Photosynthesis converts solar energy to chemical energy, which then drives the synthesis of sugars from carbon dioxide and water. Sugars play multiple roles in all aspects of plant life. First, they provide the main respiratory substrates for the generation of energy and metabolic intermediates that are then used for the synthesis of macromolecules and other cell constituents. Second, Rib and deoxy-Rib sugars form part of the structure of DNA and RNA. Third, polysaccharides are the major structural elements of plant cell walls. Fourth, linkage to sugar is required for proper functioning of many proteins and lipids. As a consequence, the abundance and depletion of sugars or their derivatives initiate various responses in plants and have profound effects on plant metabolism, growth, and development.

Plants are considered to be carbon autotrophs, but they can be considered as carbon heterotrophs during some part of their life cycle and in some of their non-green organs such as roots, stems, and flowers, which are not involved in photosynthesis. Furthermore, carbohydrate depletion can occur and is a fact of life in most plants. For instance, variations in environmental factors such as light, water, or temperature and attacks by pathogens or herbivores may lead to a significant decrease in the efficiency of photosynthesis in source tissues (such as leaves that synthesize and export carbohydrates) and thus reduce the supply of carbohydrates to sink tissues (such as the non-green tissues that import carbohydrates for respiration, growth, and development). Under certain growth conditions, such as during an annual resting season or after leaf shedding, photosynthesis is turned off or operates to a lower degree, and carbohydrate reserves must be utilized and may become limited in nonphotosynthetic tissues. In germinating seeds under unfavorable environmental conditions the mobilization of stores in the cotyledons is delayed, which may result in the depletion of available carbohydrates and a decrease in seedling vigor. Knowledge about the response to sugar starvation and adaptation mechanisms in plants is of both fundamental and agronomic importance.

In nature, the cessation of growth of a heterotrophic living organism is often brought about by a poor nutrient environment, a commonly encountered stress. Environmental changes affect various biochemical reactions, often disturbing the balanced distribution of metabolites within cells. In most instances, living cells show a rapid molecular response to overcome adverse environmental conditions. How a living organism survives during periods of environmental stress is an exciting area of research. The most extensive studies have been done with microorganisms. The ability of microorganisms to sense and respond to unscheduled changes in their environment is crucial to their survival. When cells of microorganisms encounter unfavorable nutrient conditions, they ultimately enter a stationary phase. Cells in the stationary phase are physiologically, biochemically, and morphologically different from cells growing exponentially. Studies using Escherichia coli and yeast (Saccharomyces cerevisiae) have indicated that entry into the stationary phase is a complex, highly regulated process that activates a program for long-term survival. The program includes the lack of a requirement for added nutrients and an absence of cell division. The similarities of eukaryotic and prokaryotic microorganisms in their responses to nutrient limitations suggest that such responses are based on evolutionarily conserved genetic mechanisms.

Similarly, sugar starvation initiates changes in substantial physiological and biochemical processes with the goal of sustaining respiration and other essential metabolic processes in plants. Sugar starvation also initiates changes in cellular processes to recycle cellular constituents and dramatically changes the pattern of gene expression. However, the underlying mechanisms used by plant cells to cope with sugar starvation are largely unknown, and only recently have these questions been addressed experimentally. This lack of knowledge contrasts with the situation in bacteria and yeast, where the molecular biology and physiology of mutants have yielded extensive information about responses to sugar starvation. This review discusses the recent advances made in our understanding of the molecular events that operate in microorganisms upon sugar starvation, as well as the cellular and genetic responses of plants to sugar starvation.

**SUGAR STARVATION IN BACTERIA**

The majority of bacteria spend most of their time in a nutrient-limited starvation phase and as a result have evolved mechanisms that allow them to survive under these conditions and to resume growth once nutrients become available. Some bacteria, e.g. Bacillus spp., undergo major differentiation programs that lead to the formation...
of highly stress-resistant endospores or cysts. Other bacteria, e.g. *E. coli*, even without the formation of differentiated cells, enter starvation-induced programs that allow them to survive long periods of non-growth and to restart growth when nutrients become available. These starvation-induced programs often lead to the formation of metabolically less-active cells that are more resistant to a wide range of environmental stresses. This adaptation to starvation conditions is often accompanied by a change in cell size and the induction of genes and stabilization of proteins essential for long-term survival. Evidence suggests that there is a general starvation response among various bacteria species. For example, Glc- or nitrogen-starved cultures of *E. coli* exhibit resistance to heat or hydrogen peroxide (Jenkins et al., 1988). The nitrogen-fixing bacterium *Rhizobium leguminosarum* can survive carbon, nitrogen, and phosphorus starvation for at least 2 months with little loss of viability. Upon carbon starvation, *R. leguminosarum* cells undergo reductive cell division and the levels of protein, DNA, and RNA synthesis decrease to base levels, mRNA stabilizes, and the starved cells are cross-protected against pH, heat, osmotic, and oxidative shock (Thorne and Williams, 1997).

In *E. coli*, nutrient-starved stationary-phase cells have been used as a model system for studying the molecular mechanism that regulates gene expression under nutrient starvation. Stationary-phase cells have a small spherical shape, are resistant to multiple stresses, synthesize glycogen, and survive long-term starvation. Genes expressed during adaptation to starvation conditions involve several classes of starved genes that code for special stress-resistant proteins. The two major classes of genes induced upon carbon starvation are *csi* genes, which require cAMP and enhance the cell’s metabolic potential, and *pex* genes, which do not require cAMP but play a more direct protective role against stresses (Matin, 1991). A proteic role of stress-resistant proteins is proposed due to their ability to rescue misfolded macromolecules (Matin, 1991).

Expression of the stress-resistant proteins depends on an intact *rpoS* allele (Hengge-Aronis, 1993). However, a common consensus sequence has not been found among various promoters controlled by *rpoS*, and thus a regulatory cascade that mediates expression of the *rpoS*-dependent genes has been suggested (Hengge-Aronis, 1993). The protein encoded by *rpoS* is an alternative σ factor of RNA polymerase and is designated as σ^stress^. Evidence shows that the σ^stress^ factors are regulated primarily at the post-transcriptional level by a mechanism that involves a mRNA secondary structure (McCann et al., 1993). In addition, carbon starvation in *E. coli* might be sensed through the accumulation of homoserine lactone (Huisman and Kolter, 1994).

**SUGAR STARVATION IN YEAST**

Stress conditions imposed on yeast can be as diverse as nutrient starvation, suboptimal temperatures or osmolarity, high ethanol concentrations, the presence of heavy metals or oxidation compounds, and desiccation (Ruis and Schüller, 1995). Similarity in response to these stresses has been observed and the previous exposure to one stress generally increases the acquisition of tolerance against challenge by another stress (cross-protection or cross-resistance) (Lewis et al., 1995; Ruis and Schüller, 1995). These observations indicate that cells possess one central molecular mechanism that can be activated by various factors and, upon activation, will protect cells against a number of conditions threatening their survival.

Some carbohydrates or proteins induced by various stresses have been suggested to play a protective role against stresses. For example, a close correlation was observed between the content of trehalose, one of the major reserve carbohydrates in yeast, and the stress resistance of the cells. The levels of trehalose and stress resistance increase rapidly upon exhaustion of Glc in the culture medium (Panek and Panek, 1990). The level of trehalose also increases strongly upon starvation of an essential nutrient such as nitrogen, phosphate, or sulfate in a Glc-containing medium (Attfied, et al., 1992). The same is true during sublethal heat, freeze-thaw, and desiccation treatment (Hottiger et al., 1987; Attfied et al., 1992). Genes that have been demonstrated to contribute significantly to the ability of yeast cells to survive severe stress include *CTT1* (encoding the cytosolic catalase T) and *HSP104* and *HSP70* (encoding heat shock proteins) (Ruis and Schüller, 1995).

How yeast cells respond to a wide range of stresses through a convergent molecular mechanism(s) remains largely unclear. Specific gene control elements and stress-activated transcription factors binding to them are probably shared by the stress-responsive genes. A common feature at the transcriptional level, the stress-response element (STRE), a cis-acting element with the core consensus CCCCT, has been found to be present in the promoters of genes induced by various stresses (Varela et al., 1995). STRE activity correlates well with the potential to establish stress tolerance (Ruis and Schüller, 1995). Msn2p, a transcription factor that activates STRE-regulated genes in response to stress, has been identified. Mutants defective in Msn2p exhibit pleiotropic hypersensitivity to stress factors (Schmitt and McEntee, 1996). How stress signals are transmitted to STREs is not clear, and this raises the question of whether the various stress factors create a common pathway or multiple pathways that then transmit signals to the stress-specific STREs. STRE activities have been shown to be controlled by the high osmolarity glycerol pathway and the protein kinase A pathway (signaling nutrient stress), suggesting that different signals are transmitted through different pathways (Ruis and Schüller, 1995).

Dramatic morphological changes can be observed in yeast undergoing nutrient starvation. The depletion of nutrients such as carbon, nitrogen, sulfur, or amino acids induces autophagy in yeast (Takeshige et al., 1992). Autophagy is the major route of delivery of cytoplasmic proteins to vacuoles/lysosomes under conditions in which cells require enhanced protein degradation and remodeling of components (Dunn, 1994). A Ser/Thr protein kinase gene, *APG1*, is essential for both the autophagic process and the maintenance of viability of yeast under starvation conditions (Matsuura et al., 1997). It is therefore hypothesized that autophagy-dependent reconstruction of cellular
constituents is required for long-term viability in starvation conditions and that the process involves regulation by protein phosphorylation (Matsuura et al., 1997).

PLANT CELL METABOLISM ALTERED BY SUGAR STARVATION

Over the past 20 years, carbohydrate starvation has been studied in a number of plant species. Physiological and cellular changes that occur during a plant's transition to sugar starvation are most extensively studied in excised maize root tips (Brouquisse et al., 1991; Dieuaide et al., 1992), cultured sycamore cells (Journet et al., 1986; Aubert et al., 1996), and cultured rice suspension cells (Chen et al., 1994). These studies have shown that sugar starvation generally triggers sequential changes in the following cellular events: (a) arrest of cell growth, (b) rapid consumption of cellular carbohydrate content and decrease in respiration rate, (c) degradation of lipids and proteins, (d) increase in accumulation of Pi, phosphorylcholine, and free amino acids, and (e) decline in glycolytic enzymatic activities.

It appears that changes in metabolism are involved in the adaptation response of plant cells to sugar starvation. For example, cells in roots (Brouquisse et al., 1991) and leaves (Peeters and Van Laere, 1992), cultured suspension cells (Journet et al., 1986; Chen et al., 1994), and callus cells (Tassi et al., 1992) modify their metabolism to survive in the absence of sugar. In sugar-starved cultured cells, there is a decrease in enzymatic activities related to sugar metabolism and respiration (Journet et al., 1986; Brouquisse et al., 1991), nitrate reduction and assimilation (Brouquisse et al., 1992), and protein synthesis (Tassi et al., 1992). Decreases in these enzymatic activities presumably protect cells against nutrient stress by switching off biosynthesis (i.e., growth) to conserve energy. At the same time, an increase in enzymatic activities related to catabolism of fatty acids (Dieuaide et al., 1992), amino acids (Brouquisse et al., 1992), and proteins (Tassi et al., 1992) occurs. Such a change can substitute protein and lipid catabolism for sugar catabolism to sustain respiration and metabolic processes (Journet et al., 1986; Brouquisse et al., 1991).

Although these metabolic changes appear to enhance the survival of cultured cells under Glc starvation, they finally result in irreversible damages and cell death (Brouquisse et al., 1991; Chen et al., 1994). Similar metabolic changes occur in plant organs or tissues during senescence or in postharvest situations (Noodén, 1988; King et al., 1990). A common mechanism that regulates metabolic processes during sugar starvation and senescence has been suggested (Noodén, 1988). Sugar starvation has also been described as a component of senescence (Dieuaide et al., 1992).

VACUOLAR AUTOPHAGY IN PLANT CELLS

In Suc-starved sycamore and rice suspension cells, the decline in cellular sugar and starch contents couples with the decline in metabolic activity and the increase in vacuolar autophagic activity (Journet et al., 1986; Chen et al., 1994). Triggering of such autophagic processes presumably involves the regression of cytoplasm, including the organelles, and the recycling of respiratory substrates (Journet et al., 1986; Chen et al., 1994; Aubert et al., 1996). This process is well documented in animal cells (Marzella and Glau mann, 1987) and has been implicated in the nonselective bulk degradation of proteins triggered by nutrient deprivation. Autophagy in plant, animal, and yeast systems is often associated with nutrient starvation. In Suc-provided rice suspension cells, the size of the vacuole is small (Fig. 1a). Vacuolar autophagic activity begins a few hours after Suc starvation, and vacuole size expands either by engulfing neighboring cytoplasm and organelles (except the nucleus) or by vacuoles fusing together (Fig. 1b).

After a long period of Suc starvation, the vacuole volume becomes extremely large and the cytoplasm and the leftover organelles (mostly mitochondria) are confined to a narrow area adjacent to cell walls (Fig. 1c). Plant vacuoles are rich in hydrolyses, and cytoplasm sequestered by the autophagic vacuoles is eventually degraded by these enzymes. Vacuolar autophagy has also been observed in plants undergoing senescence (Matile and Winkenbach, 1971). Due to the presence of intracellular pools of carbohydrates and the ability to control the autophagic process, plant cells can survive for some time after carbohydrate starvation.

PLANT CELL RESPONSE TO SUGAR STARVATION AT THE GENE EXPRESSION LEVEL

Sugar plays an important dual role in regulating the expression of various genes in plants. In general, sugar favors the expression of enzymes in connection with biosynthesis, utilization, and storage of reserves (including starch, lipid, and proteins). On the other hand, sugar represses the expression of enzymes involved in photosynthesis and reserve mobilization (Koch, 1996). The events of cellular responses to sugar starvation is shown in Figure 2. Generally, gene expression repressed by sugar is up-regulated by sugar starvation, whereas that enhanced by sugar is down-regulated. The alteration of gene expression by sugar starvation results in the induction of synthesis of preexisting or new proteins and repression of normally expressed proteins.

A large and specific set of genes whose expression is induced by sugar starvation has been reported (Koch, 1996). For example, sugar starvation induces the expression of photosynthetic genes in maize mesophyll protoplasts (Sheen, 1990), α-amylase genes in rice suspension cells and germinating embryos (Yu et al., 1991, 1996), Suc synthase (Sh1) gene in maize root tips (Koch et al., 1992), and malate synthase and isocitrate lyase genes in cucumber (Graham et al., 1994). At the beginning of rice seed germination, active metabolism and a rise in the respiration rate cause rapid sugar depletion in the embryo, which then triggers the expression of α-amylase genes and degradation of starch in this tissue (Yu et al., 1996). Sugar depletion is also proposed to be a primary factor in initiating the synthesis of phytohormone GA in the embryo, since sugar reduces the quantity of GA in this tissue (Yu et al., 1996).
Most studies on the mechanisms of sugar repression of gene expression in microorganisms and plants have emphasized regulation at the transcriptional level. In plants, while sugar repression of genes involved in photosynthesis (Sheen, 1990) and the glyoxylate cycle (Graham et al., 1994) operates at the transcriptional level, sugar repression of $\alpha$-amylase gene expression involves control of transcription and mRNA stability (Sheu et al., 1996; Chan et al., 1994, 1998; Lu et al., 1998). Search for cis-regulatory elements in the promoters of sugar-regulated genes is important in understanding the mechanism of sugar regulation of gene expression. Although carbohydrate depletion induces expression

**Figure 1.** Electron micrographs showing morphological changes of cultured rice suspension cells during Suc starvation. Cells were Suc-starved for 0 d (a), 1 d (b), and 2 d (c), and examined under an electron microscope. AMY, Amyloplast; CW, cell wall; M, mitochondria; N, nucleus; S, starch granule; V, vacuole. Bar = 4 $\mu$m.

**Figure 2.** Events in cellular responses to sugar starvation in plants.
of a large set of genes essential for various physiological processes, the cis-acting sugar response elements in the promoters of these genes have not been extensively studied.

A sugar response complex in the promoter region of a Suc-deprivation-induced rice α-amylase gene, \(\textit{aAmy3}\), has been identified. This complex contains three essential motifs for a high level of sugar-starvation-induced gene expression in rice cells (Lu et al., 1998). One of the motifs, a TATCCA element, along with its variants, are present at a proximity upstream of the transcription start sites of 18 α-amylase genes isolated from various plant species (Yu, 1999) and several other sugar-repressible genes. The TATCCA element is present in tandem repeat between position –116 to –105 of the transcription start site of \(\textit{aAmy3}\) (Lu et al., 1998). Nuclear proteins from rice suspension cells that bind to the TATCCA element in a sequence-specific and sugar-dependent manner have also been identified (Lu et al., 1998). A 20-bp sequence upstream of the transcription start site of the maize Suc synthase gene \(\textit{Shrunken}\) is sufficient to confer sugar inhibition of downstream reporter gene expression (Maas et al., 1990). There is no homology between the sugar response sequences of the \(\textit{aAmy3}\) and the 20-bp sequence of the \(\textit{Shrunken}\) promoters. However, the TATCCA element is present between position –136 and position –141 of the \(\textit{Shrunken}\) promoter, which could be another control element that exhibits a function similar to the 20-bp sequence (Maas et al., 1990).

**SUGAR SENSING AND SIGNAL TRANSDUCTION IN PLANT CELLS**

Information concerning the sugar status of plant cells is of great importance in initiating changes in gene expression and subsequent metabolic and developmental responses. The mechanisms used by plant cells to sense sugars and to process this information are largely unknown. Yeast has been an essential model for studies on the mechanisms of sugar sensing and signal transduction employed in plant cells. In yeast, genes required for growth on carbon sources other than Glc are repressed by the presence of Glc in the medium and can be derepressed when Glc is removed. This is the phenomenon of Glc repression that requires a mechanism for sensing the availability of Glc. Hexokinase, the enzyme that catalyzes the phosphorylation of hexose sugars at the first step of the glycolytic pathway, has been implicated as a Glc sensor in organisms as diverse as yeast (Rose et al., 1991) and mammals (Efrat et al., 1994). Recent studies suggest that hexokinase also acts as a primary sugar sensor in plants (Jang and Sheen, 1997; Smeekens and Rook, 1997). However, the notion that hexokinase is a primary sugar sensor was recently challenged, and multiple sugar-sensing pathways were proposed to exist in plants (Halford et al., 1999). The other sugar-sensing systems proposed to exist in plants are a hexose transporter and/or receptor signaling pathway and a Suc transporter and/or receptor signaling pathway (Smeekens and Rook, 1997; Halford et al., 1999).

Knowledge of the downstream components of the Glc-signaling pathway in plants has just begun to emerge. In fungi, the SNF1 protein (Suc non-fermenting 1) is required for derepression of nearly all Glc-repressed genes and is an integral component of the sugar signal transduction pathway (Ronne, 1995). SNF1 is a Ser/Thr protein kinase and the active kinase is a high-molecular-mass complex. The SNF1 complex contains three proteins that are homologs of three subunits of the mammalian AMPK (AMP-activated protein kinase) (Hardie et al., 1998). AMPK is one component of a kinase cascade that is activated in a highly sensitive manner by the elevation of AMP and the depletion of ATP. The AMPK cascade has been shown to be activated by environmental stresses that deplete cellular ATP, for example, in pancreatic β cells by Glc deprivation (Salt et al., 1998). It is therefore suggested that the SNF1 complex in yeast might be activated in a manner similar to AMPK in mammals in response to Glc deprivation, and a change in

---

**Figure 3.** Hypothetical model of genetic and cellular responses of plant cells to sugar, including a sugar signal transduction pathway and a mechanism of gene regulation. Three elements function as sugar sensors: a hexokinase, a sugar transporter, and a change in the AMP/ATP ratio. Protein phosphatase and protein kinase are involved in the signal transduction pathway. In some cases, the SNF1 complex may be a component of the signal transduction pathway. The expression level of sugar-regulated genes is determined by the control of promoter transcriptional activity and mRNA stability. In the presence of sugar, the expression of sugar-starvation-induced genes is suppressed and there is no change in metabolism or vacuolar autophagic activity. Under sugar starvation, an opposite action of these events likely occurs.
the ATP level might be the signal that indicates the availability of sugar (Halford et al., 1999).

Recently, the requirement for a SNF1-related protein kinase-1 (SnRK1) in Suc-activated expression of a Suc synthase gene was demonstrated in potato by an antisense RNA approach (Purcell et al., 1998). This study indicated that SNF1 in plants may play a role analogous to that of SNF1 in yeast (Haldorf et al., 1999). However, whether SnRK1 activity is regulated by Glc or another hexose and whether plant SNF1 homologs also play a role in the de-repression of sugar-repressible genes remains to be determined. Identification of other functional components in the sugar signal transduction pathway are also important for determining whether the mechanisms through which cells sense sugar availability and respond by changing gene expression are conserved or diverged between yeast and plants throughout evolution. Based on the available information, a model of sugar sensing, signal transduction, and mechanisms of gene regulation in plant cells is shown in Figure 3.

CONCLUSIONS

Bacteria and yeast have developed mechanisms to react to depletion of nutrients in their environment and protect themselves against damage caused by nutrient stress and other stresses. Some components of stress signal pathways have been shown to be conserved among yeast, mammal, and plant cells (Ruis and Schüller, 1995; Hardie et al., 1998). Studies on the mechanisms of signal transduction and gene regulation in response to sugar deprivation will determine which strategies nature uses to deal with problems encountered by cells living in an unfavorable environment. However, many questions with respect to the underlying molecular mechanisms employed by plants in the adaptation to sugar deprivation remain to be answered. An understanding of how plants respond to sugar starvation and regulate the mobilization of stored carbohydrates can also help us to design crops with higher stress-tolerant capacity and is thus of biotechnological importance.

ACKNOWLEDGMENTS

I thank Dr. Maarten J. Chrispeels for critical review of the manuscript, and Lin-Tze Yu and Douglas Platt for help in preparing the manuscript.

Received July 22, 1999; accepted August 10, 1999.

LITERATURE CITED

Attfield PV, Ramm A, Norcott CJ (1992) Construction of Saccharomyces cerevisiae strains that accumulate relatively low levels of trehalose, and their application in testing the contribution of the disaccharide to stress tolerance. EEMS Microbiol Lett 94: 271–276


