Plant sugar sensing and signaling – a complex reality

In plants, sugars function as a metabolic resource, but they are also important regulators of many processes associated with growth, maturation and senescence[1,2]. Their regulatory activities include both the repression and activation of many genes, and it is probable that several distinct sensing and transduction mechanisms are involved[2–4]. In response to a recent article by Nigel Halford and colleagues[5], which questioned whether hexokinase functions in sugar sensing and signaling, as well as in hexose metabolism, we consider evidence that substantiates this dual function. We also highlight some of the differences in sugar signaling between yeast and plants, which emphasize the unique ways in which plants have evolved to carry out their life cycle.

Using both genetic and biochemical approaches, there is much available evidence that plant hexokinase-dependent glucose metabolism can be separated from hexokinase-dependent glucose signaling.

Firstly, transformation of *Arabidopsis* for sense or antisense expression of AtHXK1 or AtHXK2 resulted in hyper- and hypo-sensitive plants, respectively, based on *rbcs* and *cab* gene expression and on seedling bioassays with exogenous sugars[6]. Importantly, this effect was not caused by altered HXK-dependent glucose metabolism, because *Arabidopsis* transformed with yeast HXK2 were actually less sensitive to glucose repression, in spite of a three- to fivefold increase in enzyme activity.

Secondly, glucose analogs can arrest seed germination and/or seedling development by a mechanism that affects sugar signaling independently of hexose metabolism. For example, low levels of mannose can block germination of *Arabidopsis* without affecting seed levels of ATP or inorganic phosphate[7], and mannose-dependent repression of germination can be overcome by mannoheptulose (a competitive inhibitor of hexokinase)[7]. Furthermore, germination in the presence of mannoheptulose indicates that hexose phosphorylation by hexokinase is not required for germination of *Arabidopsis*.

Finally, glucose repression of gene expression has also been examined using freshly isolated mesophyll protoplasts. Co-transfection of hexokinase substrates, glucose analogs or intermediary metabolites with reporter genes, has demonstrated: gene specificity; a requirement for hexose phosphorylation; and the lack of inhibition by hexose-phosphates, other glycolytic intermediates, ATP or inorganic phosphate[8].

These and other available data (e.g. Refs 3,9) offer compelling and unequivocal evidence that plant hexokinase plays a major role in glucose-dependent modulation of gene expression and plant growth. The recent isolation of two AtHXK1 mutants has provided definitive evidence for such a role (L. Zhou *et al.*, unpublished), but a complete understanding of this role awaits a detailed molecular determination of the encoded protein's putative signaling and metabolic functions. The isolation of suppressors in a plant hexokinase-null mutant, or the isolation of HXK mutants that can uncouple the two functions, will prove that the two roles are indeed separable.

Recent research has indicated that sugar signaling in plants also occurs by a hexose-dependent but hexokinase-independent pathway[10], as well as by a sucrose-dependent pathway[4]. The existence of multiple pathways indicates that sugar-signal transduction processes are relatively complex in plants. It has recently been suggested that plant homologs of yeast SNF1 kinase mediate both hexose and sucrose signaling mechanisms, largely at the exclusion of any role for hexokinase[5]. However, if these homologs are of central importance, then it remains to be explained why antisense expression of the gene in potato only appears to affect the expression of sucrose synthase[5].

We believe that the unique properties of plant carbohydrate biochemistry, and its interface with multiple growth processes, will necessarily lead to different models for sugar signaling in plants compared with yeast. First, in yeast, glucose-dependent repression of gene expression involves prominent negative DNA regulatory elements that control the utilization of non-fermentable carbohydrates[11]. In contrast, plant sugar repression involves positive DNA regulatory elements, which in source tissues respond to inputs from carbohydrate biosynthesis ('end-product inhibition') and in sink tissues respond to carbohydrate utilization[12]. Second, the trafficking of sugars is very different in plant cells and yeast and, as such, the relationships between sugar signaling and sugar metabolism will also be different. Plant carbohydrate metabolism involves intracellular cycles, extensive compartmentation, and partitioning to, or from, organ-level transport processes[13]. All these processes are modulated by very sophisticated, diurnal regulatory programs. Finally, plant sugar signaling pathways can involve crosstalk with hormone signaling pathways that control growth and development and are unique to plants[14]. This type of complex signaling network in a multicellular plant does not occur in the unicellular yeast. Thus, it might be inappropriate to largely restrict plant sugar signaling models to known paradigms for yeast sugar signaling[5]. Rather, it might be better to recognize that evolutionary motifs often involve a 'used once, borrowed twice' scenario.

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