Advances in Biological Regulation xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Advances in Biological Regulation

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

Regulation of ASK1 signaling by scaffold and adaptor proteins

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ARTICLE INFO

Keywords:
ASK1
Scaffold
Adaptor
MAPK pathway
Protein binding

ABSTRACT

The mitogen-activated protein kinase (MAPK) signaling pathway is a three-tiered kinase cascade where mitogen-activated protein kinase kinase kinases (MAP3Ks) lead to the activation of mitogen-activated protein kinase kinases (MAP2K), and ultimately MAPK proteins. MAPK signaling can promote a diverse set of biological outcomes, ranging from cell death to proliferation. There are multiple mechanisms which govern MAPK output, such as the duration and strength of the signal, cellular localization to upstream and downstream binding partners, pathway crosstalk and the binding to scaffold and adaptor molecules. This review will focus on scaffold and adaptor proteins that bind to and regulate apoptosis signal-regulating kinase 1 (ASK1), a MAP3K protein with a critical role in mediating stress response pathways.

1. Introduction

1.1. MAPK organizational proteins: scaffolds and adaptors

The MAPK signaling cascade is composed of many MAP3K, MAP2K and MAPK proteins which can assemble into various pathways to drive a wide array of cellular outcomes. Proper organization and localization of these kinases is critical to ensuring an incoming signal elicits the proper biological response. One mechanism that provides this coordination is the binding of scaffolding and adaptor proteins.

Scaffold and adaptor proteins often contain multiple binding sites to aid in the assembly of multi-protein complexes. While both scaffold and adaptor proteins sometimes serve the same function, the term “scaffold” is generally reserved for a protein which links two or more target proteins, while “adaptor” is usually used to describe those which connect two proteins (Bhattacharyya et al., 2006; Flynn, 2001; Langeberg and Scott, 2015; Pan et al., 2012; Pawson, 2007). By interacting with multiple proteins within a cascade, scaffolds and adaptor can insulate downstream signaling, impact cross-talk with other pathways, target proteins to a particular subcellular location, coordinate feedback loops, and alter enzymatic activity or conformation of their binding partners (Bhattacharyya et al., 2006; Good et al., 2011; Harris et al., 2001; Keshet and Seger, 2010; Langeberg and Scott, 2015; Pan et al., 2012; Shaul and Seger, 2007; Shaw and Filbert, 2009; Witzel et al., 2012; Zeke et al., 2009). They are widely used by many signaling pathways, including the MAPK cascade.

MAPK scaffolds were first identified in yeast where the MAP3K protein, Ste11, interacts with either the Ste5 or Pbs2 scaffolding proteins in response to pheromones or osmotic stress, respectively (Choi et al., 1994; Kranz et al., 1994; Marcus et al., 1994; Posas and Saito, 1997; Printen and Sprague, 1994). Ste5 insulates the Ste11-Ste7-Fus3 pathway to promote the mating response, while Pbs2

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http://dx.doi.org/10.1016/j.jbior.2017.10.003
Received 31 August 2017; Received in revised form 12 October 2017; Accepted 13 October 2017

drives glycerol synthesis via Ste11-Pbs2-Hog1 signaling (Gustin et al., 1998; Whitmarsh et al., 1998). These scaffolds are critical in coordinating the proper response to a given stimuli, as expression of chimeric Ste5 and Pbs2 proteins can swap the response to pheromones and activate the osmoresponse instead of mating (Bashor et al., 2008; Harris et al., 2001; Park et al., 2003; Tatebayashi et al., 2003).

While the MAPK cascade is conserved in eukaryotic cells, the protein diversity and complexity of this pathway has expanded throughout evolution (Widmann et al., 1999). This can especially be seen in the MAP3K tier of the cascade. Yeast cells have 4 well-described MAP3Ks, while mammalian cells have at least 20, making it the most abundant and diverse level of the MAPK cascade (Cuevas et al., 2007; Johnson et al., 2005; Uhlik et al., 2004). As the initiators of MAPK signaling, the large expansion of MAP3K proteins likely mediates downstream MAPK activation in response to the many complex stimuli in mammalian cells (Cuevas et al., 2007; Widmann et al., 1999). Importantly, activation of different MAP3K proteins can selectively promote one biological outcome over another. Scaffolding and adaptor proteins help organize and regulate the activity of the MAPK pathway to link together the proper biological outcome to an input signaling (Bashor et al., 2008; Bhattacharyya et al., 2006; Good et al., 2011; Harris et al., 2001; Pan et al., 2012; Park et al., 2003; Shaw and Filbert, 2009; Witzel et al., 2012; Zeke et al., 2009).

1.2. Apoptosis signal-regulating kinase 1

ASK1 is a MAP3K protein which directly phosphorylates MKK3/6 and MKK4/7 to lead to activation of downstream kinases, p38 and JNK, respectively (Ichijo et al., 1997). The most well-established role of ASK1 is as a pro-apoptotic signaling protein activated by a variety of cellular stressors, such as oxidative and endoplasmic reticulum (ER) stress (Hattori et al., 2009; Shiizaki et al., 2013). Over-expression of ASK1 or of a constitutively active form of the protein is sufficient to induce cell death under a variety of experimental conditions (Hatai et al., 2000; Ichijo et al., 1997; Saitoh et al., 1998).

ASK1 activity has been linked to many human diseases where ASK1-dependent cell death has both positive or negative effects on pathogenesis. In the brain, ASK1 promotes neuronal cell death that is characteristic of many neurodegenerative diseases and cerebral ischemia/reperfusion (I/R) injury (Guo et al., 2017; Lee et al., 2012; Nishitoh et al., 2002; Sturchler et al., 2011; Zhang and Zhang, 2002). In some cancers and viral infections, ASK1 activity is important in mediating chemotherapy-induced cell death and restricting viral replication and survival (Brozovic and Osmak, 2007; Chen et al., 1999; Cheng et al., 2014; Geleziunas et al., 2001; Maruoka et al., 2003; Miyakawa et al., 2015; Okazaki et al., 2015; Ryuno et al., 2017; Yuan et al., 2003). Additionally, ASK1 signaling can promote cell proliferation and inflammation, two biological processes that can drive tumor development and inflammatory diseases (Guo et al., 2010; Hayakawa, Y. et al., 2010, 2011; Hayakawa et al., 2012; Iriyama et al., 2009; Mnich et al., 2010). Because of its vital role in cell fate determination, ASK1 activity and signaling is tightly regulated in the cells, in part through the binding of scaffold adaptor proteins. Furthermore, the loss of these interactions, either through genetic or pharmacological approaches, can impact ASK1-mediating signaling in these disorders.

2. ASK1 scaffolding proteins

2.1. β-Arrestins

The arrestin family is composed of four highly homologous proteins which were first characterized based on their binding and desensitization of G protein–coupled receptors (Lefkowitz and Whalen, 2004). Arrestin1 and -4 are grouped together as visual arrestins because they are only expressed in retinal cells, while arrestin2 and -3 (termed β-arrestin1 and β-arrestin2) are expressed across tissue types (Zhuo and Klug, 2017). Yet, these proteins have been found to have other roles outside of G-protein desensitization, including as scaffolds for MAPK regulation (Lefkowitz et al., 2006; Zhan et al., 2017).

Arrestin3 serves as a scaffolding platform by binding and enhancing signaling through the ASK1-MKK4/7-JNK cascade (Kook et al., 2013; McDonald et al., 2000; Miller et al., 2001; Song et al., 2009; Zhan et al., 2013). While other arrestins are also capable of binding ASK1, MKKs, and JNK, only arrestin3 holds these kinases in the proper orientation to promote downstream signaling (Seo et al., 2011; Song et al., 2009; Zhan et al., 2014a). Further work identified a 25-amino acid region of arrestin3 that was responsible for mediating kinase binding. Over-expression of this arrestin3 peptide retains its scaffolding ability and could enhance JNK activation, making it the smallest known MAPK scaffold (Zhan et al., 2014b, 2016). Importantly, this scaffolding role of arrestin3 can also be leveraged as a drug target for the treatment of cerebral I/R-induced cell death. Here, treatment with the angiotensin antagonist, losartan, in mouse models of I/R decreased the formation of the arrestin3-ASK1-MKK scaffolding complex, ultimately reducing JNK3 activation and subsequent cell death (Zhang et al., 2012).

However, the effect of arrestins on ASK1 signaling is complex. In other contexts, arrestin3 can recruit MAP kinase phosphatase 7 (MKP7, also known as DUSP16) to the scaffold complex, resulting in JNK dephosphorylation and inactivation (Willoughby and Collins, 2005). Arrestin2 and -3 can also promote ubiquitin-mediated degradation of ASK1 through recruitment of the E3 ligase CHIP, leading to H_2O_2-induced apoptotic resistance (Zhang et al., 2009). The ability of arrestins to bind both positive and negative regulators of JNK likely allows for the integration of complex upstream signals and fine-tuning of the duration of MAPK signaling (Morrison and Davis, 2003; Willoughby and Collins, 2005).

2.2. JNK interacting proteins (JIPs)

Unlike β-arrestins, the JIP protein family was initially identified based on their ability to interact with MAPKs (Dickens et al.,