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Review

The p38 and Hog1 SAPKs control cell cycle progression in response to environmental stresses

Alba Duch, Eulàlia de Nadal *, Francesc Posas *

Cell Signaling Unit, Departament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra (UPF), E-08003 Barcelona, Spain

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ABSTRACT

In response to environmental stresses, cells need to activate an adaptive program to maximize cell progression and survival. Stress-activated protein kinases (SAPK) are key signal transduction kinases required to respond to stress. Prototypical members of SAPKs are the yeast Hog1 and mammalian p38. Upon stress, those enzymes play a critical role in mounting the adaptive responses to stress such as the regulation of metabolism and the control of gene expression. In addition, a major function of SAPKs in response to stress is to modulate cell cycle progression. In this review, we focus on the role of Hog1 and p38 in the control of cell cycle progression in response to environmental stresses.

1. Introduction

Cyclin-dependent kinase (Cdk) complexes drive cell cycle progression. In the budding yeast *Saccharomyces cerevisiae*, a sole Cdk, Cdc28 (which is the functional homologue of Cdk1) controls cell cycle by association with specific cyclins which confer substrate specificity [1–4]. In higher eukaryotes, multiple Cdk associate with multiple cyclins to regulate cell cycle progression [5]. A second layer of cell cycle control is orchestrated by proteins involved in the fine-tune regulation of these cyclin-Cdk complexes, including a vast number of cell cycle regulators which control cyclin transcription, translation, localization and degradation as well as protein cyclin-Cdk inhibitors [6,7]. All those factors ensure the proper coordination of hundreds of molecular events during cell cycle progression.

On top of that, an extra layer of control ensures the correct completion of every phase of the cell cycle before entering into the next one. This function is carried out by checkpoint proteins which are involved in controlling processes such as morphogenesis, cell size, DNA replication or spindle-assembly [8]. In general, checkpoint responses consist in a transient cell cycle arrest to provide time to the cell to overcome primary problems (e.g. an incomplete or aberrant cell cycle event). Mutations in checkpoint proteins might result, for instance, in misscoordination between the mitotic and the morphogenetic cell cycle, aneouploidy or aberrant DNA structures. In yeast and in other unicellular organisms all these defects may lead to cell death, whereas in metazoans, they are causally related with early and late stages of cell transformation and tumorigenesis [9,10]. Therefore, checkpoint pathways can be defined as surveillance mechanisms that ensure the proper coordination and completion of cell cycle events, essential to preserve cell integrity and genomic stability.

Although being part of the cell cycle regulation core, checkpoint signaling pathways have a particularly important role in response to internal or external toxic agents. To date, the most well studied kind of stress that activates a checkpoint pathway is the genotoxic stress caused by cell metabolism (reactive species of oxygen, ROS), exposition to ultraviolet light (UV) that lead to DNA damage accumulation [11,12] as well as replicative stress, which takes place during S-phase when the replication fork cannot progress because of the absence of the DNA precursors, dNTP, or the missfunction of the DNA polymerases. In response to DNA damage or replication stress, cells activate the DNA damage checkpoint pathway to arrest cell cycle, providing time to repair the DNA damage or to overcome the replication stress [8,13]. However, cells must cope with other stresses in addition to that of genotoxic stress that poses a risk for cell survival. For instance, cells are exposed to changing environmental conditions, such as changes in pH, nutrient availability, temperature, and osmolarity that directly affect cell homeostasis and physiology.

Cells have evolved a number of signal transduction pathways that serve to adapt and survive to stress. Yeast and mammals have

* Corresponding authors. Address: Departament de Ciències Experimentals i de la Salut, Cell Signaling Research Group, Universitat Pompeu Fabra, Dr Aiguader 88, Barcelona, Spain. Fax: +34 93 316 0901.

E-mail addresses: eulalia.nadal@upf.edu (E. de Nadal), francesc.posas@upf.edu (F. Posas).

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a conserved family of mitogen-activated protein kinase (MAPKs) that sense and respond to extracellular environmental changes known as stress-activated signaling pathways (SAPKs). Activation of SAPKs leads to generation of a set of adaptive responses that involves the modulation of several physiological processes such as changes in gene transcription, cell metabolism, protein translation and cell cycle progression [14–16].

It has been known for a long time that environmental stresses lead to a transient cell cycle arrest and that the bypass of this cell cycle delay is detrimental for cell survival [17–22]. Thus, cells activate checkpoint surveillance mechanisms in response to extracellular stimuli to modulate cell cycle progression and to permit adaptation to changing environmental conditions. In most of the cases, the proteins and the molecular mechanisms involved in those checkpoint responses to environmental cues remain to be elucidated. Here, we review the latest studies on how osmostress impacts on cell cycle progression and discuss the importance of novel checkpoint mechanisms in preserving genomic integrity and cell viability from budding yeast to mammals.

2. The HOG/p38 stress signaling pathways

Exposure of cells to osmostress results in rapid and transient activation of SAPKs. In budding yeast, the HOG (high osmolarity glycerol) pathway is the main mediator of cellular adaptation upon osmostress and it is one of the best characterized SAPK cascades in eukaryotes (revised in [23–26]) (see Fig. 1). Two independent sensor branches triggers the activation of the HOG pathway: the Sln1 branch and the Sho1 branch. Each sensor branch is sufficient to trigger the activation of the pathway, although the Sln1 branch is more prominent in pathway control and display higher sensitivity to respond faster and over a wide range of osmolarity changes [27–29]. The core of the pathway comprises a layer of three MAPKKK (Ssk2, Ssk22 and Ste11) which activate the unique Pbs2 MAPKK, which in turn phosphorylates and activates the Hog1 MAPK [30]. In mammalian cells, both the architecture and the main players of the pathway are highly conserved, being p38 a Hog1 homolog [31,32] (see Fig. 1). It is worth mentioning that while Hog1 is mainly activated upon osmostress, and it would play only a minor role in response to other stresses for instance heat, oxidative and unfolded protein response (UPR) stresses [33–36], p38 is activated by multitude of external stimuli such as cytokines, DNA damage, oxidative and heat stresses, osmostress, etc. The central core of the pathway is similar to HOG albeit the molecular activation mechanisms that lead to its activation to stress are not well defined. Moreover, in contrast to Hog1, p38 function is crucial not only for the acute response to cellular insults but it also plays key roles in controlling differentiation, proliferation, apoptosis, cell morphology and immune response [16,37].

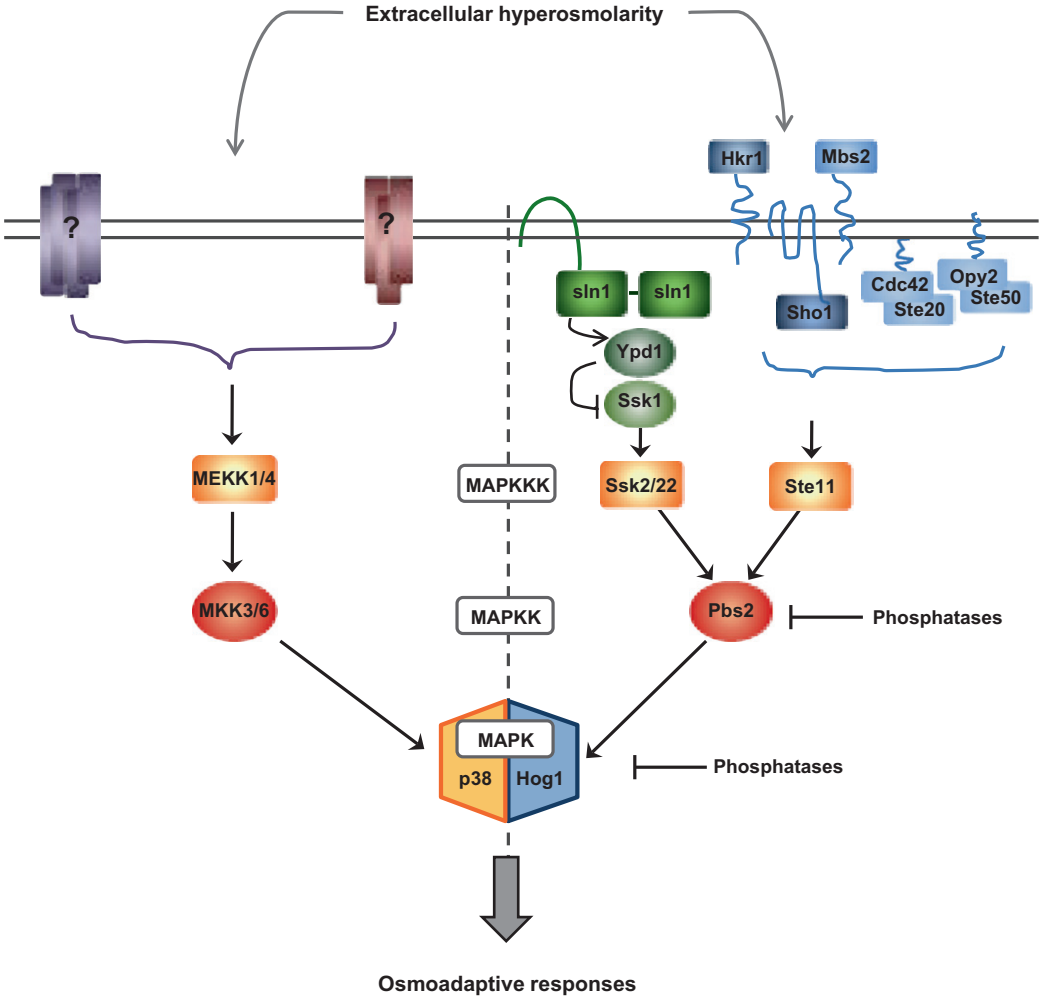

Fig. 1. Schematic diagram of the Hog1/p38 SAPK pathways. In response to osmostress different osmosensors mechanisms become activated when cells detect changes in osmolarity. While in mammalian cells (left panel) the osmosensor complexes have not been clearly defined, in budding yeast (right panel), two independent osmosensing mechanisms, the Sln1 and Sho1 branches, are activated upon osmostress. Activation of those osmosensors complexes leads to the activation of the MAPKKKs, MEKK1/4 in mammalian cells and Ssk2/22 and Ste11 in budding yeast, which in turn activate the MAPKKs Mkk3/6 and Pbs2 respectively. Activated MKK4/6 and Pbs2 phosphorylates and activates the p38 and Hog1 MAPKs respectively, which trigger the osmoadaptive response by phophorylation of multiple substrates.