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REVIEW

Advances in plant cell type-specific genome-wide studies of gene expression

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Abstract **Cell is the functional unit of life. To study the complex interactions of systems of biological molecules, it is crucial to dissect these molecules at the cell level. In recent years, major progresses have been made by plant biologists to profile gene expression in specific cell types at the genome-wide level. Approaches based on the isolation of cells, polysomes or nuclei have been developed and successfully used for studying the cell types from distinct organs of several plant species. These cell-level data sets revealed previously unrecognized cellular properties, such as cell-specific gene expression modules and hormone response centers, and should serve as essential resources for functional genomic analyses. Newly developed technologies are more affordable to many laboratories and should help to provide new insights at the cellular resolution in the near future.**

Keywords transcriptome, cell type, plant

Introduction

What constitutes a differentiated plant cell type? How much do various types of plant cell differ in their transcription of genes for the components of cellular structure and function, such as capturing energy from sunlight and assimilating essential nutrients from the air and soil? What distinguishes genes with highly specific cellular patterns of transcription from housekeeping genes expressed in all cells? The development and functions of plant tissues rely on constant interactions among distinct and non-equivalent cell types. To understand how cells work and how they interface with the environment, we need to acquire quantitative information on transcriptomes, epigenomes, proteomes, protein–protein interactions, protein-nucleic acid interactions and metabolomes at cellular resolution. In the past 20 years, several methods have been developed to understand the cell-specific gene expression and protein localization, including *in situ* RNA hybridization, immunochemistry approaches, and fluorescent protein tagging. Although these methods are widely used to study the function of individual genes and proteins, they are usually labor-intensive and are limited to small scale studies. The systems approaches emerging in biology promise to explain properties of biological systems based on genome-wide measurements of expression, interaction, regulation and metabolism (Ideker et al., 2001; Long et al., 2008). To facilitate a systems approach, it is essential to first capture such components in a global manner and ideally at cellular resolution. Here we review recent advances in the development of cellular resolution profiling technologies for mRNA and chromatin status with focus on their applications in plants, and discuss the results from analyzing the expanding catalog of cellular resolution data sets. Although this review focuses on advances in plants, most of these approaches have also proved useful in other multicellular species.

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Recent advances in cellular resolution transcriptome profiling

Until recently, a cellular level of resolution has not been available for a comprehensive view of the entire transcriptome, proteome, and metabolome afforded by profiling methods. Usually, the separation of distinct cell types implies physical manipulations, which are on the basis of distinct

appearance, location, molecular markers, or other distinguishing properties of non-equivalent cell types (reviewed in Nelson et al., 2008). For cell types that naturally exist as single cells, such as pollen and *in vitro* cell suspension culture (Demura et al., 2002; Engel et al., 2003; Honys and Twell, 2004; Pina et al., 2005), cell types on surfaces, such as trichomes and root hairs (Wienkoop et al., 2004), and cell types that are differentially resistant to mechanical and enzymatic procedures, such as guard cells (Leonhardt et al., 2004), means for separation are relatively straightforward. New technologies are required for the profiling of most other cell types in plants, which will be further discussed in this review. A quick summary for the principle, advantages and pitfalls of each approach are also provided in Table 1.

Laser microdissection (LM)

Laser microdissection (LM) is a method for separating and isolating specific cells of interest from microscopic regions of tissues. Under a microscope, a thin tissue section, typically 5–10 μm thick, is visualized and specific cells of interest are identified as individual cells or clusters of cells for isolation. Current LM technology has two major strategies – laser capture microdissection (LCM) and laser cutting (Nelson et al., 2006). Both methods utilize sectioned plant tissues that must be fixed or frozen. For LCM, the desired cells are affixed to a transfer film, which overlays the original tissue section, by use of a pulsed infrared laser that melts and fuses the film at the locations of cell targets. The cells are then harvested by collecting the film. By contrast laser cutting employs a tissue-ablating UV laser to cut free target cells, which can be collected either by laser pressure catapulting or gravity-based ejection toward a collection vessel, or by film-based collection as used by LCM. Applications of LM to plant samples include transcriptome analysis of maize shoot epidermal and leaf tissues, apical meristem, and root pericycle cells (Nakazono et al., 2003; Emrich et al., 2007; Dembinsky et al., 2007; Brooks et al., 2009; Li et al., 2010), *Arabidopsis* embryos, stamen abscission zone, and female gametophyte (Casson et al., 2005; Spencer et al., 2007; Cai and Lashbrook, 2008; Wuest et al., 2010), and a collection of 40 different cell types from rice seedlings (Jiao et al., 2009). Since LM does not require cell-specific markers or tags, unique genetic lines, or special tissue or cell properties, cells could be selected entirely on the basis of their appearance and location in histological sections.

The limited number of cells that can be harvested by this approach compromises the quality of target materials, such as RNA, so that efficient RNA isolation on a femtogram to picogram scale and downstream amplification are required. *In vitro* transcription is usually used, which is based on two to three rounds of antisense RNA (aRNA) amplification (first described in Van Gelder et al. 1990), and involves a series of enzymatic reactions resulting in linear amplification of exceedingly small amounts of RNA obtained by LM. However, the resulting aRNA population after the above procedure may not maintain representation of the starting mRNA population. Furthermore, the obtained aRNA

Table 1 Summary and comparison of cell-specific transcriptome/translatome profiling methodologies. Please refer to corresponding sections for references.

Profiling methodologies	Isolation target	Isolation method	Profiling target	Characteristics	Limitations
Laser microdissection	Cells from tissue sections	Histological tissue sectioning followed by laser capture microdissection or laser cutting	Total mRNAs inside cells	Cells selected based on their appearance and location in sections; no unique genetic lines required	RNA amplification required from limited number of target cells obtained; specialized equipment required
Fluorescence -activated cell sorting	Fluorescently labeled proto-plasts	Digestion of tissues followed by flow cytometry-based protoplast isolation	Total mRNAs inside cells	Cells sorted based on the fluorescent protein they express; chemical and mechanic protoplasting involved	Protoplasting and sorting affect transcription profiles; RNA amplification required from limited number of target cells obtained; specialized equipment required; extensive genetic manipulation of plants required; cell-specific promoters required
Translating ribosome affinity purification	Affinity-tagged polysomes	Immunopurification of tagged polyribosomal complex as well as the associated mRNAs	mRNAs being translated	Cell-specific purification of polysomes for translating mRNA profiling; relatively high yield of target mRNAs; relatively low cost	Extensive genetic manipulation of plants required; cell-specific promoters required
Nuclear isolation	Fluorescently labeled or affinity-tagged nuclei	Nuclear isolation and enrichment based on fluorescence-activated sorting or affinity-based purifica-tion	Nuclear mRNAs	Cell-specifically labeled nuclei are isolated; no protoplasting required; can be extended to profiling chromatic features in addition to gene expression	Cytoplasmic mRNAs cannot be profiled; extensive genetic manipulation of plants required; cell-specific promoters required; specialized equipment required for nuclei sorting

molecules are truncated compared with the starting mRNA. A recently developed more sensitive technique can efficiently amplify mRNA from a single mouse blastomere (Tang et al., 2009) and can be seamlessly integrated with the next-generation sequencing technology. We expect that the combination of this new amplification technique and LM will lead to next-generation transcriptome profiling at the single-base resolution.

Fluorescence-activated cell sorting (FACS)

Flow cytometry is a routinely used technique for counting and examining blood cells, by suspending them in a stream of fluid and passing them through an electronic detection apparatus. However, employment of flow cytometry for the analysis of higher plants remains limited, largely due to the unique challenge that plant organs and tissues are complex three-dimensional assemblies attached by cell walls. The use of flow cytometry to analyze protoplasts demands the development of novel cytometric methods. Nevertheless, the combination of protoplasts sorting techniques and fluorescent protein-based labeling of specific cell types has made the analysis of the spectrum of transcripts found within protoplasts possible.

In a landmark paper, Birnbaum et al. provided transcriptional profiles of *Arabidopsis* root cell types that were obtained by fluorescence-activated sorting of cells released by digestion of roots from transgenic lines containing root cell type-specific GFP markers. By harvesting cells from three root zones corresponding to different stages of maturation, they were able to resolve distinct developmental patterns within the transcriptional profiles of several root cell types—patterns they termed "digital *in situ*". This FACS approach has been applied to over a dozen root cell types for transcriptome analysis (Birnbaum et al., 2003; Nawy et al., 2005; Levesque et al., 2006; Lee et al., 2006; Brady et al., 2007). In addition to root cell types, FACS has recently been used successfully to isolate four different cell types in shoot apical meristems (Yadav et al., 2009).

Similar to LM, only limited amount of cells and subsequently RNA can be obtained by FACS. Multiple rounds of RNA amplification is commonly used in practice. Furthermore, although FACS provides a general means to isolate GFP-tagged cell types (Galbraith and Birnbaum, 2006), its application to transcriptome profiling of most cell types may still need technical improvement. Also, current protocols for harvesting, protoplasting, and sorting of cells may cause clear changes in the cellular transcriptome (Lee et al., 2005). Similar to LM, the application of FACS requires specialized instrumentation that is expensive to use, and available to a limited range of plant research laboratories.

Translating ribosome affinity purification (TRAP)

The steady-state level of an mRNA reflects its synthesis and decay and may not be well correlated with the level of the encoded protein. The subset of mRNA population associated with polyribosomal complexes, termed translatome, is a better proxy to protein synthesis of living cells. More importantly, by isolating polyribosomal complexes from cell types of interest, it is possible to obtain cell type-specific translating transcripts for genome-wide profiling.

By epitope tagging 60S ribosomal protein L18 (RPL18) in cell types of interest, it is possible to label polyribosomal complexes for immunopurification without affecting the biochemical functions of ribosomes and the physiology of *Arabidopsis* plants (Zanetti et al., 2005). This TRAP technology has the ability to be extended to profiling of mRNA populations at the cell-specific level by expressing the tagged RPL18 with cell type-specific promoters. By using this TRAP approach to label ribosomes in selected cell types, translating transcriptome has been profiled in root cell types and in early developing floral organs (Mustroph et al., 2009; Jiao and Meyerowitz, 2010).

In addition to the preferential selection of translatome as a better representation of protein synthesis, TRAP can usually achieve high RNA yield to eliminate information-loosing, bias-introducing, and high-cost RNA amplification, which makes it possible to directly combine TRAP with the RNA-seq technology (Jiao and Meyerowitz, 2010). Different from LM or FACS, TRAP does not require expensive and specialized equipment that is not generally available and can be more widely afforded.

Nuclei isolation

A conceptually similar alternative approach for cell type-specific transcriptome profiling is to isolate nucleus, rather than the whole protoplast or ribosomes, the translation centers of cells. Nuclear isolation and sorting are significantly easier and faster than cell protoplasting and sorting (Zhang et al., 2008). Two variants of nuclei sorting are available to date, one relies on fluorescence-activated sorting and the other is an affinity-based method.

The first approach is similar to FACS except that the GFP or other fluorescent protein marker must be nuclear-targeted (Zhang et al., 2008). Instead of protoplasting, nuclei are isolated for sorting. The significant reduction in size makes nuclei sorting much more efficient than protoplast sorting.

The second approach, termed INTACT for Isolation of Nuclei TAgged in specific Cell Types, is somewhat similar to TRAP that nuclei are biotin-labeled through a nuclear envelope protein for affinity isolation (Deal and Henikoff, 2010). Total nuclei are isolated from transgenic plants and biotin-labeled nuclei are then purified using streptavidin-coated magnetic beads. Comparably high yield and purity can be achieved by INTACT as in TRAP (Deal and Henikoff, 2010; Jiao and Meyerowitz, 2010). Also, INTACT does not require specialized equipment and should be widely applicable.

Both methods for nuclei isolation have one potential

drawback that RNA profiles of nuclei are clearly different from cytoplasmic mRNA profiles, and therefore not representative of mRNAs being translated into proteins. However, the isolated nuclei can be used to profile chromatin features in addition to gene expression. In fact, it has been tested that chromatin immunoprecipitation (ChIP) can be coupled with INTACT to understand chromatin features-selected cell types (Deal and Henikoff, 2010).

Results from cell type-specific transcriptome profiling

Although the number of transcriptome (and translatome) profiles at cellular resolution is still far from comprehensive and largely enriched with certain organs (such as roots), an early glimpse of the cellular transcriptional landscape appears to be information-rich for properties of both the genes from which the transcripts are derived, and of the cell types.

One goal of cellular-level transcriptional profiling is to discover the function of genes that contribute to cell specialization. Whereas the definition of a cell-specific gene is still under debate (Nelson et al., 2008), it is generally believed that from several hundred to over a thousand transcripts are unique to one or a few types of specialized cells. For example, about 200–400 *Arabidopsis* genes are considered uniquely expressed in only one of the five root cell types isolated by FACS (Birnbaum et al., 2003). In addition, a total of 54% genes expressed in roots are differentially expressed in root subzones (Birnbaum et al., 2003). A developmental profile of maturing pollen indicated that the transcriptome appears to change significantly during development, which is reflected by the poorly correlated earliest stage and latest stage pollen transcriptomes obtained from mechanically separated pollen (Honys and Twell, 2004). Similarly, temporal variation evident as distinct longitudinal expression patterns has been identified for root cells isolated by FACS (Brady et al., 2007). An analysis of 40 cell types obtained by LM within the RiceAtlas shows that individual rice cell types express between 8000 and 16000 genes. Cell type profile comparisons within the RiceAtlas reveal that a total of several thousand genes are expressed only in one or a few cell types, and several thousand are common to every cell type (Jiao et al., 2009). These housekeeping genes were enriched with hormone-responsive genes. It is worth mentioning that cell specificity may be more common than organ specificity, as smaller portions of genes unique to major organs in *Arabidopsis* and maize have been identified (Cho et al., 2002; Schmid et al., 2005; Ma et al., 2005). This finding further strengthens the needs for highly refined gene expression maps, which will greatly facilitate our understanding of plant cell differentiation, function and development.

The comparison of the expression of specific genes across all or selected cell types can provide quantitative global information not captured by any prior method. Analysis of gene expression in *Arabidopsis* root cells identified patterns of gene expression that traverse traditional anatomical boundaries (Birnbaum et al., 2003; Brady et al., 2007). Many functional categories, as defined by Gene Ontology (GO), are associated with characteristic expression patterns across cell types, including categories of cells that bear no obvious connection (Brady et al., 2007; Jiao et al., 2009; Jiao and Meyerowitz, 2010). Furthermore, putative localized hormone signaling centers were implicated in roots and shoots (Birnbaum et al., 2003; Jiao et al., 2009; Jiao and Meyerowitz, 2010).

The progress in high-resolution transcriptional profiling has greatly advanced the identification of physiological and developmental roles of novel cell-specific genes through detailed molecular genetics approaches. For example, following the transcriptional profiling of mechanically-separated guard cells, a T-DNA disruption mutant of a guard-cell-specific phosphatase 2C was found to be ABA hypersensitive in regulation of stomatal closing and seed germination (Leonhardt et al., 2004). Similarly, among the genes found enriched in the poles of embryos isolated by LM, one insertional mutation in a transcription factor was determined to confer a dominant phenotype for basal-pole-specific embryonic patterning (Casson et al., 2005). Isolation of a xylem-specific proteoglycan (xylogen) has led to the identification of the *AtXYP1* and *AtXYP2* genes, double knockout of which shows defects in vascular development (Motose et al., 2004).

High-resolution gene expression profiles also allow the identification of new components of gene regulatory networks. A pilot study of selected root-tissue-enriched transcription factors, which are from the root spatial expression profiles, suggests that the upstream non-coding sequence was sufficient to recapitulate the gene expression pattern for 80% of them (Lee et al., 2006). Posttranscriptional regulation, including intercellular protein movement and miRNA-mediated mRNA degradation, appears also to be frequent, as about a quarter of the tested transcription factors are affected (Lee et al., 2006). Related motifs are associated with specific transcripts in similar cell types. For example, the CCAAT-box, a common promoter *cis*-acting element with complex roles in regulating plant development (Edwards et al., 1998), was found associated with genes specific for several rice shoot cell types (Jiao et al., 2009). Distinct flanking sequences were found associated with the same common core motif in gene sets selected on the basis of specific expression in a cell type.

Concluding remarks

It is widely accepted that gene regulation is a major mechanism in the processes of differentiation and development. In addition, there is growing evidence that responses to

environmental stimuli, such as light or abiotic stress, occur differentially at the cell or tissue level (Jiao et al., 2007; Dinneny et al., 2008). Thus, to better understand gene regulatory circuits, gene expression need to be analyzed at the cell level. LM and FACS are two better established methodologies that have been used to provide cellular transcriptional profiles. A few early cellular level transcriptome studies provide global patterns in cell specificity, showing that much of the genome is regulated on a fine spatiotemporal scale. New generation methods, such as TRAP and INTACT, can expand our knowledge by providing more precise estimations of protein synthesis and understanding of chromatin profiles. The availability of these technologies should make cell-specific profiling possible and affordable to many laboratories to make our understandings of plant development and response to the environment more precise.

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