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Review article

Glutathione – linking cell proliferation to oxidative stress

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ABSTRACT

Significance: The multifaceted functions of reduced glutathione (gamma-glutamyl–cysteinyl–glycine; GSH) continue to fascinate plants and animal scientists, not least because of the dynamic relationships between GSH and reactive oxygen species (ROS) that underpin reduction/oxidation (redox) regulation and signalling. Here we consider the respective roles of ROS and GSH in the regulation of plant growth, with a particular focus on regulation of the plant cell cycle. Glutathione is discussed not only as a crucial low molecular weight redox buffer that shields nuclear processes against oxidative challenge but also a flexible regulator of genetic and epigenetic functions.

Recent advances: The intracellular compartmentalization of GSH during the cell cycle is remarkably consistent in plants and animals. Moreover, measurements of *in vivo* glutathione redox potentials reveal that the cellular environment is much more reducing than predicted from GSH/GSSG ratios measured in tissue extracts. The redox potential of the cytosol and nuclei of non-dividing plant cells is about −300 mV. This relatively low redox potential maintained even in cells experiencing oxidative stress by a number of mechanisms including vacuolar sequestration of GSSG. We propose that regulated ROS production linked to glutathione-mediated signalling events are the hallmark of viable cells within a changing and challenging environment.

Critical issues: The concept that the cell cycle in animals is subject to redox controls is well established but little is known about how ROS and GSH regulate this process in plants. However, it is increasingly likely that redox controls exist in plants, although possibly through different pathways. Moreover, redox-regulated proteins that function in cell cycle checkpoints remain to be identified in plants. While GSH-responsive genes have now been identified, the mechanisms that mediate and regulate protein glutathionylation in plants remain poorly defined.

Future directions: The nuclear GSH pool provides an appropriate redox environment for essential nuclear functions. Future work will focus on how this essential thiol interacts with the nuclear thioredoxin system and nitric oxide to regulate genetic and epigenetic mechanisms. The characterization of redox-regulated cell cycle proteins in plants, and the elucidation of mechanisms that facilitate GSH accumulation in the nucleus are keep steps to unravelling the complexities of nuclear redox controls.

Contents

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1. Introduction

Glutathione (GSH) is a ubiquitous low molecular weight thiol in eukaryotes. The 2GSH/glutathione disulfide (GSSG) redox couple is crucial in the regulation of cellular redox homeostasis. High GSH/GSSG ratios are maintained by the activity of glutathione reductase (GR), which ensures that the 2GSH/GSSG and NADP/NADPH redox couples are in thermodynamic equilibrium and hence at the same redox potential.

Considerations of antioxidant functions in the prevention of oxidative stress still overshadow much of our current philosophy and understanding of the importance of GSH in animals and plants. However, accumulating evidence demonstrates that GSH is required for the operation of a diverse range of processes that include growth, stress tolerance and cell suicide programs [1,2]. Within this context, the requirement for GSH is undoubtedly linked to signalling function, particularly interactions with nitric oxide (NO) and participation in thiol-dependent post-translational protein modifications, which modulate activities, sub-cellular localization, stability or their interactions with partner proteins in plants and animals.

Plant growth is driven initially by cell proliferation and primary morphogenesis, followed by cell expansion, secondary morphogenesis and endoreduplication [3]. While the requirement for GSH biosynthesis for mitosis and root formation is well established in plants, the broader functions of GSH-regulation in the orchestration of plant organ formation is poorly understood, not least because of the diverse range of potential target genes and proteins that are involved in the promotion or inhibition of component pathways or processes.

GSH is abundant in the plant cell cytosol, chloroplasts, mitochondria and nucleus (Fig. 1). Like other small molecules, GSH diffuses freely between the cytosol and nucleus through the nuclear pore complex [4]. It is rather surprising therefore that the nuclear GSH pool is much more resistant to depletion than the cytosolic pool, a property that is particularly important during cell proliferation [5–8]. Although relatively little is known about the nuclear thioredoxins (TRX) and glutaredoxins (GRXs) or their functions in plants [9] it is probable that these redox proteins participate in the plethora of thiol-dependent redox regulation mechanisms and post-translational modifications that are required for plant growth and development, particularly through functions in the nuclei. The many important roles of glutathione in plants have been well documented in recent reviews [1,2,10] and hence the following discussion will focus on how GSH functions as a regulator of plant development, with a particular focus on the nuclear GSH and the regulation of mitosis.

2. GSH and redox signalling

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) act as signalling molecules to transfer extracellular or intracellular information to the nucleus to elicit specific and appropriate responses. In its classic function as an antioxidant, GSH serves to remove ROS and hence limit the lifetime of the oxidative signal. However, accumulating molecular genetic evidence suggests that GSH is also important in potentiating ROS signals in plants, particularly through interactions with plant stress hormones such as salicylic acid (SA) and jamonic acid [11–13].

Redox-sensitive cysteines, which can undergo a diverse spectrum of thiol modifications, play a central role in coupling changes in intracellular redox state to metabolic and molecular responses through the ROS- and RNS-dependent signalling pathways. The reactivity of any protein thiol group is largely determined by the structural environment of the cysteine, together with its pK_a value. Most protein thiols have pK_a values greater than 8.0, which means that the thiol group is predominantly protonated and largely nonreactive at cellular pH values. However, the thiol groups of redox-sensitive cysteines have much lower pK_a values ranging

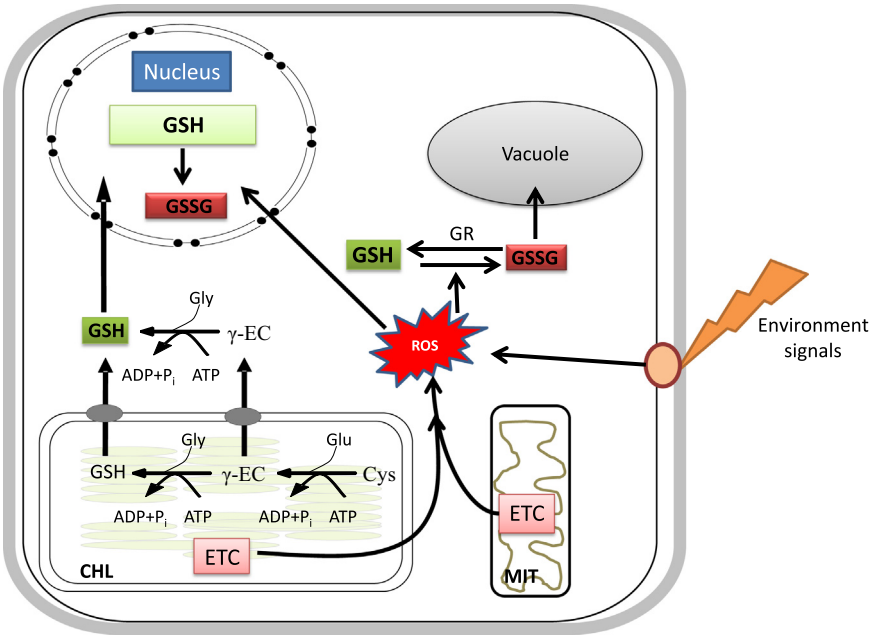

Fig. 1. Intracellular compartmentation of glutathione in plants. CHl, chloroplast; MIT, mitochondria; ETC, electron transport chain.