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Review

The metabolomics of oxidative stress

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ABSTRACT

Oxidative stress resulting from increased availability of reactive oxygen species (ROS) is a key component of many responses of plants to challenging environmental conditions. The consequences for plant metabolism are complex and manifold. We review data on small compounds involved in oxidative stress, including ROS themselves and antioxidants and redox buffers in the membrane and soluble phases, and we discuss the wider consequences for plant primary and secondary metabolism. While metabolomics has been exploited in many studies on stress, there have been relatively few non-targeted studies focused on how metabolite signatures respond specifically to oxidative stress. As part of the discussion, we present results and reanalyze published datasets on metabolite profiles in catalase-deficient plants, which can be considered to be model oxidative stress systems. We emphasize the roles of ROS-triggered changes in metabolites as potential oxidative signals, and discuss responses that might be useful as markers for oxidative stress. Particular attention is paid to lipid-derived compounds, the status of antioxidants and antioxidant breakdown products, altered metabolism of amino acids, and the roles of phytohormone pathways.

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1. Introduction

Most environmental challenges involve redox adjustments linked to enhanced accumulation of reactive oxygen species (ROS), a condition commonly known as oxidative stress. Many developmental processes also involve signalling through ROS that are probably generated at lower, less stressful levels. While still ill-defined, the state of oxidative stress can perhaps be considered as one in which ROS impinge on and produce significant changes in overall cellular redox state, with various, potentially wide-ranging consequences for the metabolic processes that power plant growth. Such a condition can be produced, to varying degrees, by conditions such as excess light, cold or heat, drought, invasion by pathogenic microorganisms, and oxidizing atmospheric pollutants.

In its very broadest sense, metabolomics could describe measurements of any component of the metabolome (ie, metabolite). However, it is often used to refer to large-scale analyses able to measure numerous metabolites at once. In this sense, metabolomics often implies an approach using techniques such as mass spectrometry, which is able to measure several classes of chemical compounds in a relatively non-targeted fashion (Fernie et al., 2004). Because of the chemical diversity of metabolites, which include both hydrophilic and hydrophobic compounds, and the incomplete nature of reference databases, no technique yet exists that is able to measure the majority of them in a single analysis, and comprehensive profiling of specific chemical classes can also fall under the definition of metabolomics.

The lack of a single analytical protocol to measure the majority of metabolites present in an extract of plant tissue contrasts with commonly used methods in transcriptomics, which provide more comprehensive information. Despite this drawback, changes in metabolites could be considered to be potentially more informative on plant function than changes in transcripts because metabolites can contribute directly to plant phenotypes. Thus, non-targeted metabolite profiling is clearly an interesting approach in the analysis of plant stress responses (Shulaev et al., 2008). However, relatively few studies have reported such analyses on plants in which the stress unambiguously originates from increased ROS availability. Examples of such studies include several that have used pharmacologically induced ROS production (Baxter et al., 2007; Obata et al., 2011) and others that have exploited a genetic approach based on mutants deficient in catalase (Chaouch et al., 2010, 2012; Han et al., 2013a).

This review aims to discuss some aspects of how metabolites are involved in oxidative stress and how this stress impacts on their status. Our ever-increasing knowledge of plant metabolic pathways potentially allows changes in individual metabolites or metabolite patterns to be defined as markers that are likely to be useful in assessing the degree or chemical and compartmental specificity of oxidative stress. While certain secondary metabolites or lipid derivatives have long been a focus of studies in this area, growing evidence points to equally important interactions with primary metabolism, leading to a more integrated view of the response of metabolism to increased cellular oxidation. In this review, we pay particular attention to unresolved issues surrounding measurements of ROS themselves, the roles of the key metabolites with which they interact directly, and some of the primary and secondary metabolic pathways that are responsive to oxidative stress. To highlight aspects of the discussion, we present new or reanalyzed data on metabolites measured in the catalase-deficient Arabidopsis *cat2* mutant. Loss of *CATALASE2* function in this line induces changes in cell redox state and metabolites through an unambiguously oxidative trigger (Mhamdi et al., 2010a). Advantages of using such systems are that (1) H_2O_2 is produced inside the cell by physiologically relevant pathways and that (2) the production can be both more readily controlled and more sustainably applied than when oxidative stress is induced pharmacologically.

2. Physiological manifestation and impact of oxidative stress

Numerous reviews have covered ROS and their metabolism in plants (eg, Møller et al., 2007; Van Breusegem et al., 2008; Foyer and Noctor, 2009; Fischer et al., 2013) and so the sources of these molecules will only be briefly introduced here. Primary ROS (ie, direct inorganic derivatives of molecular oxygen) include singlet oxygen, superoxide, hydrogen peroxide (H_2O_2), and the hydroxyl radical. All of these molecules are significantly more reactive than ground state triplet O_2, can modify numerous cellular components (Møller et al., 2007), and can be produced by various cellular sources (Foyer and Noctor, 2009; Fischer et al., 2013). The best known source of singlet oxygen is photodynamic excitation of triplet O_2 in photosystem II during photosynthesis (Fischer et al., 2013). In contrast, production of superoxide or H_2O_2 involves reduction of oxygen, for example by chloroplast and mitochondrial electron transport chains or by enzymes located in compartments such as the peroxisomes (eg, glycolate oxidase) or at the cell surface/apoplast (NADPH oxidases, peroxidases; Torres et al., 2002; Foyer and Noctor, 2003; del Río et al., 2006; Bindschedler et al., 2006; O'Brien et al., 2012a,b). The hydroxyl radical can be produced by reductive cleavage of H_2O_2, notably catalyzed by Fenton reagents such as iron and other transition metals, although it can also be produced from H_2O_2 by radiation, eg, with ultra-violet light (Halliwell, 1996). Among the frequently used pharmacological agents in oxidative stress research are redox cycling quinones like menadione, and paraquat, the latter mainly acting to transfer electrons from the photosynthetic electron transport chain to oxygen. Both of these agents produce superoxide from which other ROS can subsequently be produced, but paraquat is often used as a fairly specific stimulus of ROS production in the chloroplast.

It is now clear that at least some of the effects of ROS are mediated by signalling pathways (Wagner et al., 2004; Achard et al., 2008), and that both the chemical nature and subcellular location of ROS production may be important in determining cellular responses (Gadjev et al., 2006). Thus, it is possible that superoxide/H_2O_2 produced in the mitochondria trigger different signalling pathways from the same molecules produced in the chloroplast. A key distinction may well be the roles of ROS produced inside the cell, where antioxidative capacity and redox buffering are high, and those generated at the cell surface (Foyer and Noctor, 2009; Miller et al., 2009). The apoplast is a significantly more oxidized compartment than much of the cell interior (Pignocchi and Foyer, 2003) and the hydroxyl radical, which is considered to be the most short-lived ROS, is an essential chemical in cell wall metabolism (Müller et al., 2009). Intracellular and extracellular ROS may be involved in an intricate crosstalk that determines the metabolic and signalling outcome of oxidative stress (Chaouch et al., 2012).

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