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Glucose and Stress Independently Regulate- and Stress-Related Gene Expression via a Complex Signal Transduction Network and Multiple Control Mechanisms

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Abstract

In plants, sugars are required to sustain growth and regulate gene expression. A large set of genes are either up- or down-regulated by sugars; however, whether there is a common mechanism and signal transduction pathway for differential and coordinated sugar regulation remain unclear. In the present study, the rice (Oryza sativa cv Tainan 5) cell culture was used as a model system to address this question. Sucrose and glucose both played dual functions in gene regulation as exemplified by the up-regulation of growth-related genes and down-regulation of stress-related genes. Sugar coordinately but differentially activated or repressed gene expression, and nuclear run-on transcription and mRNA half-life analyses revealed regulation of both the transcription rate and mRNA stability. Although coordinately regulated by sugars, these growth- and stress-related genes were up-regulated or down-regulated through hexokinase-dependent and/or hexokinase-independent pathways. We also found that the sugar signal transduction pathway may overlap the glycolytic pathway for gene repression. α-Amylase and the stress-related genes identified in this study were coordinately expressed under sugar starvation, suggesting a convergence of the nutritional and environmental stress signal transduction pathways. Together, our studies provide a new insight into the complex signal transduction network and mechanisms of sugar regulation of growth and stress-related genes in plants.

INTRODUCTION

In plants, sugars do not only function as metabolic resources and structural constituents of cells, they also act as important regulators of various processes associated with plant growth and development. A variety of genes, whose products are involved in diverse metabolic pathways and cellular functions, are either induced or repressed depending upon the availability of soluble sugars. In general, sugars favor the expression of enzymes in connection with biosynthesis, use, and storage of reserves (including starch, lipid, and proteins), while repressing the expression of enzymes involved in photosynthesis and reserve mobilization (Koch, 1996). A large and specific set of genes has been reported to be positively regulated by sugars. Examples include: (a) genes that encode storage proteins, e.g. patatin in potato and sporamin in sweet potato (Hattori et al., 1990; Jefferson et al., 1990); (b) genes that encode protein pyrophosphorylase (Müller- Röber et al., 1990); (c) genes that encode defense proteins, e.g. proteinase inhibitor II in potato (Kim et al., 1991); and (d) genes that encode proteins for Suc metabolism, e.g. invertase and Suc synthase (Sus1) (Koch et al., 1992; Roitsch et al., 1995). In contrast, a variety of genes are negatively regulated by sugars, and their expression is induced by sugar deprivation, e.g. sugar represses expression of α-amylase genes in rice (Oryza sativa cv Tainan 5) suspension cells and germinating embryos (Yu et al., 1991, 1996); endopeptidase, Suc synthase (Sh1), and Asn synthase genes in maize root tips (Koch et al., 1992; James et al., 1993; Chevalier et al., 1995); and malate synthase and isocitrate lyase genes in cucumber cotyledon and suspension cells (Graham et al., 1994). It is not known whether a common mechanism is responsible for differential sugar regulation.

Plants are considered to be carbon autotrophs, during some part of their life cycle or in some of their non-green organs like roots, stems, and flowers that 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 and thus reduce the supply of carbohydrates to sink tissues. Under conditions of sugar deprivation, substantial physiological and biochemical changes occur to sustain respiration and other metabolic processes (Yu, 1999a). When Suc is omitted from the nutrient medium of cell cultures or isolated tissues, cell growth ceases and the cellular starch and sugar levels, respiration rates, and metabolic activities dramatically decline (Journet et al., 1986; Brouquisse et al., 1992; Chen et al., 1994). Sugar starvation may also trigger an autophagic process involved in the regression of cytoplasm, including organelles and in the recycling of respiratory substrates (Chen et al., 1994; Aubert et al., 1996; Yu, 1999a).

Understanding the mechanisms involved in sugar signal transduction and sugar regulation of gene expression in plants is still in its early stages. Most studies on the mechanisms of sugar activation and sugar repression in plants have emphasized regulation at the transcriptional level (Sheen, 1990; Chan et al., 1994; Graham et al., 1994; Lu et al., 1998). However, sugar repression of α-amylase gene expression involves control of both transcription and mRNA stability (Sheu et al., 1994, 1996). A sugar response complex (SRC) in the promoter region of a Suc deprivation highly inducible rice α-amylase gene, αAmy3, has been identified. This SRC contains three essential motifs for a high level of sugar starvation-induced gene expression in rice cells (Lu et al., 1998). Studies on αAmy3 mRNA have also identified essential sequences in its 3′-untranslated region (3′-UTR) that control sugar-dependent mRNA stability (Chan and Yu, 1998a, 1998b). The 3′-UTR of a cell wall invertase gene (Incw1) recently was shown to be involved in translational control of Incw1 by sugars in cultured maize suspension cells (Cheng et al., 1999).

A considerable amount of information concerning the sugar signal transduction pathway is available from research in yeast (Carlson, 1987; Entian and Barnett, 1992; Gancedo, 1992). However, very few yeast homologs in plants have been studied or shown to serve similar functions or to be regulated in a manner similar to the yeast system. Hexokinase, the enzyme that catalyzes the phosphorylation of hexose sugars at the first step of the glycolytic path ms as diverse as yeast (Rose et al., 1991) and mammals (Efrat et al., 1994). Recent studies suggest that hexokinase also acts as the primary sugar sensor in plants (Jang et al., 1997; Smeekens-and Rook, 1997). However, multiple sugar sensing pathways have also been proposed to exist in plants (Halford et al., 1999; Sheen et al., 1999; Smeekens, 2000). A gene (SnRK1) encoding the yeast Ser/Thr protein kinase (SNF1) homolog isolated from potato was recently shown to be required for activation of Suc synthase gene expression (Purcell et al., 1998). Whether SnRK1 activity is regulated by Glc or some other hexose and whether SnRK1 plays a role in the derepression of sugar-repressible genes in plants as in yeast (Ronne, 1995) are not known.

Expression of genes regulated by sugars can also be affected by various other factors, such as light (Sheen, 1990), phosphate (Sadka et al., 1994), hormones (DeWald et al., 1994; Zhou et al., 1998), pathogen infection (Herbers et al., 1996), as well as wounding and anaerobiosis (Salanoubat and Belliard, 1989). The mechanisms underlying the crosstalk between sugar and other signal transduction pathways and gene regulation are not clear. It will be interesting to determine whether different internal and external signals are integrated to result in the coordinated regulation of gene expression. The aim of the present study was to explore whether there is a common mechanism for differential and coordinated sugar regulation and to better understand the mechanism that connects the sensing and transmission of sugar signals with the regulation of gene expression in plants. Rice suspension cell culture, which is readily amenable to exogenous metabolic manipulations, was used as a model system for these studies. The usefulness of this type of cell culture in such studies is well documented (Graham et al., 1994; Ehness et al., 1997; Cheng et al., 1999; Yu, 1999a). In the present studies, some growth- and stress-related genes up- and down-regulated by Suc, respectively, were identified and found to be differentially and coordinately regulated by Suc, and the regulation involves control of both transcription rate and mRNA stability. Hexokinase-dependent and -independent pathways were found to be involved in up- and down-regulation of gene expression. Based on several lines of experimental evidence, we propose two potential complex signal transduction networks for differential and coordinated regulation of gene expression: one which connects the sugar signal transduction pathway to the sugar metabolic pathway and one

RESULTS

Sugars Have Dual Functions in Gene Regulation

To study the mechanism that switches on and off sugar-dependent gene expression, it was necessary to identify genes whose expression are up- or down-regulated by sugars. Cells were first provided with Suc for 72 h, starved of Suc for 72 h, then provided with Suc for 24 h. Total RNA was purified from these cells and subjected to gel-blot analysis. Several cDNAs that encode proteins known to be required for cell growth, e.g. actin (Act), glyceraldehyde-3-phosphate dehydrogenase (G3PD), Histone H3 (His), and Suc synthase P-2 (SSP2), as well as various proteins related to stress response, e.g. alcohol dehydrogenase (ADH2), heat shock protein 86 (HSP86), and ubiquitin precursor (Ubi), were used as probes for the gel-blot analysis. The mRNA levels of α-amylase genes (α-Amy) increased after the onset of Suc starvation and decreased as cells were provided with Suc (Fig. (Fig.1a).1a). These observations were consistent with our previous report (Sheu et al., 1994). In contrast, the mRNA levels of Act, ADH2, G3PD, His, HSP86, and SSP2 genes were initially high in Suc-provided cells and then decreased significantly after Suc starvation. Somewhat different expression patterns were observed for His and HSP86 genes. Accumulation of the His mRNA was dramatically and transiently increased 1 h after shifting cells from Suc-free to Suc-containing medium (Fig. (Fig.1a,1a, lane 15). Accumulation of HSP86 mRNA progressively decreased and reached the lowest level 8 h after starvation (Fig. (Fig.1a,1a, lane 9) and progressively increased afterward while cells remained under starvation. Three hybridization signals were observed for Ubi genes: one decreased after Suc starvation, one increased after Suc starvation, and the other one increased with culture age. To identify genes whose expression is down-regulated by sugars, we performed a differential screening of a cDNA library constructed from poly(A+) mRNA prepared from 4-h Suc-starved rice cells. More than 100 cDNA clones whose expression increased after Suc starvation were isolated. Twelve cDNA clones whose signals were significantly stronger by hybridization with cDNA probes of Suc-starved cells compared with cDNA probes of Suc-provided cells were selected for further characterization. By hybridization with the αAmy8-C probe, three of the cDNAs were found to be α-amylase genes and were not further characterized. Partial 3′-end nucleotide sequence analyses of the other nine cDNAs suggested that they were derived from six different genes. To confirm preferential induction by sugar starvation, the six selected genes were used as probes to hybridize to replicated gel blots of total cellular RNA as shown in Figure Figure1a.1a.

realistic and these two possible outcomes. Analysis of the subsequent interviews (as well as reanalyzing previous interviews) revealed that these providers had experiences with patients whose unrealistic understandings led to burdensome treatment decisions and thus to deaths with unnecessary pain, suffering, overly aggressive treatment, and unresolved family issues. At this point a theoretical decision was made to pursue an understanding of the processes of shifting goals and treatment decisions.

Subsequent theoretical sampling was designed to discover whether any predictable or patterned differences existed among provider types (e.g., nurses and physicians), work settings (e.g., acute or home care), and work experience (e.g., experienced or novice). It was hypothesized that these might explain which providers or what conditions were likely to result in a provider engaging in strategies to achieve a good death or avoid a bad one and which were not. Further exploration of this relationship in subsequent interviews suggested that experience with dying patients was common to providers who were concerned about and organized their strategies around quality of death. Experience itself, however, did not necessarily lead to such an approach. Additional theoretical sampling was done in order to provide some comparisons around length of experience as a health care provider and, in particular, with patients who were dying.

Several procedures were integrated into the methodological design of this study to maximize the credibility of the results (Guba & Lincoln, 1989; Strauss, 1987). All interviews were transcribed verbatim, checked for accuracy, and entered into a computer software program designed to assist qualitative data management (QSR NUD*IST 4, 1997). Memos and matrices were used to track the evolving theory and the methodological choices made by the researcher during the study. The principal researcher met weekly with a multi-disciplinary grounded theory dimensional analysis group. The researcher was engaged in data collection and analysis for 22 months, but the majority of the data was collected during the first 16 months. Analysis and member checks continued until the study was completed. Member checks were ongoing throughout the study and included second interviews with three provider participants (chosen for the breadth and depth of their experience), fieldwork, and interactive presentations of findings to small groups of providers similar to those who participated.

Results

This section begins with a brief synopsis of the grounded theory of reconciling decisions near the end of life (Norton, 1999), which provides the con-

Reconciling Decisions Near the End of Life

Health care providers often described knowing a patient's death was imminent before the patient or family knew. When these providers believed a patient's death was near, they shifted the purpose of their interventions toward helping the patient achieve a good death. With that in mind, providers worked toward changing patients' and families' treatment decisions from what providers believed were unrealistic curative choices to more realistic palliative choices. In this context, unrealistic decisions were those intended to cure, and realistic decisions were those intended solely to palliate symptoms or to forego curative treatments.

Providers reported that when patients or families continued to make unrealistic (curative) treatment decisions near the end of life, the patient would probably not experience a good death, possibly even having a bad one. A good death was characterized by all providers in a similar way as one that includes time to resolve personal business, time to reconnect with family, time to forgive and be forgiven, time to achieve important goals, and time to say good-bye to loved ones, while maintaining good pain and symptom control. A difficult or bad death was characterized by not being able to say good-bye; having unfinished business, unresolved conflict and anger, and difficulty grieving; undergoing futile treatment, creating bad memories for the family; and having poor symptom and pain control.

According to providers, changing the patient's or proxy's understanding, that is, their "big picture," to one in accord with the providers' assessment led the patient and family to realistic goals and thus to palliative treatment choices. From the providers' perspective, the big picture was a gestalt of the patient's condition constructed from information about the diagnosis, test results, prognosis, general assessment findings (including physical, emotional, and spiritual factors), treatment options, treatment efficacy, treatment burdens, and patient goals. This information, filtered through providers' knowledge, insights, and experience, formed providers' overall picture of what was going on with the patient. In this context it was the big picture, as perceived by providers, that determined whether goals and treatment decisions were realistic.

Providers expressed a belief that understanding the big picture would probably lead to realistic decisions that in turn would lead to a good death. On the other hand, lack of understanding or acceptance of the big picture increased the likelihood of making unrealistic treatment decisions that would result in unnecessary pain and suffering and in missed opportunities for a good death (e.g., not being able to say good-bye to loved ones). Providers often imputed a lack of understanding and/or acceptance of the overall big picture as the cause of patients' or proxies' adherence to unrealistic goals. Unrealistic goals were goals that the patients could not achieve and/or that led to burdensome aggressive treatments that made it difficult, if not impossible, for patients to achieve a good death. One provider described a dying patient who wanted to continue chemotherapy:

This patient was described as having an angry and bitter death. The provider was frustrated by the patient's unwillingness to accept a realistic big picture and her continued adherence to curative treatment decisions. It is the provider big picture that providers said must be shared by patients and family members in order for them to make realistic decisions. Therefore, changing the patient's big picture became the focus of provider interactions.

Providers responded differently to perceived unrealistic patient or proxy goals. These responses included: (a) avoiding interactions with the patient and family, (b) referring the patient and family to another provider, and (c) using strategies aimed at shifting patients' unrealistic goals and treatment decisions to more realistic ones. Providers' often responded to unrealistic patient or proxy goals and decisions by using strategies to shift the patient or family picture, and to increase their understanding of what was happening. Early on these strategies were intended to "lay the groundwork" for a new picture. Laying the groundwork was typically followed by strategies focused on shifting the patient or family to a new picture. Finally, once a patient had shifted to a new, more realistic picture, provider strategies focused on helping the patient and the patient's family to accept and keep that realistic picture. Once a patient and family accepted a new picture, their treatment decisions were most likely to be palliative and thus more likely to ultimately result in a good death (Fig. 1). The individual strategies presented in the following sections are grouped under general purposes. However, most strategies were used for more than one purpose (e.g., teaching could be used to lay the groundwork, to shift the understanding of a patient or family toward the patient's picture, and/or to help the patient or family accept a new picture).

Providers' perspectives are presented here. The intent was not to imply that only one picture exists, that all providers share one picture, or even that there is such a thing as an accurate picture. Rather, the intent was to illustrate providers' behaviors when they conclude that the patient or proxy does not have an accurate big picture.

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