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The response to inositol: Regulation of glycerolipid metabolism and stress response signaling in yeast☆

Susan A. Henry*, Maria L. Gaspar, Stephen A. Jesch

Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY 14853, USA

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ABSTRACT

This article focuses on discoveries of the mechanisms governing the regulation of glycerolipid metabolism and stress response signaling in response to the phospholipid precursor, inositol. The regulation of glycerolipid lipid metabolism in yeast in response to inositol is highly complex, but increasingly well understood, and the roles of individual lipids in stress response are also increasingly well characterized. Discoveries that have emerged over several decades of genetic, molecular and biochemical analyses of metabolic, regulatory and signaling responses of yeast cells, both mutant and wild type, to the availability of the phospholipid precursor, inositol are discussed.

Contents

* Corresponding author at: Department of Molecular Biology and Genetics, Cornell University, 245 Biotechnology Building, Ithaca, NY 14853, USA. Tel.: +1 607 254 8717; fax: +1 607 255 6249.
E-mail address: sah42@cornell.edu (S.A. Henry).

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1. Introduction

In the yeast, *Saccharomyces cerevisiae*, as in other eukaryotes, regulation of lipid metabolism is extremely complex, involving coordination of the biosynthesis and turnover of an enormous number of lipid classes and species. All eukaryotic cells share the challenge of regulating and coordinating the complex and interconnected pathways of lipid metabolism across multiple, spatially distinct membrane compartments, adjusting for shifting precursor availability and membrane expansion in the course of cell division, growth and metabolism. The genes, enzymes and pathways of lipid metabolism in yeast share substantial homology with those in higher eukaryotes, including mammals, making yeast an attractive model system for biomedical research (Henry et al., 2012).

S. cerevisiae, as a free-living unicellular organism, must continuously monitor and coordinate endogenous metabolic activity in response to ever changing availability of precursors of lipid biosynthesis in the growth medium. Indeed, many insights into fundamental mechanisms of genetic regulation of phospholipid metabolism in yeast have come from studies of the cellular responses to the availability of exogenous precursors of phospholipid biosynthesis, especially inositol. The cellular consequences of inositol depletion have also been studied in mammalian cells and compared to yeast in the context of exposure to inositol depleting drugs lithium and valproic acid (Deranieh and Greenberg, 2009). Various aspects of regulation and signaling related to lipid and inositol metabolism in yeast have been extensively reviewed (Carman and Han, 2011; Carman and Henry, 1999; Chen et al., 2007; Dickson, 2008; Gaspar et al., 2007; Greenberg and Lopes, 1996; Henneberry and Sturley, 2005; Henry et al., 2012; Jesch and Henry, 2005; Majerus and York, 2009; Strahl and Thorner, 2007; Tsui and York, 2010). Thus it is not the intention of this article to provide a comprehensive coverage of the broader topics of lipid and inositol metabolism in regulation and signaling in eukaryotic cells in general. Rather, this article has a primary focus on the discoveries of mechanisms governing the regulation of glycerolipid metabolism and the signaling roles of specific lipids in yeast that have been made possible by genetic, molecular and biochemical analyses of the cellular response to the availability of the phospholipid precursor, inositol (Fig. 1).

Inositol serves as an essential precursor in yeast, as in other eukaryotic cells, for the synthesis of phosphatidylinositol (PI) (Fig. 1), which in turn serves as precursor to many important signaling molecules, including phosphoinositides, inositol polyphosphates (Carman and Han, 2011; Carman and Henry, 1999; Henry et al., 2012; Jesch and Henry, 2005; Majerus and York, 2009; Strahl and Thorner, 2007; Tsui and York, 2010) and inositol containing sphingolipids (Breslow and Weissman, 2010; Deranieh and Greenberg, 2009; Dickson, 2008), as well as glycosylphosphatidylinositol (GPI) anchor proteins (Pittet and Conzelmann, 2007). When inositol is added to the growth medium of actively proliferating yeast cells adapted to growth in its absence, the rate of PI synthesis and accumulation increases rapidly and dramatically (Gaspar et al., 2006, 2011; Loewen et al., 2004). Thus, inositol availability has the potential to influence many signaling pathways in yeast (Jesch et al., 2005, 2006). Moreover, inositol availability also influences the synthesis of all lipids derived directly or indirectly from phosphatidic acid (PA) (Fig. 1), itself a powerful signaling lipid (Carman and Henry, 2007; Henry et al., 2012).

In wild type cells under conditions of inositol limitation, hundreds of genes are activated, the most highly regulated of which is *INO1*, encoding inositol 3-phosphate synthase (Ino1p), the enzyme that catalyzes the rate limiting step in the de novo synthesis of inositol (Henry et al., 2012; Jesch et al., 2005, 2006; Santiago and Mamoun, 2003). However, in addition to genes involved in inositol and phospholipid biosynthesis, the list of genes activated in response to inositol limitation also includes many that are known to be activated by stress response pathways, including the unfolded protein response (UPR) (Chang et al., 2002, 2004; Cox et al., 1993; Cox and Walter, 1996; Mori et al., 1992, 1993), the glucose response pathway (Shirra et al., 2001) and the protein kinase C (PKC) pathway (Jesch et al., 2010; Nunez et al., 2008).

Thus, the experimental exploitation of yeast mutants defective in diverse aspects of lipid metabolism and regulation, coupled with manipulation of the exogenous supply of phospholipid precursors, especially inositol, offers the potential to generate powerful insights into the diverse regulatory and signaling roles of eukaryotic lipids. This article will focus on the metabolism, genetics and molecular biology associated with these discoveries in yeast.

2. Biosynthesis of inositol in *S. cerevisiae*: biochemistry, genetics and regulation

2.1. Isolation and characterization of mutants defective in inositol biosynthesis and regulation

The rate-limiting step in synthesis of inositol in yeast (Donahue and Henry, 1981b), as in other eukaryotes, many archaea, and some hyperthermophilic bacteria (Majumder et al., 1997; Michell, 2007) involves the conversion of D-glucose 6-phosphate to D-*myo* inositol-3-phosphate in the cytoplasm by a reaction catalyzed by the inositol 3-phosphate synthase (IP synthase, Ino1p). Inositol 3-phosphate is subsequently dephosphorylated by inositol 3-phosphate monophosphatase (Inm1p) (Murray and Greenberg, 1997). However, yeast *inm1*Δ mutants are not inositol auxotrophs and retain considerable inositol 3-phosphate phosphatase activity (Murray and Greenberg, 2000), suggesting that enzymes in addition to Inm1p are able to catalyze the dephosphorylation of inositol 3-phosphate. The activity of IP synthase is dramatically reduced in yeast cells grown in the presence of inositol, indicating that the enzyme is repressible (Culbertson et al., 1976). The isolation and characterization of *S. cerevisiae* mutants unable to grow in the absence of inositol (Ino^- phenotype) permitted the identification