Chemistry & Biology 13, 919–921, September 2006 DOI 10.1016/j.chembiol.2006.09.004

Innovations

Spray-On Special Effects
Mendel Biotechnology Uses Chemical Genetics to Help Plants Cope with Stress

Agriculture has always been at the mercy of the elements and blessed by the gods. But instead of praying for rain, farmers in the near future may use chemical genetics to help crops better cope with heat, cold, and drought. Chemical genetics uses small molecules to modulate biochemical pathways to discover how gene products function. If, in plants, this method is implemented on transcription factors that regulate gene expression, it can complement selective breeding or genetic modification of crops, or, in some cases, replace them altogether. For instance, resistance to drought can be instilled by selectively breeding the most tolerant plant in your patch, by genetically modifying the plant, or by switching on the biochemical pathway that makes the plant transpire less water in a heat spell.

Research in chemical genetics in the late 90s was pioneered by Stuart Schreiber, Ph.D., professor and chair of the Department of Chemistry at Harvard and director of the Chemical Biology Program at the Broad Institute. Schreiber and others use small molecules to study biochemical pathways predominantly in yeast and mammalian cells. High throughput screening of chemical libraries against plant targets has only been done in the last five or six years. “It’s been exhilarating to watch and to learn from the pioneers of plant biology who had the vision to explore plant circuitry with small molecules,” said Schreiber. “Plants are ideal in many respects to dissect using this approach. In the process of revealing underlying principles, agents with considerable promise in agriculture are being revealed.”

At the heart of chemical genetics is the idea is that if you change a specific protein by attaching a small molecule, either covalently or non-covalently, you either activate the protein or disable it. The molecule acts like a switch. The end result is the alteration of a measurable phenotype. For instance, if you discover a molecule that binds to a particular protein, and, by doing so, find it enhances the organism’s sensitivity to heat, then by tracing the genes that encode the proteins involved in that biochemical chain, you may discover the genetic basis for heat tolerance. This can be a challenge, as molecules can bind to multiple protein targets, and determining the key protein or pathway is crucial.

Mendel intends to synthesize chemicals that regulate relevant transcription factors that can be delivered as a crop spray to mitigate environmental stressors and modify the growth cycle.

Chemical genetics borrows much from classical genetics, which relies on mutations. However, in classical genetics, if a mutation is lethal, it will kill your plant, but you may not know why. Chemical genetics allows a remarkable degree of control, including dose amount and treatment time that is unavailable in mutational screens. Moreover, it enables you to investigate genes that are redundant [1].

Under the Watchful Eye of Zeus

Mendel Biotechnology, Inc. (www.mendelbio.com), is located in a Hayward, California office park improbably adorned with white-washed statues of Greek gods and nymphs. They came with the place, commented Neal Gutterson, Ph.D., Mendel’s president and chief operating officer. Gutterson is no stranger to the fantastic. His prior company sought to develop a blue rose, a horticulturally glamorous feat, but not a particularly lucrative one. “You will never get enough money back from selling blue roses to justify the ungodly amount of money that went into producing them,” Gutterson said. Mendel Biotechnology, on the other hand, concentrates on major commercial crops and uses *Arabidopsis thaliana*, the prosaic workhorse of plant genetics, for its research. “We think a lot about what is really worth doing from a business standpoint.” Gutterson said. Mendel’s warehouse-like laboratories house several temperature-controlled chambers stacked with trays of *Arabidopsis* seedlings, as the plants like it cool.

The 55 person company, founded in 1997, is privately held. It has raised $12 million in equity, but has supported itself since its inception through funded collaborative research mostly for Monsanto, which owns a small equity stake in Mendel.

Agriculture changes at a stately pace. Mendel looks for trend-insensitive crops to balance their revenue cycles. “There is not a thing that we do that takes less than eight years to reach the market,” Gutterson says, “Improved yield in corn is going to be desirable for a long time to come.” Mendel recently started growing varieties of poplar, switchgrass, and miscanthus for cellulosic ethanol.

About three and a half years ago, Mendel inaugurated a program in chemical genetics. “We recognized that there were crops for which genetic solutions would be very difficult in the marketplace." Gutterson said. "People aren't going to be tearing out their cabernet vineyards to plant [genetically engineered] grapevines anytime soon." Mendel intends to synthesize chemicals that regulate relevant transcription factors that can be delivered as a crop spray to mitigate environmental stressors and modify the growth cycle. For example, if a heat spell is predicted in spring when avocado trees are blossoming, farmers can spray them with an agent to keep them from dropping their flowers. Growth hormones have been used in agriculture for decades, but while hormones affect plant biology broadly, Mendel's chemical regulation of genetic transcription factors represents a more targeted approach.

Follow the Biochemical Pathways

Arabidopsis has 27,000 genes, which are potentially regulated by 1,800 transcription factors. According to the company, all the genes responsible for a particular plant function or biochemical pathway can typically be controlled by a single transcription factor. This includes complex traits like the ability to withstand extreme conditions, disease resistance, and nitrogen dependency. According to Gutterson, the company is looking for small molecules that can upregulate a particular transcription pathway and thus be used as a "switch" to modulate its activity. "Really, in the last couple of years, we have worked on proof of principle, identifying pathways we know a lot about in *Arabidopsis* through our genomics program and then identifying chemistry that regulates these pathways," said Joshua Armstrong, Ph.D., researcher in chemical genetics at Mendel.

However, a small molecule may work differently on natural variants within a population than it does on laboratory strains, so translation from the lab to the field may not be straightforward. Potential complicating issues include compound metabolism, target binding, and specificity. Uptake of the compound needs to be considered, as well as toxicity and bioaccumulation issues. Another concern is that changing one variable can influence another; for example, imparting drought resistance to a plant can make it grow more slowly. Pathways may also overlap, such as the ones for freezing and dehydration, in such a way that it may be hard to implement a program for a particular trait.

Mendel expects to submit their chemicals to the Environmental Protection Agency for approval in what will probably be a process similar to those for other agricultural chemicals. According to Gutterson, manipulating plants through chemistry could be cheaper than modifying plants transgenically since the chemistry is potentially applicable to many different crops, each of which would have to be individually genetically modified. Mendel is also working on chemical regulation of disease pathways by activating plants' innate immunity pathways as well as reducing crop requirements for nitrogen. However, "the holy grail of getting plants like corn to make their own nitrogen is a long way off," said Gutterson.

Ceres Cultivates Drugs

Ceres, Inc. (www.ceres.net), in Thousand Oaks, California, lacks the mythological lawn statues, but is named for the Roman goddess of agriculture. Since 2002, Ceres has been developing corn and soybeans for traits including enhanced yield, stress resistance, and more efficient nitrogen utilization as part of a $137 million license-based agreement with Monsanto. The privately held company engineers energy crops as well. Ceres is also using plants to produce clinically relevant compounds like taxol, artemesinin, and derivatives of opiates.

"We are a functional genomics company, and we are engineering metabolic pathways in plants to produce plant-derived drugs more efficiently," said Dr. Steven Bobzin, director of natural products chemistry. To do this, Ceres identifies the genes that encode biosynthetic enzymes in plants that produce the desired compounds and manipulates them. Ceres is specific in its focus. "We are not proposing to put pharmaceuticals in corn flakes," Bobzin says, "we are producing small molecules in the biosynthetic pathway."

According to Bobzin, Ceres owes its progress to the advancement in genetic sequencing capacity. He cites the example of taxol, an expensive compound produced from yew. "We can increase the yield significantly…within the plant," said Bobzin. According to Bobzin, the company has already identified some of the genes involved in the biosynthesis of taxol and is on the way to identifying the rest. Once completed, those genes will be transferred to another plant that will serve as a biosynthetic platform for production of large amounts of material in a more cost-effective way. Other genetically engineered candidates in the pipeline include opiate derivatives that will not cross the blood-brain barrier. Ceres does this by manipulating environmental conditions, as certain stresses improve yield. The company also uses transgenic approaches to express a targeted molecule in all tissues of the plant.

But there is still much to discover. "There are going to be cases where these things don't work," said Glenn Hicks, Ph.D., associate research plant cell biologist, who works in collaboration with Dr. Natasha Raikhel at the Center for Plant Cell Biology (CEPCEB) at the University of California, Riverside. "Evolution being what it is, there are going to be fundamental similarities between all plant species, but when it comes down to it, there are going to be some differences." According to Hicks, while genes involved in the biosynthesis of specialized metabolites might not translate from *Arabidopsis* to maize, properties such as stress tolerance or photosynthesis are more fundamental and could equally apply to all plants.

Companies like Mendel and Ceres can develop compounds to proof of concept stage, but will partner with a major agricultural company like Monsanto for the resources needed for commercialization, Hicks said, because proof of concept is a small percentage of the total costs of development and commercialization. "The agricultural industry went through this chemical boom in the 70s and 80s where everyone was interested in growth regulators and adding hormones to plants and enhancing yield," said Hicks. "A lot of it turned out to be a bust." According to Hicks, now, particularly as biotechnology advances are being implemented in agriculture, "the reality of some of the advances in genomics and automated chemistry is settling in, and although these approaches will not resolve all of our challenges, they are going to result in some great advances."

Selected Reading

1. Raikhel, N., and Pirrung, M. (2005). Plant Physiol. *138*, 563–564.

Wendy Wolfson (wendywolfson@nasw.org) is a science technology writer based in Oakland, CA.