cells, and deletion of *LAG1* increases the life span of haploid yeast cells, suggesting a role for this synthase in cellular aging (*5*). Expression of wild-type *hyl-2* in yeast cells lacking both *LAG1* and *LAC1* genes restored yeast viability, indicating that *hyl-2* encodes an authentic ceramide synthase.

Ceramide synthases acylate sphingoid bases with different lengths of fatty acid chains, ranging from 14 to 26 carbon atoms, to produce a family of ceramides (*6*). Ceramides serve as intermediates for sphingolipids, a major component of cell membranes. Beyond their structural role, ceramides have been implicated as signaling molecules in diverse biological processes in mammalian cells including inflammation, cellular differentiation, and cellular stress responses (*7*–*10*). In response to various stresses such as hypoxia and restricted blood supply (ischemia), total cellular ceramide concentration increases, which in turn can activate molecules that induce cell death (apoptosis) (*7*, *11*).

But *C. elegans* has two other ceramide synthase gene homologs, *hyl-1* and *lagr-1*. Both *hyl-1* and *lagr-1* are required for radiation-induced apoptosis, and germline injection of the 16-carbon ceramide can restore germline apoptosis in a *hyl-1* or *lagr-1* deletion mutant (*12*). Thus, ceramide (at least the 16-carbon ceramide) appears to promote radiation-induced germline apoptosis in *C. elegans*. Unlike worms lacking *hyl-2*, *hyl-1* deletion mutants were more resistant to anoxia than wild-type cells, as might be expected for loss of a proapoptotic gene. Like HYL-2, HYL-1 expression in yeast can rescue the lethal phenotype of a *lag1 lac1* double-deletion mutant (*13*). Thus, *hyl-1* also encodes an authentic ceramide synthase.

The contrasting anoxic sensitivity phenotypes of the *hyl-1* and *hyl-2* mutants indicates that the two ceramide synthases have distinct functions. By measuring the abundance of ceramide and sphingomyelin species in *hyl-1*(null), *hyl-2*(null), and wild-type worms by mass spectrometry, Menuz *et al*. determined that *hyl-1* mutant worms contained more 20- to 22-carbon ceramides and sphingomyelin species than wild-type worms, whereas *hyl-2* mutant worms had decreased amounts of these ceramide and sphingomyelin species compared to wild-type worms. Measurement of ceramide synthase activity in isolated microsomes of mutant and wild-type animals confirmed that HYL-1 and HYL-2 have distinct fatty acyl specificities, with *hyl-1* mutant microsomes synthesizing more 20- to 22-carbon ceramides and *hyl-2* mutant microsomes more 24- to 26-carbon ceramides. Together, these data suggest that 20- to 22-carbon ceramide and/or sphingomyelin molecules produced by HYL-2 are protective against anoxic injury. Alternatively, these ceramides and sphingomyelins may not be inherently protective against anoxic injury; rather, their synthesis by HYL-2 in a particular cellular or subcellular context or distribution may be protective.

Given the link between ceramides and apoptosis, Menuz *et al*. examined the relation between the well-defined apoptosis pathway in *C. elegans* and *hyl-2*. A double-mutant strain carrying a loss-of-function mutation of the apoptosis caspase gene *ced-3* and a *hyl-2* deletion mutation had anoxic sensitivity similar to that of the *hyl-2* deletion mutant strain, indicating that *hyl-2* does not require the canonical apoptosis pathway to control anoxic sensitivity. Menuz *et al*. also examined the relation between *hyl-2* and *daf-2*. *daf-2* encodes an insulin/insulin-like growth factor receptor homolog that negatively regulates worm life span, stress resistance, and hypoxia resistance (*14*, *15*). The authors found that a *daf-2* reduction-of-function mutant was anoxia resistant. The anoxia resistance of the *daf-2;hyl-2* double mutant was intermediate between that of the two single mutants, which suggests that the two pathways function in parallel to control anoxic sensitivity.

Most of what we know about the function of ceramides in hypoxic and ischemic injury is that they promote cell death in mammals. The findings by Menuz *et al*. indicate a broader role of ceramides beyond their established proapoptotic one in hypoxic cellular injury. Thus, inhibition of ceramide synthesis is unlikely to be a panacea for hypoxic injury. Rather, development of subtype-specific ceramide synthase inhibitors will likely be necessary. Are ceramide synthases a friend or foe in hypoxic injury? The answer is yes.

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ENGINEERING

Can Technology Get Your Eyes Back on the Road?

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Technology can provide alerts as well as long-term feedback to help drivers pay attention to the road.

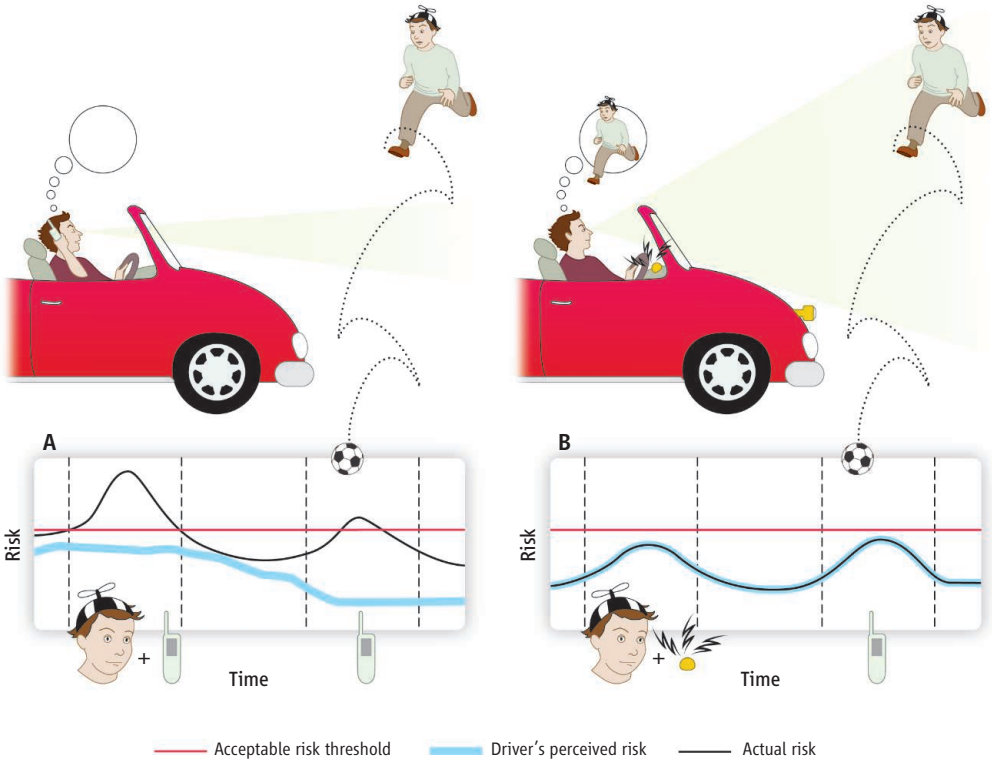
Paying attention to the right thing at the right time is important for many activities in daily life. For one—driving—it is critical. In the United States, more than 40,000 people die in motor vehicle crashes every year. More people die each month in crashes than the total killed in the terrorist attacks of 9/11 (*1*). Although alcohol impairment and speeding account for most of these fatalities, failures of attention also play an important role. The increasingly ubiquitous technology in our vehicles can either impair or improve how we distribute our attention, thus diminishing or enhancing safety. Driving provides a stark illustration of the importance of technology-mediated attention.

The degree to which technological distractions contribute to crashes is difficult to identify, because a glance away from the road leaves no physical evidence. To document driver behavior, small groups of volunteers have been filmed while they drive. In one such study, data collected with unobtrusive video cameras and instrumentation in 109 cars over 12 to 13 months found that failures of attention—including both drowsiness and distraction (performing nondriving tasks such as talking on a phone or adjusting

the radio)—contributed to 78% of the 69 crashes and 65% of the 761 near-crashes (*2*). Distraction associated with nondriving tasks contributed to 22% of crashes and near-crashes.

Increased complexity of the distracting task increased the likelihood of crashes and near-crashes; relative to undistracted driving, such incidents were about three times as likely for highly complex tasks (such as dialing a phone) and twice as likely for moderately complex tasks (such as inserting a CD). The frequency with which drivers engaged in distracting activities was strongly associated (correlation of 0.72) with drivers' involvement in attention-related crashes and near-crashes (*3*). Attention-related failures are thus not random occurrences. They are a consequence of enduring behavior patterns, in which frequent episodes of inattention make crashes more likely.

Driving, particularly while engaged in distracting activities, challenges the attentional capacity of people—it requires a constant shifting in the center of the driver's attention between competing demands and rapid reactions to "unexpected" events. Even when a driver's eyes are directed to the road, the cognitive demands of a nondriving task, such as a cell phone conversation, can disrupt scanning the environment around the vehicle (*4*) and can lead drivers to neglect important hazards (*5*). The more mentally demanding the task is, the greater the disruption (*6*). When the driver's eye movements are concentrated on the center of the road, critical hazards, such as the pedestrian on the right, can go unnoticed (see the figure, panel A).



Attention and risk. (**A**) Technology such as cell phones can introduce distractions, as illustrated by a driver paying attention to a phone call and not the child pedestrian. The neglect of hazards and gaze concentration increases risk (shown in the graph as a solid black line) above an acceptable threshold (shown in red). Drivers usually underestimate risks (shown as the blue line). (**B**) Technology may mitigate distraction by helping drivers to distribute their attention and guiding them to engage distractions only when roadway demands are low. The driver, alerted to the hazard, now attends to driving. The cell phone interaction is now separated in time from the pedestrian encounter, and with repeated encounters, perceived risk is closer to the actual risk.

The failure to adequately attend to the roadway also contributes to a more insidious problem: Drivers who have been distracted might not be aware that they have had a near-miss of a crash—they cannot remember what they have not noticed. Drivers do not receive adequate feedback concerning how much distracting activities undermine their driving safety (even when they crash). Poor feedback contributes to a poor correspondence between actual and perceived performance decrements associated with distractions (*7*), which may lead drivers to adopt dangerous patterns of behavior.

Most drivers tend to overestimate their abilities (*8*). In a survey, 88% judged themselves to be safer than the average driver. Another survey found that this superiority bias persisted even with expert police drivers when they rated their ability relative to that of their peers (*9*). Drivers often fail to adjust their behavior even after surviving a crash involving a fatality (*10*). A similar bias afflicts those who engage in distracting activities; drivers who use a cell phone tend to perceive the probability of a distraction-related crash to be lower for themselves than for their peers (see the figure, bottom part of panel A) (*11*).

Technology need not only lead to distractions, however; it can also mediate driver attention to enhance driving safety. Drivers can be given an alert that directs their attention away from distractions and back to the roadway if they look away from the road for too long (*12*). Emerging technology can also record a history of distraction (such as drivers' eye movements and gadget usage) and the associated decline in driving performance. This information can then be shared with drivers to enhance their appreciation for the risks associated with driving while distracted.

Recent studies suggest that such postdrive feedback holds substantial promise for improving driver performance (*13*, *14*). Feedback given to people after they drove while engaging in distracting activities led these drivers to respond faster to vehicles braking ahead and to keep their eyes on the road (*15*). Another study tracked teenaged drivers who drove with a camera that captured abrupt braking and steering responses (*13*). The videos and a summary of these events were shared with the teens and their parents weekly. Results showed an 89% decline in the number of events triggered by risky drivers. Even after the feedback was removed, the rate of events remained low until the end of the study 6 weeks later. Enhanced feedback can thus lead to lasting changes in how drivers attend to the road. This positive influence of technology on driver attention might outweigh the negative effects of distracting technology (see the figure, panel B).

Whether such technology-mediated attention enhances or diminishes safety remains a critical question. Answering this question will require precisely controlled driving simulator studies to further understand the dynamics of technology-mediated attention, as well as naturalistic studies that collect information on how technology affects people's behavior on the road.

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CELL BIOLOGY

Two Lipids That Give Direction

Precise and sequential intracellular signaling events involving two phospholipids direct an immune cell toward an attractant molecule gradient.

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Neutrophils are highly motile cells of the human immune system that specialize in clearing pathogens from infected tissue. Achievement of this task is no small feat: A neutrophil must relentlessly track its moving target (such as a bacterium) in a full-speed race, abruptly changing direction as needed before closing in on its prey. All this requires that neutrophils sense very small amounts of chemicals, known as chemoattractants, which are released by the escaping pathogens. Receptors on the surface of neutrophils recognize these attractants and initiate cascades of intracellular signaling events that ultimately polarize cell movement in the direction of the pathogen. On page 384, Nishikimi *et al.* (*1*) report that two phospholipids initiate this cellular polarization.

The morphological changes that allow a neutrophil to alter its direction of movement requires polarized remodeling of the actin cytoskeleton. At the center of these changes is Rac, a member of the Rho family of small guanine nucleotide (GTP)–binding proteins (GTPases), whose activation induces rapid actin polymerization. This event supports physical extension of the cell's plasma membrane (as a pseudopod) toward the pathogen (*2*). Previous studies have highlighted an important role for the atypical guanine exchange factor (GEF) DOCK2 in neutrophil polarization and migration (*3*). DOCK2 belongs to a family of Rho GTPase regulators that lack a canonical GEF signaling motif (Dbl-PH). Instead, these DOCK-related proteins use a DOCK homology region–2 (DHR-2) domain to mediate activation of target Rho GTPases (*4*–*6*). In addition, all DOCK proteins harbor a DHR-1 domain that binds to the phospholipid phosphatidylinositol 3,4,5-trisphosphate (PIP_3) (*7*). PIP_3 is generated at membranes by the phosphorylation of phosphatidylinositol 4,5-bisphosphate, a phospholipid component of membranes (*8*). Both the DHR-1 and -2 domains are required for properly localizing the activation of Rho GTPases by DOCK proteins (*9*). Kunisaki *et al.* showed that neutrophils lacking DOCK2 demonstrate impaired Rac activation, and consequently, fail both to polarize and display chemotaxis in response to chemoattractant (*3*).

How do neutrophils initiate polarization? PIP_3 is rapidly produced by phosphoinositide 3-kinases (PI 3-kinases) in response to activated chemoattractant receptors, and accu-

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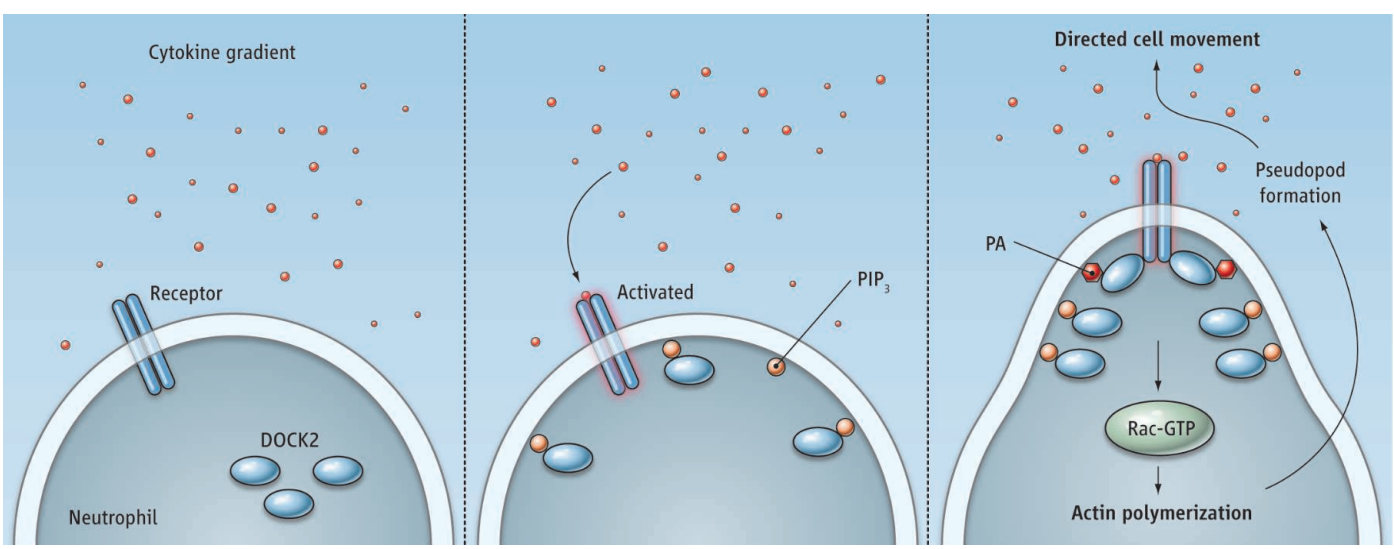

Preparing to move. As a nonpolarized neutrophil senses a gradient of chemoattractant (such as a cytokine), signaling events lead to the localization of DOCK2 at the cell's leading edge in two stages, each dependent upon a different phospholipid—PIP_3 and phosphatidic acid (PA). This refinement of DOCK2 localization ensures rapid neutrophil movement toward the chemoattractant gradient.

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