the whole animal is further emphasized by the the mouse mutant *Motheaten*. Mice carrying this mutation show marked abnormalities in hematopoiesis and dysfunction of the immune system (*14*). The mutation was recently traced to the *Hcph* gene, which encodes the hematopoietic cell protein (HCP) tyrosine phosphatase (*15*). Defective HCP function may abrogate colony stimulating factor (CSF)–1 signaling, because wild-type HCP is rapidly phosphorylated in macrophages after the binding of CSF1-1 to its receptor (*16*).

Until recently little was known of serine-threonine phosphatases in cytokine signaling, although tumor necrosis factor (TNF) and IL-1 activate multiple protein kinases by means of hsp27 kinase, MAP kinase, β-casein kinase, and other unidentified tyrosine kinases in primary human fibroblasts (*3*, *17*). Treatment of primary human cells with TNF and IL-1 initiates the rapid enhancement of phosphorylation of more than 100 phosphoproteins, including several transcription factors (*3*). Among the cytokines tested (TNF, IL-1, epidermal growth factor, and IFN-α, -β, and -γ), the pattern of changes in early protein phosphorylation is ligand-specific, with TNF and IL-1 (both have similar biological activities) producing almost identical changes in cellular protein phosphorylation. Treatment of cells with inhibitors of protein phosphatase–1 and –2A (okadaic acid, calyculin A, and cantharidin) but not inhibitors of protein phosphatase–2B also produces changes in early protein phosphorylation and gene transcription, which are remarkably similar to those observed with TNF and IL-1 treatment (*3*). This striking symmetry in the effects of cytokines and inhibitors of protein phosphatases (*3*, *4*) implies that the phosphorylation of cellular substrates by TNF- and IL-1–activated protein kinases is tightly regulated by these inhibitor-sensitive phosphatases. The inactivation of the phosphatases by the inhibitor alters the balance between the opposing phosphorylation and dephosphorylation reaction in favor of net phosphorylation. Similarly, TNF and IL-1 treatment could lead to the inactivation of inhibitor-sensitive protein phosphatases (see figure, Model 4). This inhibition of dephosphorylation would increase the phosphorylation of cellular protein substrates by the opposing protein kinase. Thus, the inactivation of a protein phosphatase could serve as a signaling mechanism (*3*). Indeed, the protein phosphatase that is rapidly inactivated in primary human fibroblasts after TNF treatment is a redox-sensitive class of protein phosphatase–2A or related phosphatases regulated by the cellular redox potential (*3*).

In these several examples, phosphatases do not behave in a way consistent with their previous yin-like status as simple counter-regulators for kinases and are taking a more active yang-like role in cytokine signaling. It will not be surprising if they turn out to be as ubiquitous and crucial as the protein kinases.

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Plant Biotechnology in China

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China is the largest agricultural country in the world. The nation's farmers, who account for about two-thirds of China's 1.2 billion inhabitants, face an enormous challenge: They must produce enough food for 20% of the world's population in a country with only 7% of the world's cultivable land. Plant biotechnology, which draws on the molecular biology methods developed during the 1960s and 1970s, is likely to play an important role in meeting this challenge.

From the beginning, scientists in China have made many important contributions to the development of plant biotechnology, particularly in the area of tissue, cell, and protoplast culture (see figure). This research has received strong support from the Chinese government. In 1986, the government launched a National High Technology Plan in which plant biotechnology was listed as a top priority. Currently, more than 100 laboratories are supported by grants from this plan as well as other government funds. Several foreign governments and international organizations such as the World Bank and the Rockefeller Foundation have also provided financial assistance to plant scientists in China. With this support, China has become a leader in plant biotechnology among Asian countries (*1*, *2*). In this perspective, we provide a brief overview of the agricultural problems to which this technology is being applied.

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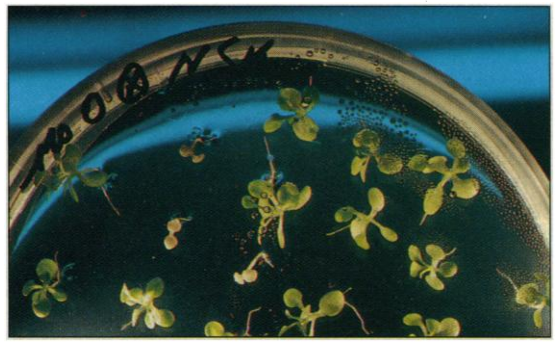
Developing pathogen-resistant plants

Plant viruses have caused significant reductions in crop yield in China, and consequently there is great interest in developing new antiviral strategies. After the observation by Beachy's laboratory in 1986 that tobacco plants transformed with the coat protein gene of tobacco mosaic virus (TMV) acquire resistance to the virus (*3*), scientists in China began testing coat protein genes from the Chinese strains of pathogenic viruses for similar antiviral activity. This is now the most active area of plant biotechnology research in the country (*1*).

The coat protein genes of TMV, cucumber mosaic virus (CMV), potato viruses X and Y, soybean mosaic virus, rice dwarf virus, and other viruses have been cloned and characterized (*4*). Some of these genes have been engineered into plants and are being tested for antiviral activity in the field. Tobacco transformed with the TMV coat protein gene has been planted in 500 hectares of land in 12 Chinese provinces (*5*), and transgenic tomatoes carrying the CMV coat protein are being similarly tested (*6*). Early results from researchers at the Institute of Microbiology, Chinese Academy of

Sciences, indicate that the transfer of TMV and CMV coat protein genes into two popular tobacco cultivars, NC89 and SD-8703, does indeed enhance resistance to viruses. In the future, other viral genes—such as those encoding virus replication or transport proteins—will also be tested for their ability to confer resistance. It is hoped that the insights gained from these initial experiments with tobacco can later be adapted to the important food crops of China.



Young tobacco plants grown in a petri dish from cultured protoplasts. Protoplasts, plant cells that have been stripped of their cell wall, can be manipulated in various ways to express foreign genes. Regeneration of whole plants from these isolated cells is a critical technique in plant biotechnology. Researchers in China have successfully regenerated plants from protoplasts of rice, wheat, millet, soybean, *Brassica*, *Medicago*, and other species. [P. Plailly/Photo Researchers]

Other efforts to develop virus-resistant plants involve transformation with resistance genes isolated from plants that are naturally resistant to these pathogens. Trichosanthin (TCS), a protein in the Chinese medicine herb *Trichosanthes kirilowii*, is a good example. TCS has ribosome inactivating activity and has been shown to inhibit the growth of several human viruses, including human immunodeficiency virus. Researchers at the National Laboratory of Protein Engineering and Plant Genetic Engineering, Peking University, have cloned the TCS gene and transferred it into *Escherichia coli*, yeast, and tobacco (*7*). Experiments to test the virus resistance of the transgenic plants are under way.

Bacteria and fungi are also economically important plant pathogens in China; rice bacterial blight, for example, is a disease that can reduce rice yield by 10%. Geneticists in China are combining a relatively new technology, restriction fragment length polymorphism (RFLP) mapping, with traditional plant breeding approaches to select for resistance traits. Other laboratories are searching for natural products that confer resistance. Many different plant species and >1000 bacterial strains that are natural antagonists of the pathogens have now been screened for such products and several candidate inhibitors have been identified (*8*). Ultimately the genes encoding these inhibitors will be used to produce transgenic plants that will then be tested for resistance.

Rice studies

Rice, China's staple for generations, continues to be studied and improved. Semidwarf and hybrid varieties that were developed by traditional plant breeding methods during the 1950s and 1970s now cover 16 million hectares of farmland. These cultivars have increased rice yield substantially (*9*). Currently, scientists are working to develop apomictic rice (rice that produces seeds asexually); this may reduce the number of breeding lines in rice hybridization and fix hybrid vigor. Several rice cultivars have been successfully bred from anther or pollen cultures. One of these cultivars, the Zhong-hua series, is widely planted in China and is well known for its high yield, better quality, and pathogen resistance.

In August 1992, the Chinese government announced the initiation of the "Rice Genome Project," a 15-year scientific endeavor whose ultimate goal is to define the complete sequence of the rice genome. Six research institutions in China are currently participating in the project, under the direction of G. Hong and Z. L. Chen. Given the size of the rice genome (4.6×10^8 base pairs of DNA), successful completion of this project will require many collaborations and exchanges with foreign countries.

Other research areas

Several laboratories in China have directed their attention to the problem of low nitrogen availability in the soil. In principle, increasing the levels of assimilable nitrogen would translate to increased crop yields. One strategy under investigation exploits the natural symbiosis between certain plants such as legumes and the nitrogen-fixing soil bacterium, *Rhizobium*. Scientists have developed recombinant strains of these bacteria that have a higher efficiency of nitrogen fixation. These strains have been spread over more than a million hectares of rice and soybean fields and preliminary results show that crop yield can increase from 5 to 10%.

Pollution of farmland by heavy metals is another serious problem in China. To address this, a research group at Peking University has engineered a human gene encoding metallothionein (a protein that binds heavy metals) into tobacco. The transgenic plants survive exposure to cadmium concentrations that are 25 times greater than the dose that kills control plants. More importantly, the transgenic plants absorb cadmium from the soil (*10*). The researchers are now engineering this gene into weeds, with the hope of using the transgenic weeds to reduce heavy metal contamination on farmland. In addition, by using root-specific gene promoters, they are attempting to direct metallothionein expression specifically to root tissue; this approach may reduce heavy metal contamination of seeds.

Finally, in conjunction with traditional plant breeding, molecular approaches are also being used to improve the nutritional quality, the starch and oil content, and the stress-resistance of various crops.

Future prospects

Because of the combined efforts of scientists, the government, and international organizations, China has already made important inroads in plant biotechnology. Nevertheless, we still have several challenges to meet. First, basic molecular biology research in China is rather weak in comparison to that in developed countries, a situation attributable in part to insufficient funds and manpower. Second, like many developing countries, China is facing a "brain drain": Many qualified scientists are emigrating to developed countries where there are better funding opportunities. Finally, until recently, China has lagged behind Western countries with respect to developing biosafety policies for controlling and managing the release of transgenic organisms. The government has now formulated such regulations, however, and is seeking to cooperate with foreign organizations, research institutions, and scientists on this issue.

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