of the cell. Signal transduction couples extracellular chemical signals, such as neurotransmitters and growth factors, to intracellular responses including protein synthesis and degradation, and transcription. These are all essential activity-dependent pathways that remain highly dynamic in adult stages. At an integrated level, these cellular pathways are apparent in biological functions relevant for ASDs, in particular synaptogenesis, axon guidance, dendritic and spine morphology, and synaptic plasticity. This has led to the hypothesis that abnormal synaptic homeostasis could play a key role in the pathogenesis of ASDs (*3, 4*).

The other milestone in the field is the notion that neurodevelopmental defects are not necessarily permanent, but may be reversible. There has been a long-standing view that neurodevelopmental disorders are congenital inborn errors of brain development that leave the patient with irreversible defects. This traditional view was first challenged by the reactivation of a silenced gene encoding methyl CpG-binding protein 2 (MeCP2) in a mouse model of Rett syndrome (*5*). Induction of *Mecp2* expression dramatically reversed behavioral and electrophysiological abnormalities in developing and adult mice. Selective reversal of abnormalities was also observed in other ASD models. For example, phenotypes in mice lacking the gene encoding the protein tuberous sclerosis 1 (TSC1) could be reversed by the small molecule rapamycin. Rapamycin blocks mammalian/mechanistic target of rapamycin complex 1 (mTORC1), which controls protein synthesis. The TSC1-TSC2 complex controls mTORC1 activity (*6*). In mouse models of fragile X syndrome [mice that lack the gene encoding fragile X mental retardation protein 1 (FMRP1)], treatment with an antagonist of the metabotropic glutamate receptor 1/5 class (mGluR1/5) also reversed disease characteristics (*6*). Signaling by mGluR1/5 is coupled to synaptic response involving FMRP1. Moreover, insulin-like growth factor I has been successfully used to ameliorate autistic-like phenotypes in mouse models of Rett syndrome and Phelan-McDermid syndrome. *SHANK3* is the prime gene culprit causing the latter disorder. Interestingly, selective rescue of autistic-like phenotypes in a mouse model was established by reexpression of *Shank3* (*7*).

SHANK3 is a synaptic scaffolding protein in the postsynapse that connects receptors and ion channels in the membrane with intracellular signaling proteins and downstream processes (see the figure). Yi *et al.* propose that through direct interaction, SHANK3 may enrich hyperpolarization-activated cyclic nucleotide–gated channels at postsynaptic sites. *SHANK3* (haplo)deficiency severely impaired hyperpolarization-activation (I_h) current conductance, explaining increased input resistance, a neuronal phenotype in Phelan-McDermid syndrome. Bidinosti *et al.* generated cells with a genetic defect reminiscent of *SHANK3* variants seen in Phelan-McDermid syndrome and sporadic ASD, and encountered a deregulated pathway that has been implicated in other forms of ASD. The AKT-mTORC1 signaling pathway is a hub for many cellular processes and is down-regulated as a consequence of *Shank3* deletion in mice. This is opposite of the effect of several other ASD gene mutations on the AKT-mTORC1 pathway. Apparently, an imbalance in this pathway in either direction can elicit autistic-like features. Bidinosti *et al.* discovered that the down-regulation involves a cascade of events tracing back to an increase in Cdc2-like kinase (CLK2); this is attributed to reduced CLK2 degradation by the ubiquitin-proteosome pathway. How mutated *Shank3* affects ubiquitination remains unclear. This may result from a loss-of-function of SHANK3 protein, or perhaps a gain-of-function of other SHANK3 isoforms as a consequence of genetic interference. An intriguing speculation is that it relates to I_h-channel impairment.

The findings of Bidinosti *et al.* suggest that small molecules that activate AKT or inhibit CLK2 may be used to adjust the activity of a critical signaling pathway in ASDs. Indeed, Bidinosti *et al.* reversed abnormalities at the molecular level (AKT phosphorylation) and cellular level (density of dendritic spines; miniature excitatory postsynaptic currents) with such compounds in *Shank3*-deficient neurons, and also reversed abnormal social behaviors in *Shank3*-deficient mice. These are important proofs of principle for drug targets to be taken further in the direction of drug development.

Previously, mGluR1/5 antagonists that successfully rescued phenotypes in genetic animal models of fragile X syndrome had disappointing results in patients with the disorder (*8*). Other candidate compounds are in queue to take this translational route, like compounds related to the mTORC1-inhibitor rapamycin. Bidinosti *et al.* add new targets to intervene with the pathogenesis of ASDs. The decade to come will show whether this finding can reach patients. ■

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MICROBIOLOGY

Feeding on plastic

A bacterium completely degrades poly(ethylene terephthalate)

By **Uwe T. Bornscheuer**

An estimated 311 million tons of plastics are produced annually worldwide; 90% of these are derived from petrol. A considerable portion of these plastics is used for packaging (such as drinking bottles), but only ~14% is collected for recycling (*1*). Most plastics degrade extremely slowly, thus constituting a major environmental hazard (*2*), especially in the oceans, where microplastics are a matter of major concern (*3*). One potential solution for this problem is the synthesis of degradable plastics from renewable resources (*4*). This approach provides hope for the future but does not help to get rid of the plastics already in the environment. On page 1196 of this issue, Yoshida *et al.* (*5*) address this problem by reporting an organism that can fully degrade a widely used plastic.

"...if the terephthalic acid could be isolated and reused, this could provide huge savings in the production of new polymer without the need for petrol-based starting materials."

Poly(ethylene terephthalate) (PET) is a widely used, colorless polymer with an annual worldwide production of more than 50 million tons. Although this polyester is made from two simple monomers joined via ester bonds (see the figure), its enzymatic or biological degradation has turned out to be very challenging. Until recently, no organisms were known to be able to decompose it. Yoshida *et al.* now describe a

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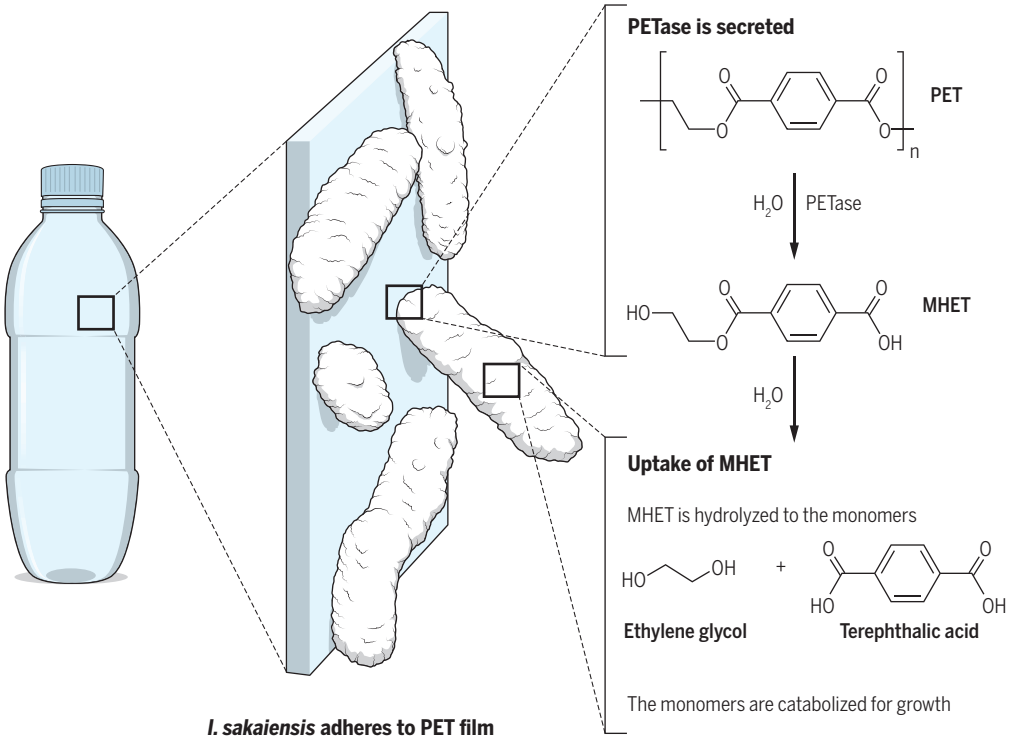

Delicious plastic. The *I. sakaiensis* bacterium discovered by Yoshida *et al.* (*5*) can attach to PET. It produces two hydrolytic enzymes (PETase and MHETase) that catalyze the degradation of the PET fibers to form the starting monomers. The monomers are then catabolized by the bacterium as its sole carbon source.

bacterium, *Ideonella sakaiensis*, that completely degrades and assimilates PET as its sole carbon source.

The authors identified this strain by screening 250 environmental samples at a PET bottle recycling site. Initially, they discovered an entire microbial consortium, but subsequent experiments confirmed that the *I. sakaiensis* strain—a Gram-negative, aerobic beta-proteobacteria—is the sole microorganism responsible for degrading PET.

Using genetic and biochemical analyses, the authors identified two key enzymes involved in PET hydrolysis. First, the bacterium adheres to the PET material and secretes a PETase, which generates the intermediate mono(2-hydroxyethyl) terephthalic acid (MHET). MHET is taken up by the cell and then hydrolyzed by the second enzyme, the intracellular MHET hydrolase, to furnish the two starting monomers (see the figure). The organism produces these monomers from PET to facilitate its growth.

The degradation process is relatively slow; complete degradation of a small PET film took 6 weeks. Nevertheless, the discovery may have important implications for PET recycling. It also raises questions about the principles of enzyme evolution.

So far, only a few hydrolytic enzymes have been known to cleave the ester bonds in PET when used as isolated enzymes: a hydrolase from *Thermobifida fusca* and cutinases (*6*). The PETase shows only 51% sequence homology to its closest known relative, the hydrolase enzyme from *T. fusca*, and its substrate spectrum is remarkably different from all of them. The MHETase belongs to the tannase enzyme family but is not active on typical aromatic esters converted by tannases. It thus seems that both enzymes—PETase and MHETase—are unique and play a distinct role in the *I. sakaiensis* strain. Yoshida *et al*. further show that the genes encoding the two hydrolases are upregulated in the presence of PET, implying that the dedicated role of the enzymes is the degradation of the polymer.

Human-made PET has been present in the natural environment for about 70 years. Did both hydrolytic enzymes evolve during that relatively short period to enable the bacterium to access a novel carbon source and hence provide an advantage for survival? Examples for such rapid natural evolution are scarce, but one prominent case is an atrazine chlorohydrolase. Atrazine is a herbicide widely used since the 1950s. The atrazine chlorohydrolase is now able to cleave the C-Cl bond evolved from a melamine deaminase, which is active on a C-N bond. The two enzymes differ by only nine amino acid mutations; atrazine chlorohydrolase has lost the deaminase activity (*7*).

In this context, one often-discussed aspect (*8*) is how novel (promiscuous) enzyme activities evolve and, hence, how natural adaption of enzymes takes place. Answering this evolutionary question will require three-dimensional structures of the PETase and the MHETase proteins, as well as sufficient data about phylogenetically related enzymes.

Another important question is how the *I. sakaiensis* cells can access the PET polymer fibers in the smooth plastic surface. Specific proteins such as carbohydrate-binding modules (CBM) are crucial for the degradation of cellulose: By lifting fibers from the cellulose surface, these proteins make the fibers accessible for glycosidases and other hydrolytic enzymes (*9*). It remains to be shown whether similar proteins are present in *I. sakaiensis* or whether CBM-like enzymes can be developed to assist PET degradation.

The assimilation of PET by *I. sakaiensis* bacteria may be advantageous for removing this plastic material from the environment. However, if the terephthalic acid could be isolated and reused, this could provide huge savings in the production of new polymer without the need for petrol-based starting materials. To establish such a process, it may be possible to integrate the PETase/MHETase pair into common production strains via metabolic engineering or the use of enzyme cascade systems (*10*). Further research in this area will hopefully provide concepts and solutions for the degradation and recycling of other degradation-resistant plastic materials that are currently used and disposed. ■

ILLUSTRATION: P. HUEY/*SCIENCE*

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