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REVIEW

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Genome sequencing and functional genomics approaches in tomato

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Abstract Tomato genome sequencing has been taking place through an international, 10-year initiative entitled the "International Solanaceae Genome Project" (SOL). The strategy proposed by the SOL consortium is to sequence the approximately 220 Mb of euchromatin that contains the majority of genes, rather than the entire tomato genome. Tomato and other Solanaceae plants have unique developmental aspects, such as the formation of fleshy fruit, not afforded by *Arabidopsis* or rice. Divergent phenotypes and habitats of the Solanaceae also make the family an ideal model to explore the bases of diversification and adaptation. Current progress in genome sequencing, genetic and genomic resources, and functional genomics approaches for tomato is summarized. Given the foreseen wealth of information in the upcoming genome sequence, the role of the laboratory-grown miniature tomato cultivar Micro-Tom as a valuable functional genomics tool for plant pathology and emerging areas of biology, such as "omics" biology, is emphasized.

Key words Micro-Tom · EST · Full-length cDNA · VIGS · Transcriptome · Metabolome

Introduction

Tomato (*Lycopersicon esculentum*) genome sequencing has begun through the action of an international initiative entitled the "International Solanaceae Genome Project" (SOL). The Solanaceae, especially tobacco and tomato, have played key roles in emerging research areas of plant molecular biology in the past two decades. Tobacco has been used widely as a host in *Agrobacterium*-mediated plant transformation, particularly before the development of in planta transformation of *Arabidopsis*. In wound response research, the first peptide hormone, systemin, which plays a key role in defense against herbivorous insects, was isolated from tomato (reviewed in Ryan and Pearce 2003), and the first mitogen-activated protein kinase, WIPK, was identified in tobacco (Seo et al. 1995). In plant–pathogen interactions, unique R genes such as *Pto* and *Cf* were identified in tomato (Pedley and Martin 2003). Virus-induced gene silencing (VIGS) technology was first shown in *Nicotiana benthamiana* (Kumagai et al. 1995). The isolation of a quanitative trait locus (QTL) gene was first reported for tomato (Frary et al. 2000). In cytology, the tobacco BY2 cell line (Takeda et al. 1992) has been widely used for a long time. The Solanaceae plants also provide unique aspects for research, such as fleshy fruit formation, not afforded by *Arabidopsis thaliana* or rice, the genomes of which have already been sequenced. As a model for the Solanaceae family, tomato will provide necessary diversity to reinforce findings based on our most informative model plant, *Arabidopsis*, because these two plants diverged from their common ancestor early in the radiation of dicots. The well-conserved genomic organization of Solanaceae species makes the family an ideal model for exploring the molecular basis of diversification and adaptation. In addition, research on tomato is the most advanced among commercially important vegetables in terms of fleshy fruit research (Giovannoni 2004). With the wealth of genetic and genomic resources for tomato, the forthcoming genome sequence will advance not only functional genomics for the Solanaceae plants, but also other emerging sciences such as systems biology.

A detailed description of the tomato genome sequencing project and background information on Solanaceae species is available in the white paper of the SOL consortium (http://www.sgn.cornell.edu/solanaceae-project). In this review, I summarize the current status of the genome sequencing endeavor, available genetic and genomic resources, and functional genomics approaches for tomato. I also emphasize the value of the laboratory-grown miniature tomato cultivar Micro-Tom as a functional genomics tool for plant pathology and emerging areas of biology such as "omics" biology.

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Tomato, a reference for the Solanaceae plants

Among the Solanaceae, which contains about 2800 species, tomato was selected as a family reference for genome sequencing. Tomato fulfils the basic requirements for genome sequencing, which include a moderately sized genome (950 Mb) applicable to recent sequencing technology and the availability of homozygous inbred lines and well-characterized genetic and genomic resources. Many DNA markers distributed almost evenly on all chromosomes are available so that fluorescence in situ hybidization (FISH) can be used to anchor Bacterial Artificial Chromosome (BAC) clones as starting points of genome sequencing. Its economic value as one of the most valuable vegetables is also an important reason for genome sequencing this species; genome sequencing is expected to benefit breeding and gene engineering programs of Solanaceae crops and fleshy fruit vegetables.

Most of the solanaceous plants are unique in having the same basic chromosome number (x = 12), indicating that no large-scale duplication events occurred early in the radiation of the family. Solanaceous plants can adapt to diverse niches and have numerous phenotypes. However, the genome structures among tomato, potato, pepper, and eggplant are relatively well conserved (Doganlar et al. 2002), which will allow us to study the evolution of orthologous genes for understanding diversification of these plants.

The genome sequencing of tomato will fill the gap between the rosid and asterid clades in terms of genome diversity. Current genome sequencing efforts are biased toward a limited number of clades among about 300 000 higher plant species. Genome sequencing of *Arabidopsis thaliana* (Brassicaceae) and rice (Poaceae) has been completed. Currently, the genomes of the legumes *Lotus japonicus* and *Medicago truncatula* (Favaceae) and those of poplar (Salicaceae) and maize (Poaceae) are being sequenced. These species were selected from only two rosid clades (Fig. 1) and from the monocots (Poaceae). The tomato (Solanaceae) genome is the first selected for sequencing from the asterids (Fig. 1), which diverged from the lineage leading to the rosids as many as 150 million years ago – early in the radiation of dicots. The asterid clade also contains many major crops, such as coffee, sunflower, and lettuce. Filling this gap will accelerate our understanding of the bases of genome evolution in higher plants.

Tomato genome sequencing

One of the major actions for the first stage of the 10-year SOL initiative is to obtain a high quality sequence of the tomato genome to use as a reference sequence for the Solanaceae. Before the start of the SOL consortium, considerable efforts were devoted to preparing genome sequencing resources such as BAC libraries, with over 15 000 DNA markers, and to mapping populations between tomato cultivars and wild relatives. First, researchers in The Netherlands started to sequence chromosome 6, and then funding agencies of other countries supported the sequencing of other chromosomes: Italy, chromosome 12; the United States, chromosomes 1, 5, 10, 11; France, chromosome 7; and Korea, chromosome 2. As a Japanese contribution, the

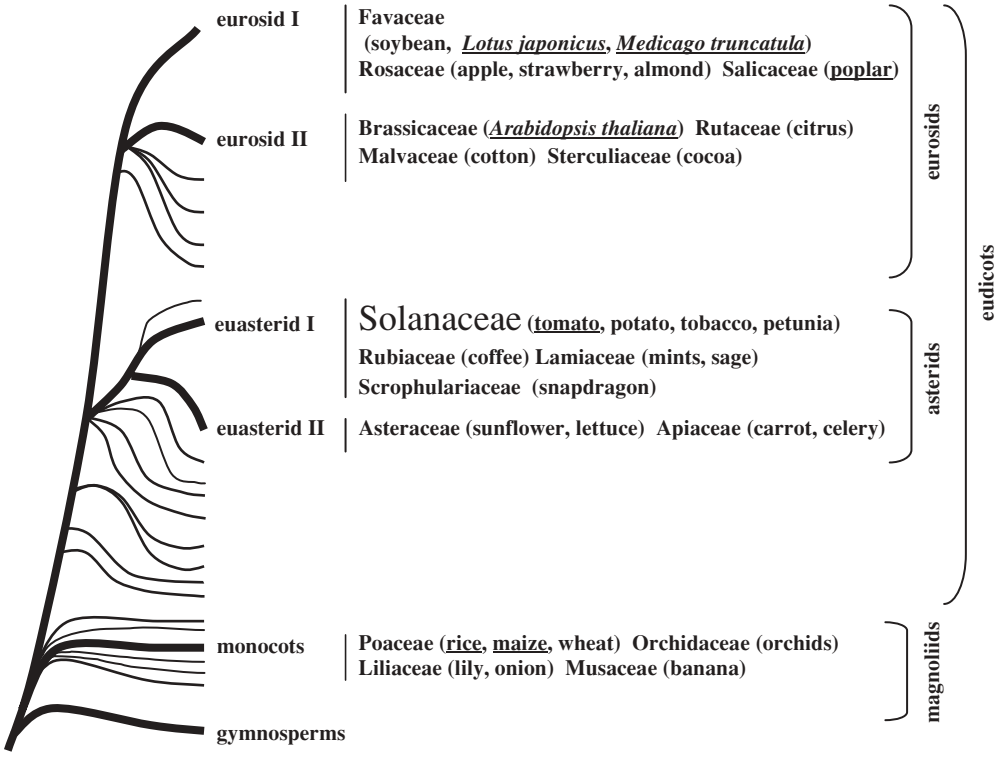

Fig. 1. Simplified phylogenic relationships of angiosperms. The nomenclature of clades and larger groups is from Soltis et al. (1999). Those plants that have their genome completely sequenced or are being sequenced are underlined

Kazusa DNA Research Institute (Chiba, Japan) is participating in the genome sequencing of chromosome 8, which was originally assigned to the U.S. effort.

The tomato genome, comprising 12 chromosomes, contains 950 Mb of DNA (Arumuganathan and Earle 1991) and is 6.5-fold larger than the *Arabidopsis thaliana* genome (146 Mb, Hosouchi et al. 2002). More than 75% of the DNA is heterochromatin, which is largely devoid of genes (Peterson et al. 1996). Contiguous stretches of gene-rich euchromatin (less than 25% of the DNA) largely compose the distal portions of each tomato chromosome. Therefore, the euchromatin regions are 1.9-fold larger than those of *Arabidopsis*, if it is assumed that the *Arabidopsis* euchromatin regions are 115 Mb in size (Arabidopsis Genome Initiative 2000). The strategy of the SOL consortium is to sequence the approximately 220 Mb of euchromatin that contains the majority of the genes, rather than to sequence the entire tomato genome. The modest size of the euchromatin justifies the genome sequencing of tomato among the Solanaceae family. Based on a computational analysis of a large set of tomato expressed-sequence tags (ESTs) and the sequences of several BACs, the tomato genome is estimated to have more than 30 000 genes (Van der Hoeven et al. 2002).

The details of this sequencing strategy are described in "Appendix 1. Technical Document for an International Consortium to Sequence the Tomato Genome" of the white paper "The International Solanaceae Genome Project (SOL): Systems Approach to Diversity and Adaptation" (available from the web site: http://www.sgn.cornell.edu/solanaceae-project). To obtain high quality sequences, sequencing will proceed on a BAC-by-BAC basis.

Tomato resources for functional genomics

In the last decade, we have seen an exciting burst in *Arabidopsis* research – perhaps the best example of our progress in molecular plant science. In addition to the completion of the *Arabidopsis* genome sequencing, the free availability of many resources for this species and the efforts to obtain these resources were key to this success and have stimulated further deposits of new *Arabidopsis* resources into the public domain. Extensive genetic and genomic resources of tomato and Solanaceae plants available to the public and the upcoming availability of the genome sequence of tomato should greatly facilitate our understanding of vegetables. The Solanaceae Genome Network (SGN) (http://www.sgn.cornell.edu) is one of the best web sites for resource information on Solanaceae plants.

A large collection of wild relatives and monogenic mutants affecting many aspects of plant development and responses, including disease resistance, are available for tomato, through such centers as the Tomato Genetics Resource Center (TGRC, http://tgrc.ucdavis.edu/index.cfm), which has one of the world's most comprehensive collection of genetic stocks and wild relatives for tomato. Recently, from the genetic background of the inbred variety M82, a comprehensive mutant population was generated and the mutant phenotypes in the population were classified for *in silico* searches (Menda et al. 2004). In 13 000 M_2 families, 3417 mutant phenotypes have been cataloged and are searchable at the Solanaceae Genome Network's web site, Genes That Make Tomatoes (http://zamir.sgn.cornell.edu/mutants).

Based on the strong background of tomato genetics, DNA marker technology has facilitated construction of interspecific introgression line populations that carry single introgressed chromosome segments from wild tomato species (Eshed and Zamir 1995). These lines are a valuable resource for identifying QTLs and subsequently isolating the genes that control each QTL. The isolation of the QTL for tomato fruit size (Frary et al. 2000) is the first example among all organisms.

ESTs are currently the most-sequenced nucleotide commodity from plant genomes in terms of the number of sequences and the total nucleotide count (Rudd 2003). A large tomato EST collection (>150 000 entries) has been deposited in the public domain (Van der Hoeven et al. 2002). In an effort to provide more genomic resources, we recently deposited >35 000 ESTs derived from leaves and fruit of the miniature tomato cultivar Micro-Tom in the public database DDBJ. The abundance of ESTs from different tomato cultivars allowed us to mine >2000 candidate single-nucleotide polymorphisms (SNPs) and insertions/deletions (indels) between Micro-Tom and other tomato inbred lines (Yamamoto et al. unpublished manuscript).

Analysis of a collection of 120 892 single-pass ESTs, derived from 26 different tomato cDNA libraries and reduced to a set of 27 274 unique consensus sequences (unigenes), revealed that 70% of the unigenes have identifiable homologs in the *Arabidopsis* genome (Van der Hoeven et al. 2002). The majority of the about 30% of the tomato genes that did not significantly match any *Arabidopsis* genes have unknown functions. Therefore, the wealth of knowledge from *Arabidopsis* might accelerate annotation of the majority of tomato genes, while EST or full-length cDNA sequences will be useful for confirming computed predictions for the remaining genes.

Full-length cDNA sequencing is complementary to genome sequencing. Computed prediction of transcribed regions, including protein-coding regions and intron/exon boundaries from eukaryotic genome sequences, is still a subject for bioinformatics. Without information on transcript sequences, especially for genes with no sequences homologous to those of other organisms, the reliability of the prediction decreases. In general, cDNA molecules synthesized by a standard method for EST sequencing are not expected to be full length. Recent technologies offer us protocols for full-length cDNA synthesis (Maruyama and Sugano 1994; Carninci et al. 1997), in which more than 90% of cDNAs are expected to be full-length, as shown by the large-scale full-length cDNA sequencing of *Arabidopsis* (Seki et al. 2002) and rice (Kikuchi et al. 2003). To provide tomato full-length cDNA clones, our laboratory is preparing full-length cDNA libraries from ripening fruits and

leaves that were infected with several pathogens. Full-length cDNA sequencing will facilitate proper prediction of gene structures of the tomato genome. The full-length cDNA clones also provide a useful resource for functional analysis of tomato genes.

Functional genomics approaches

Insertional mutagenesis is a powerful tool for identifying causative genes in tomato (reviewed in Emmanuel and Levy 2002). Native transposons have been used successfully to isolate causative genes in maize and petunia. Subsequently, maize transposons such as *Ac*/*Ds* and *En*/*Spm* were transferred to heterologous host plants including *Arabidopsis* (Smith et al. 1996) and tomato (Jones et al. 1994). In tomato, several genes were isolated by transposon tagging with *Ac*/*Ds*, including *Cf-9*, *Cf-4*, *Dwarf*, *Defective Chloroplasts and Leaves* (*DCL*), *Feebly*, and *Defective embryo and meristems* (*Dem*) (Emmanuel and Levy 2002). *Ac*/*Ds* has also been used to deliver the firefly luciferase reporter gene for promoter trapping and the β-glucuronidase (*GUS*) gene for enhancer trapping in tomato (Meissner et al. 2000). In this research, 200 000–300 000 Ds insertions, derived from several unlinked T-DNAs, were roughly estimated to be sufficient to achieve a high (approximately 90%) probability of insertion into any specific target gene. Recently, the chromosomal location of 405 individual inserts with a modified *Ds* transposable element was determined in tomato (Gidoni et al. 2003). These insertion lines could facilitate gene cloning, especially those which were closely linked to one of the *Ds* loci.

As another approach, transcriptional enhancers on a binary vector were delivered into the tomato genome to generate 10 427 independent transgenic lines (Mathews et al. 2003). Endogenous genes might be tagged with the enhancers in the vicinity of the T-DNA insertion site (called activation-tagging), resulting in ectopic expression of the genes as dominant mutations. In the T0 population, 1338 transgenic lines (13%) had one or more visually observable characteristics that differed from the wild type. These results demonstrate the utility of the activation-tagging approach to induce genetic mutants in tomato.

Despite the limited number of tagged transgenic lines, these resources are valuable for dissecting gene function by reverse genetics approaches. However, unless a high-throughput transformation protocol is developed for tomato, functionally analyzing all genes with tagging approaches is not realistic. Knocking out the expression of a gene by VIGS, however, does not require genetic transformation of the plant and is an attractive alternative. VIGS was first demonstrated in the Solanaceae species *Nicotiana benthamiana* (Kumagai et al. 1995), and subsequently in other plant species, including *Arabidopsis*, rice, and tomato. The broad range of applications for this technology has been reviewed in Burch-Smith et al. (2003). When the genome information obtained by EST sequencing was combined in a large-scale gene suppression experiment for tomato (Liu et al. 2002), cDNA clones with EST information were introduced into a virus vector using the Gateway system. Regardless of the power of VIGS, however, quarantine regulations may constrain the use of nondomestic viruses or virus vectors that may be used for VIGS. To avoid the problem, in some cases domestic viruses from the home country have been used to develop VIGS vectors (Hori and Watanabe 2003; Hori et al. 2004).

Transcriptome profiling monitors the relative abundance of transcripts for many genes simultaneously under various experimental conditions. In early studies, a limited number of tomato cDNA clones (300–600) were used for DNA array analyses, particularly for plant defense-related phenomena such as fusicoccin-induced gene expression (Frick and Schaller 2002), the virulence of *Pseudomonas syringae* pv *tomato* (Zhao et al. 2003) and systemic wound response (Strassner et al. 2002). The tomato microarray with approximately 12 000 unigene elements (TOM1 microarray), designed from information from a large collection of tomato ESTs (>150 000 entries) and recently available through the Center for Gene Expression Profiling (CGEP) at the Boyce Thompson Institute (http://bti.cornell.edu/CGEP/CGEP.html) has been widely used (Sagi et al. 2004; Uppalapati et al. 2003; Alba et al. 2004).

Metabolome analysis, one of the "omics" approaches, is a new way to dissect biological systems. Numerous analyses of tomato metabolites, especially of ripening and matured fruits, have been reported in the past. However, metabolomics approaches to comprehensively analyze metabolites have just begun for tomato (Fig. 2). Instead, metabolome analyses of potato have been on the frontier of plant metabolomics (Roessner et al. 2000, 2001). Metabolitic pathway databases, which are fundamental for metabolome research, are provided by KEGG (Kyoto Encyclopedia of Genes and Genomes, http://www.genome.ad.jp/kegg) for microbial organisms, animals, and plants (Kanehisa et al. 2002) and by AraCyc for *Arabidopsis* (http://www.arabidopsis.org/tools/aracyc) (Mueller et al. 2003). Although the latter database is also useful for plants other than *Arabidopsis*, some metabolic pathways such as alkaloid synthesis, which is not present in *Arabidopsis*, are not included. Recently, MAPMAN, a tool to display transcriptome and metabolome data sets on diagrams of metabolic pathways and other biological processes has been developed (Thimm et al. 2004). In a complementary approach, we have developed a new tool that displays both transcriptome and metabolome data sets on single maps (Tokimatsu et al. unpublished manuscript).

Micro-Tom, a laboratory-grown tomato

As exemplified by the fruit fly, *Drosophila melanogaster*, which attracted researchers into the then new biology of genetics, small organisms are the choice for model systems. The fruit fly continues to hold a secure position as a model in frontier sciences such as molecular genetics and, more recently, systems biology. Although *Arabidopsis* has been used as such a model in plant biology, the miniature tomato Micro-Tom also fulfils the criteria for a model system that

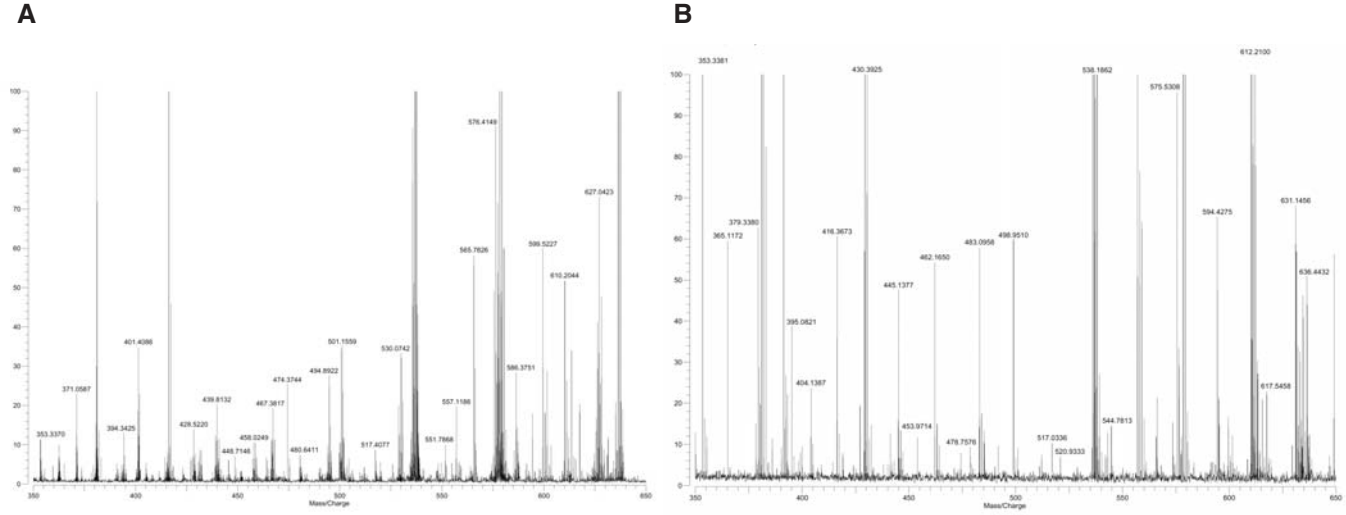

Fig. 2A,B. Fourier transform ion cyclotron mass spectrometry (FT-MS) analysis of metabolites of ripening tomato fruits from the green stage (**A**) and the red stage (**B**). Tomato fruit extracts were directly infused into the MS instrument using the soft ionization technique to obtain fingerprints of the molecular ions. The accurate masses of the molecular ions allow determination of the elemental composition of each metabolite, which may lead to the identification of the putative metabolite or of the class of metabolite (Aharoni et al. 2002). The data were kindly provided by Drs. Akira Oikawa and Daisaku Ohta (Osaka Prefectural University)

Fig. 3. Micro-Tom as a laboratory-grown tomato. Micro-Tom is much smaller than the commercial cultivar Momotaro (*left*) and is easy to grow well throughout its life cycle, even on a laboratory shelf with artificial light (*right*)

complements *Arabidopsis*. The miniature cultivar was developed originally for home gardening (Scott and Harbaugh 1989), but soon the potential of the cultivar as a tomato model for functional genomics was recognized (Meissner et al. 1997). Because most genetic resources for tomato have been prepared for breeding, researchers with no experience in growing tomatoes as experimental tools or with limited access to fields or greenhouses might hesitate to use the tomato plant as a model. However, Micro-Tom is easy to grow well, even on a laboratory shelf with artificial light, similar to *Arabidopsis* (Fig. 3). The cultivar can grow well at a density as high as 1357 plants/m^2 and has a rapid life cycle (70–90 days) (Meissner et al. 1997). The usefulness of the cultivar extends not only to such newcomers, but also to long-time tomato researchers. Micro-Tom has been used widely as a host for transposon and activation tagging (Meissner et al. 2000; Mathews et al. 2003), VIGS (Liu et al. 2002), and cDNA libraries for EST (Yamamoto et al. unpublished manuscript) and full-length cDNA sequencing (our unpublished data). Although pilot experiments to produce tagged mutant lines and an ethylmethane sulfonate (EMS)-mutagenized population of Micro-Tom were successful, a key issue of concern is how to supply such mutant lines or populations continuously to the research community.

Tomato has contributed to our understanding of plant–pathogen interactions, as shown by work on R genes such as

Pto and *Cf* (Pedley and Martin 2003), which is somewhat complementary to work done with *Arabidopsis*. To provide fundamental information about the susceptibility of Micro-Tom to pathogens, the cultivar was challenged with 16 well-known tomato pathogens (Takahashi et al. 2005). The fungi *Athelia rolfsii*, *Botryotinia fuckeliana*, *Oidium* sp., *Phytophthora infestans*, and *Sclerotinia sclerotiorum*; the bacteria *Ralstonia solanacearum* and *Agrobacterium tumefaciens*; and the viruses *Tomato mosaic virus*, *Tomato aspermy virus*, and *Cucumber mosaic virus* had compatible interactions on tomato, but the fungi *Alternaria alternata*, *Corynespora cassiicola*, and *Fusarium oxysporum* and the bacteria *Pseudomonas syringae* pv. *tomato*, *P. s.* pv. *tabaci*, and *P. s.* pv. *glycinea* were restricted by either hypersensitive resistance or nonhost resistance. Thus, Micro-Tom can serve as a tomato model to dissect the mechanisms involved in the compatible and incompatible interactions with these pathogens. Given the wealth of genetic and genomic resources for Micro-Tom and the upcoming tomato genome sequence, this laboratory-grown miniature tomato should provide further insights into plant–pathogen interactions.

The need for Micro-Tom plants is likely to increase, especially when accurate and reproducible results are required for "omics" approaches such as transcriptome or metabolome profiling under strictly controlled environments. Our laboratory is currently working on transcriptome and metabolome profiling using EST-based macroarray and gas chromatography/time-of-flight mass spectrometry (GC-TOF-MS), respectively, of Micro-Tom's fruit, from plants grown under controlled artificial environments. Combining these profiling data with the approaches of systems biology will advance our understanding of fleshy fruit formation.

Conclusions

The strong background of tomato genetics and international efforts of the SOL consortium with the support of Solanaceae researchers from many countries led to the start of tomato genome sequencing in 2004. With the expected wealth of genome sequence information, the rich genetic and genomic resources of tomato will not only facilitate research on the Solanaceae or vegetables but also will aid research in emerging plant sciences, such as systems biology, in which tomato will play a complementary role to other reference plants such as *Arabidopsis*, rice, and the legumes *Lotus japonicus* and *Medicago truncatula*, whose genome sequences are available or will become available within the next few years. The miniature tomato Micro-Tom, which grows well over its entire life cycle even under ordinary laboratory conditions, should attract researchers from various disciplines who have not yet used tomato as a research tool but want to branch into new research areas. Because Micro-Tom has been shown to be a suitable host for several pathogens, the cultivar is likely to help propel research in functional genomics in tomato. Continuously supplying genetic and genomic resources for Micro-Tom to the research community will become an important endeavor.

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