Abbreviations: Bmh, Brain Modulosignalin Homologue; Rad, RADiation sensitive; YPA, yeast extracts peptone potassium acetate (pre-sporulating media); SPM, sporulating media; CIP, catabolite inactivation pathway; CRD, cystine-rich domain; PTM, posttranslational modification; SPB, spindle pole body; Cdc, cell division cycle.

* Present address: Section of Molecular Biology, Division of Biological Science, University of California San Diego, La Jolla, California-92093-0322, USA.
E-mail address: raj86tau@gmail.com

http://dx.doi.org/10.1016/j.ejcb.2017.02.006
0171-9335/

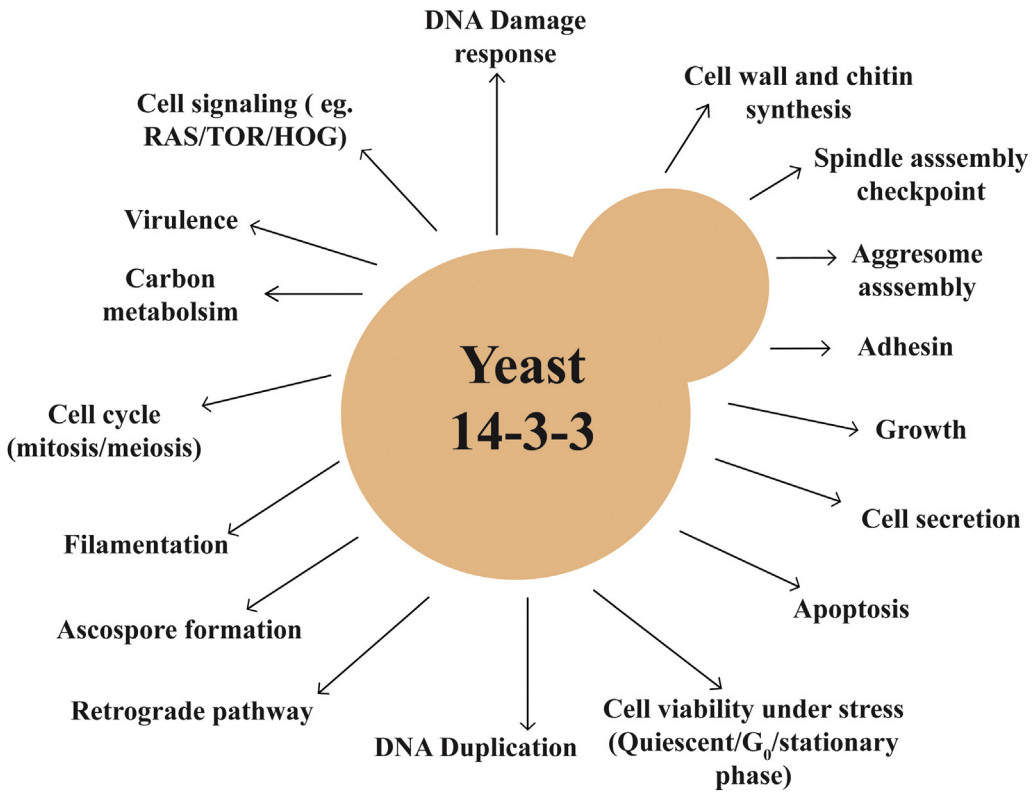

Fig. 1. Schematic showing various biological processes in which yeast 14-3-3 proteins have been implicated.

ization or cellular distribution, abundance, expression pattern, interaction, role in normal cellular physiology.

1.1. Distribution and conservation of 14-3-3 across Eukarya domain

14-3–3s are among the most conserved proteins in almost all eukaryotic cells. Both the number and 14-3-3 isoforms vary with species. For example, so far seven isoforms have been reported in mammals e.g. *Homo sapiens* (Ichimura et al., 1988; Martin et al., 1993; Aitken et al., 1995) and more than a dozen in plants like *Arabidopsis thaliana* (Wilson et al., 2016; Rosenquist et al., 2000). Both budding and fission yeast possess two isoforms of 14-3-3 proteins. Budding yeast homologs of 14-3-3 are encoded by two distinct but related genes *viz BMH1* which encodes for Bmh1 (major form) (van Heusden et al., 1992; Irie et al., 1994), while *BMH2* encodes Bmh2 (minor form) (van Heusden et al., 1995; Gelperin et al., 1995). In fission yeast, 14-3–3s are represented as Rad24 and Rad25 (Ford et al., 1994; Ozoe et al., 2002). Unlike budding or fission yeast, till date, only one isoform of 14-3-3 have been reported in *C. albicans* (Cognetti et al., 2002; Palmer et al., 2004). 14-3-3 isoforms along with gene symbol for different eukaryotic species are shown in Table 1. Thus it can be said that the number and 14-3-3 isoforms vary with eukaryotic species.

Apart from wide distribution across almost all eukaryotic species (mentioned above), 14-3-3 proteins also exhibit a remarkable conservation between all eukaryotic species studied so far (Wang and Shakes, 1996). For example, *Saccharomyces cerevisiae BMH1* and human epsilon (14-3-3ε) isoforms are approximately 70% similar at the amino acid level while within species amino acid sequence similarity reaches to more than 90%. For instance, the similarity between budding yeast Bmh1 and Bmh2 is around 98% at the protein level. Apart from conservation of 14-3-3 at the gene or amino acid residue level, various studies also showed conservation at the level of protein function, and expression of 14-3-3 from one species was able to rescue or complement the role of the endogenous or native protein in another species. For example, *T. Reesei* 14-3-3, *FTTI, FTTII* and expression of *D. discoideum* 14-3-3 were able to rescue yeast bmh1/2 defects (Vasara et al., 2002; Knetsch et al., 1997). Table 2 highlighting various studies where expression of heterologous 14-3-3 complements the function of the native or endogenous protein. Thus it can be said that expression of 14-3-3 from one species into another species was able to supplement the role of endogenous or native proteins despite wide evolutionary distance or divergence. Notwithstanding the conservation at the gene, protein as well as at the level of function it is observed that C-terminal of yeast 14-3-3 and higher eukaryotes shows significance difference. For example, C-terminal of yeast 14-3-3 proteins is longer with polyglutamine stretch (Veisova et al., 2010).

Redundancy, shared functions and technical limitations associated with simultaneous disruption of all the isoforms makes the analysis and establishing the role of 14-3-3 proteins in cell viability a bit challenging in multicellular eukaryotes (example in plants and mammals). While the presence of only one or two isoforms, ease of genetic manipulation in yeast (example budding or fission yeast) help in understanding the importance of 14-3-3 proteins not only in cell viability but also in other cellular processes. Disruption of either of the budding yeast *BMH* genes has little effect on cell viability, growth, sporulation efficiency, spore viability whereas the simultaneous disruption of both genes is lethal in most of the background except Σ1278 (Roberts et al., 1997; van Heusden et al., 1992, 1995; van Heusden and Steensma, 2006; Gelperin et al., 1995; Andoh et al., 1998) and recently in the SK1 background (Slubowski et al., 2014) suggesting essential nature of 14-3-3 proteins. It is also known that Bmh1 is not required during the growth in rich media. In Σ1278 and SK1 background 14-3-3 proteins are not essential, but deletion of both *BMH* genes results in a severe growth defects