of zeolite structures smaller than the crystal unit cell) by control of nucleation and growth (9) and then form thin films by coating and assembling them on a support. However, the smallest zeolite crystals that can be achieved by systematic optimization of hydrothermal growth rarely go below the target size of 50 nm (10).

An alternative approach to zeolite nanocrystals is provided from a class of materials called hierarchical zeolites, which have mainly been investigated for their catalytic activity. They consist of nanometer-sized zeolite domains connected to each other and separated by mesopores. Hierarchical zeolites include materials derived from layered zeolites (11) and materials made by confined synthesis in ordered mesoporous templates (12) or by use of dual-templating strategies (13). It is conceivable that through appropriate disassembly methods, hierarchical zeolites or their precursors can be fragmented to highly crystalline zeolite particles with one or more dimensions in the 1- to 10-nm range. Thinner films enabled by the disassembled structures allow the use of more expensive materials. Ten dollars or more per milligram of zeolite could be justified for thin films in the 50-nm range and allow for the use of expensive structure-directing agents and other sacrificial templates, such as ordered mesoporous carbons and polymers.

Recently (12, 14), a very precise replication scheme starting from amorphous silica spheres to form crystalline zeolite particles as small as 10 nm was demonstrated. As depicted in the figure, nanometer-sized silica spheres are first used to template mesoporous carbon with precisely sized cages that are connected to neighboring cages via smaller openings. Next, zeolite crystals nucleate and grow in these interconnected cages, forming hierarchical zeolites. These hierarchical zeolites can then be fragmented into individual particles with a size similar to that of the carbon cages (and of the silica spheres used to template them). Selective membranes can be prepared by depositing these fragments as seed crystals on a support and creating a continuous film through a second round of zeolite growth (14).

Technical and fundamental challenges abound. In addition to isotropic particles, other shapes, like highly anisotropic lamellae, could conceivably be made and used in novel ways to form thin films (15). It may also be possible to tailor hierarchical zeolites and their precursors with disassembly in mind to obtain the desirable fragments in higher yield. Effective deposition methods should be developed, and mechanical and chemical stability of such thin films should be addressed. To harvest the high flux of the thin zeolite films, high flux supports and innovative module design will be required. Flux and selectivity in these films will likely be dominated by adsorption on the external surfaces and pore entrance rate processes rather than by transport in the zeolite pores. New experimental techniques (16) that could address these issues are emerging and will be powerful tools in understanding and tailoring nanometer-thin zeolite membrane performance.

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CELL BIOLOGY

Anatomy of Prostaglandin Signals

Nephi Stella

Membrane metabolism generates many lipid signals that regulate diverse cellular processes. Although most membrane-metabolizing enzymes are specific to one lipid family, some act on a range of substrates and produce lipid signals with different bioactivities. These multisubstrate enzymes act as nodes that can change the flow of information carried by the lipid signaling network by, for example, boosting the production of one family of lipids while dampening that of another. On page 809 of this issue, Nomura et al. (1) show that the enzyme monoacylglycerol lipase (MAGL) (2) is a critical node within the lipid signaling network, coordinating the brain’s defense mechanism to neurodegeneration. They also show that inhibiting MAGL prevents neurodegeneration and chronic neuroinflammation in a mouse model of Parkinson’s disease, opening a new potential avenue for treating neurodegenerative diseases.

The brain is separated from the rest of the body by the blood–brain barrier, which insulates the central nervous system against toxins as well as peripherally circulating immune cells. It has its own specialized immune system orchestrated by microglia, a type of macrophage that constantly patrols brain parenchyma (3, 4). Microglia become activated in response to pathogens and neuronal damage, rapidly changing into effector cells that initiate and control immune responses. Indeed, microglia are activated by HIV, malaria, tumors, ischemic insults, autoimmune events, and neurodegeneration. However, the phenotype of these activated cells varies depending on the pathology, from releasing toxins that harm adjacent cells, to decreasing the production of toxins and producing immune mediators that protect and repair adjacent cells (5).

The molecular mechanisms that determine the phenotype of activated microglia are controlled by lipid signals. For example, prostaglandins promote (6), whereas endocannabinoids dampen (7), microglia activation. Accordingly, modulating cannabinoid receptor and prostaglandin receptor activity can regulate the duration and outcome of the brain’s innate immune responses. Unfortunately, the development of therapies based on synthetic receptor ligands is hampered by the compensatory desensitization or sensitization that follows long-term receptor activation or inactivation, respectively (8). Indeed, the intense search for therapeutic compounds targeting cannabinoid
These actions, which dampen microglial
reduced prostaglandin signaling in the brain.
boosted endocannabinoid signaling and
a compound that inhibits MAGL (JZL184)
inian mouse model, oral administration of
11
erbate the degeneration of these neurons (

The consequential chronic microglia activa-
tions, such as cell migration and viability (9).
and prostaglandin receptors has yet to produce
viable medicines. By contrast, cyclooxygenase
1 (COX1) and COX2 inhibitors, which block
prostaglandin synthesis, are well-established
treatments that benefit many patients (although
a prominent toxicity is gastrointestinal bleed-
ing). By inhibiting the enzymes that produce
and inactivate lipid signals, one could control
the efficacy of their signaling only where and
when active endogenous signaling is already
taking place. This is especially important in
endocannabinoid signaling because the most
abundant endocannabinoid, 2-arachidonoyl-
glycerol (2-AG), activates multiple receptors,
including cannabinoid 1 (CB1) and CB2, as
well as unidentified G protein–coupled recep-
tors that control fundamental biological pro-
cesses, such as cell migration and viability (9).
The results of Nomura et al. point to a new
node of the lipid signaling network, MAGL, as
a potential therapeutic target.

Parkinson’s disease is associated with the
degeneration of dopamine-containing neu-
rons originating from the substantia nigra.
The consequential chronic microglia activa-
tion and release of harmful molecules exacer-
bate the degeneration of these neurons (10, 11).
Nomura et al. show that in a parkinson-
ian mouse model, oral administration of a
compound that inhibits MAGL (JZL184)
boosted endocannabinoid signaling and
reduced prostaglandin signaling in the brain.
These actions, which dampen microglial
cell activation, reduced the release of proinflam-
matory cytokines and prevented degen-
eration of dopamine-containing neurons.
Although it is currently thought that phos-
holipase A2 (PLA2) is the primary enzyme
for producing prostaglandins in brain, the
authors show that it contributes less to pro-
taglandin synthesis than the MAGL pathway
(see the figure). The finding therefore rede-
finishes the textbook view of prostaglandin
synthesis in this particular organ.

The study of Nomura et al. points to a po-
sible new avenue for developing therapeutics
that target the brain’s own defense mechanism
against neurodegeneration. However, it is not
clear why the MAGL inhibitor produced such
a predominant effect in the brain, because the
enzyme is also expressed by peripheral tis-
nues. In fact, the utility of compounds that
target MAGL may expand beyond treatment
of chronic inflammation and degeneration.
MAGL inhibitors reduce the production of
fatty acid signaling lipids that mediate the
migration, invasion, and survival of tumor
cells, and reduce tumor growth in mouse
models of cancer (12). However, it is impor-
tant to emphasize that chronic and complete
MAGL blockade by such compounds causes
tolerance, impaired endocannabinoid-depen-
dent synaptic plasticity, and desensitized
brain CB1 receptors in mice (13). It will
therefore be necessary to identify the sig-
naling events affected by MAGL inhibitors

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