activator protein-1, leading to the expression of multiple inflammatory proteins that amplify the inflammatory response. In response to several stimuli, ceramide also induces apoptosis, apparently by activating caspases and inducing clustering of death receptors in the cell membrane[5].

As if that were not enough, ceramide also has a powerful metabolite, sphingosine 1-phosphate (S1P)[5]. Within cells, S1P can mediate the actions of various intracellular kinases and phosphatases. Extracellular S1P can interact with endothelial differentiation gene G-protein-coupled receptors, which are highly expressed on endothelial cells and activate multiple signal transduction pathways. S1P can also stimulate the release of PAF from endothelial cells[6].

Several studies implicate sphingomyelin hydrolysis in acute lung injury, as a mediator of stimulatory factors such as TNF-α, Fas/Apo ligand, acid and ionizing radiation. Lung cells express high levels of sphingolipid enzymes and derivatives, and intratracheal administration of TNF-α in rats stimulates ASM activity in bronchoalveolar lavage fluid and boosts ceramide concentrations. Tracheal administration of both TNF-α and ceramide induces rapid lung microvascular leakage and decreases surfactant production, which might contribute to the development of lung injury[7]. Most importantly, ceramide is a potent inducer of apoptosis in pulmonary cells[8], which could contribute substantially to irreversible lung injury. Indeed, apoptosis of alveolar cells is now recognized as a feature of ARDS and might account for its poor response to drug therapy[9].

Göggel *et al.* show that PAF, like TNF-α, increases ceramide concentrations in alveolar fluid by activating an extracellular ASM[2]. The authors found that PAF-induced pulmonary edema was reduced in ASM-deficient mice. A ceramide-specific blocking antibody, as well as the nonspecific ASM inhibitors D609 and imipramine, also reduced PAF-induced edema. D609 also inhibited the pulmonary leakage induced by lipopolysaccharide and acid, suggesting that many inducers of acute lung injury use the ASM-ceramide pathway.

Fumonisin B1, an inhibitor of ceramide synthase, had no effect on pulmonary edema, suggesting that *de novo* synthesis is an unlikely source of ceramide. Instead, endothelial cells are probably the major source of extracellular ASM and ceramide. Extracellular ceramide may act directly on endothelial and alveolar epithelial cells to induce apoptosis and the separation of cells, thus prying open the capillaries. Intracellular ceramide, on the other hand, may lead to formation of S1P (**Fig. 1**).

How well might the new data apply to humans? Several studies indicate that ceramide may have a role in the human disease. Ceramide derivatives are markedly elevated in bronchoalveolar lavage fluid of patients with ARDS[10], and plasma ceramide is increased in sepsis patients and correlates with mortality[11]. However, the role of ceramide in acute lung injury will only be established when specific inhibitors of sphingomyelin pathways are available for clinical use.

A number of therapies tested for ARDS may interfere with the ceramide pathway, but not very effectively. Glucocorticoids have a broad spectrum of anti-inflammatory actions but provide little or no clinical benefit in ARDS[1]. Glucocorticoids inhibit ASM by ~30%, indicating that they may, at least partially, reduce the generation of ceramide[12]. Göggel *et al.* also show that dexamethasone reduced both generation of ceramide and PAF-induced lung leakage. More specific inhibitors of the ASM-ceramide pathway may provide a more effective approach in the future, particularly if they prevent the apoptosis of alveolar cells. Specific inhibitors of ASM are now in development, and may have potential as a new treatment for acute lung injury.

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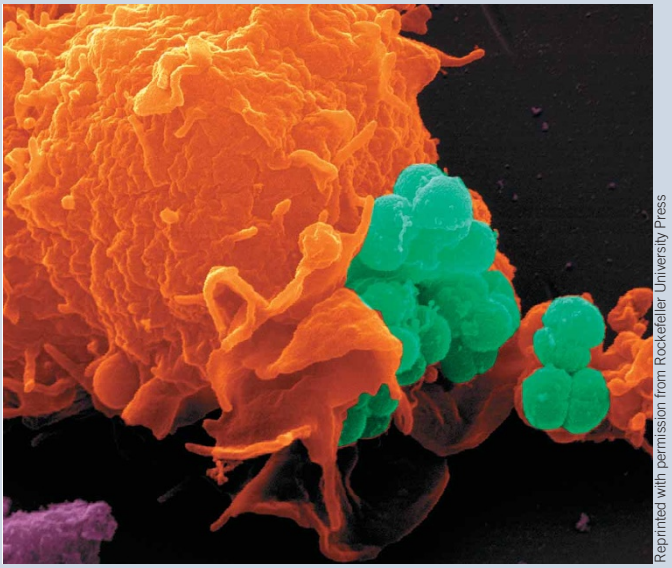
Gonorrhoeae glue

Neisseria gonorrhoeae, Haemophilus influenzae and a handful of other Gram-negative pathogens cling to and invade human cells by co-opting a family of human host cell adhesion molecules called CEACAMs (carcinoembryonic antigen–related cell adhesion molecules). Humans have evolved a counterstrategy: phagocytic cells express CEACAMs , which enable them to efficiently mop up the bacteria (human granulocyte shown here, shoveling in *N. gonorrhoeae*).

In the 5 January *Journal of Experimental Medicine*, Tim Schmitter *et al*. identify CEACAM3 as the main mediator during granulocyte uptake, and show that CEACAM3 operates via the small GTPase Rac. The authors found that blocking CEACAM3 or interfering with Rac stimulation reduced phagocyte clearance of *N. gonorrhoeae* and other CEACAM-binding bacteria. These bacteria do not infect nonhuman primates or rodents, but they regularly colonize mucosal surfaces in people. When the normally benign balance between bacterial invasion and bacterial clearance tilts, the microbes become dangerous.

Charlotte Schubert



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