Available online at www.sciencedirect.com
SCIENCE DIRECT®
Mutation Research 569 (2005) 13–27
Fundamental and Molecular Mechanisms of Mutagenesis
www.elsevier.com/locate/molmut
Community address: www.elsevier.com/locate/mutres

Review

Yeast signaling pathways in the oxidative stress response

Aminah Ikner, Kazuhiro Shiozaki*

Section of Microbiology, Division of Biological Sciences, University of California, Davis, CA 95616, USA

Received in revised form 17 February 2004;

Abstract

Oxidative stress that generates the reactive oxygen species (ROS) is one of the major causes of DNA damage and mutations. The "DNA damage checkpoint" that arrests cell cycle and repairs damaged DNA has been a focus of recent studies, and the genetically amenable model systems provided by yeasts have been playing a leading role in the eukaryotic checkpoint research. However, means to eliminate ROS are likely to be as important as the DNA repair mechanisms in order to suppress mutations in the chromosomal DNA, and yeasts also serve as excellent models to understand how eukaryotes combat oxidative stress. In this article, we present an overview of the signaling pathways that sense oxidative stress and induce expression of various anti-oxidant genes in the budding yeast *Saccharomyces cerevisiae*, the fission yeast *Schizosaccharomyces pombe* and the pathogenic yeast *Candida albicans*. Three conserved signaling modules have been identified in the oxidative stress response of these diverse yeast species: the stress-responsive MAP kinase cascade, the multistep phosphorelay and the AP-1-like transcription factor. The structure and function of these signaling modules are discussed.

Keywords: Yeast; Oxidative stress; DNA; Stress-activated protein kinases (SAPK); Reactive oxygen species (ROS)

Contents

* Corresponding author. Tel.: +1 530 752 3628; fax: +1 530 752 9014.
E-mail address: kshiozaki@ucdavis.edu (K. Shiozaki).

0027-5107/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.mrfmmm.2004.09.006

1. Introduction

Cells in a human body metabolize approximately 10^{12} oxygen molecules per day during the normal respiration process, and ~1% of the oxygen metabolized results in the formation of reactive oxygen species (ROS), such as the superoxide anion (O_2^-), the hydroxyl free radical ($OH^\bullet$) and hydrogen peroxide (H_2O_2) [1]. Some of heavy metals and various genotoxic agents, including UV irradiation and alkylating agents, also generate oxidative stress. Because of its high reactivity, ROS derived from various sources described above bring about damages, either directly or indirectly, to various cellular macromolecules, including DNA [2,3]. For instance, oxidative DNA damage can alter purine and pyrimidine bases as well as cleave the phosphodiester DNA backbone [1]. One of the most studied mutations caused by ROS is 8-hydroxyguanine (8-OH-Gua), which leads to GC → TA transversions unless repaired before the DNA is replicated [4]. It is approximated that 20,000 bases in chromosomal DNA are damaged in each human cell by ROS [1,5]. Indeed, ROS have been implicated in several human processes and diseases, including cancer, heart disease, and neurodegenerative diseases [3,4,6,7].

In order to counteract oxidative DNA damage, cells have evolved several repair mechanisms including the direct reversal of the mutation, mismatch repair and DNA excision pathways [8]. However, it is equally important to eliminate ROS promptly, in order to prevent further damage to DNA. Thus, aerobically growing organisms developed multiple ways to decompose ROS, through the production of detoxifying enzymes (i.e., catalase, superoxide dismutase and peroxidase) and molecular scavengers such as glutathione and thioredoxin [9]. Perhaps these molecules serve as the first line of defense against oxidative damage, and the cellular mechanisms that induce production of these molecules in response to oxidative stress are often termed "oxidative stress response".

Extensive studies on the oxidative stress response in bacteria, particularly *Escherichia coli* and *Salmonella typhimurium*, have identified two independent mechanisms that respond to different types of oxidants (reviewed by Pomposiello and Demple [10]). Exposure to hydrogen peroxide leads to the activation of a transcription factor, OxyR, which regulates the expression of nine genes required for the protection against oxidative stress, including catalase and glutathione reductase. *oxyR* mutants exhibit high spontaneous mutation rates even in the absence of hydrogen peroxide, suggesting that OxyR plays a role in preventing oxidative damage to DNA also during normal aerobic growth [11,12]. On the other hand, superoxide anion activates the SoxR transcription factor, which induces expression of another transcription factor, SoxS, as well as other genes. Together, SoxR and SoxS regulate induction of ~40 genes, including superoxide dismutase and DNA repair enzymes [10].

Detoxification of ROS in eukaryotic cells is also achieved by the enzymes and molecular scavengers similar to those utilized by bacteria [13,14], although oxidative stress response in eukaryotes utilize signaling mechanisms that show little resemblance to the OxyR and SoxRS systems. In this article, we will review the signal transduction pathways that sense oxidative stress and induce gene expression in yeasts, particularly, the budding yeast *Saccharomyces cerevisiae*, the fission