only specific synapses receive signals, and in the blood vessels to prevent secretion into the bloodstream. If PAF were secreted into the bloodstream, generalized activation of leukocytes would result, causing 'downstream' organ damage (for instance in the lung). Plasma PAF acetylhydrolase is presumably a guardian that prevents the escape of PAF from its useful sphere of activity. Complementary DNA sequences provide strong evidence that this enzyme occupies a different location to that of the intracellular form, because the plasma form has a signal sequence[1].

During ischaemia and convulsions, phospholipase $A_2$ is activated and PAF[8] accumulates in the brain along with free arachidonic acid[9]. In ischaemia-reperfusion brain damage, PAF antagonists are neuroprotective[10]. Moreover, membrane phospholipids can undergo oxidative damage to yield compounds that have structures with shorter peroxidized residues at their second carbon (see figure) and that mimic the action of PAF. In endothelial cells[7] and brain[11], PAF acetylhydrolase catalyses the hydrolysis of these oxidized phospholipids and may be an important mechanism to prevent amplification of inflammation.

Recombinant PAF acetylhydrolase could be a therapeutic alternative to PAF antagonists, at least in some instances, because the enzyme may be able to break down PAF or PAF-like lipids at sites of inflammation, even when their concentrations are very high. Although the concept is exciting, as are the supporting data provided by Tjoelker *et al.*[1], it remains to be seen whether the approach is clinically viable, particularly when treatment is not begun until the inflammatory response is underway. Treatment with PAF acetylhydrolase may also represent a form of replacement therapy, especially in cases of acquired deficiency. Other uses might be found for recombinant intracellular PAF acetylhydrolase, if it can be produced similarly and delivered effectively into the appropriate cells.

There are other pathological situations in which PAF acetylhydrolase may provide protection. PAF is an activator of immediate–early transcription factors[12], and of the inducible gene for prostaglandin synthase[13]. The PAF signal mediated via this inducible gene leads to increased prostaglandin synthesis, and in turn, the prostaglandins exacerbate inflammation. PAF also activates the expression of certain metalloproteinases that may degrade the extracellular matrix[14]. This genomic arm of signal transduction in inflammation may generate corneal ulcers in severe ocular inflammation and destroy cartilage in arthritis[14]. Moreover PAF is synergistic with the adhesion protein, P-selectin, in the induction of cytokine gene expression[15] and heparin-binding EGF-like growth factor[16] in human monocytes. So PAF, or related lipids, may be involved in the inflammatory and cell-proliferation aspects of atherosclerosis. In addition, PAF acetylhydrolase blocks the generation of modified low-density lipoprotein resulting from oxidative stress[17]: oxidized phospholipids have been implicated in this process, so protection presumably results from the hydrolysis of such lipids before they can modify proteins or signal inflammatory cells.

In experimental models, PAF reproduces many of the manifestations of asthma. An increased prevalence of severe asthma has been reported in children in a Japanese population that is deficient in PAF acetylhydrolase[18], and elucidation of the molecular basis of this recessive trait will help to define the enzyme's physiological and pathological functions.

The rapid turning off of a pathological signal of the inflammatory response by recombinant PAF acetylhydrolase may limit or prevent cell damage and derangement of the intercellular matrix. Given the widespread effects of PAF, there is broad therapeutic potential in diverting the pathological PAF-way with Tjoelker and colleagues' recombinant enzyme. □

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1. Tjoelker, L. W. *et al. Nature* **374**, 549–553 (1995).
2. Hattori, M., Adachi, H., Tsujimoto, M., Arai, H. & Inoue, K. *J. biol. Chem.* **269**, 23150–23158 (1994).
3. Stafforini, D. M., Elstad, M. R., McIntyre, T. M., Zimmerman, G. A. & Prescott, S. M. *J. biol. Chem.* **265**, 9682–9687 (1990).
4. Stafforini, D. M., Prescott, S. M. & McIntyre, T. M. *J. biol. Chem.* **262**, 4223–4230 (1987).
5. Hattori, M., Adachi, H., Tsujimoto, M., Arai, H. & Inoue, K. *Nature* **370**, 216–218 (1994).
6. Kato, K., Clark, G. D., Bazan, N. G. & Zorumski, C. F. *Nature* **367**, 175–179 (1994).
7. Zimmerman, G. A., Prescott, S. M. & McIntyre, T. M. *Immun. Today* **13**, 93–99 (1992).
8. Kumar, R., Harvey, S., Kester, N., Hanahan, D. & Olsen, M. *Biochim. biophys. Acta* **963**, 375–383 (1988).
9. Bazan, N. G. *Biochim. biophys. Acta* **218**, 1–10 (1970).
10. Panetta, T., Marcheselli, V. L., Braquet, P., Spinnewyn, B. & Bazan, N. G. *Biochem. biophys. Res. Commun.* **149**, 580–587 (1987).
11. Tokomura, A., Kamiyasu, K., Takauchi, K. & Tsukatani, H. *Biochem. biophys. Res. Commun.* **145**, 415–425 (1987).
12. Squinto, S. P., Block, A. L., Braquet, P. & Bazan, N. G. *J. Neurosci. Res.* **24**, 558–566 (1989).
13. Bazan, N. G., Fletcher, B. S., Herschman, H. R. & Mukherjee, P. K. *Proc. natn. Acad. Sci. U.S.A.* **91**, 5252–5256 (1994).
14. Bazan, H. E. P., Tao, Y. & Bazan, N. G. *Proc. natn. Acad. Sci. U.S.A.* **90**, 8678–8682 (1993).
15. Weyrich, A. S., McIntyre, T. M., McEver, R. P., Prescott, S. M. & Zimmerman, G. A. *J. clin. Invest.* (in the press).
16. Pan, Z., Kravchenoko, V. V. & Ye, R. D. *J. biol. Chem.* **270**, 1–4 (1995).
17. Stafforini, D. M., Zimmerman, G. A., McIntyre, T. M. & Prescott, S. M. *Trans. Ass. Am. Physicians* **CV**, 44–63 (1992).
18. Miwa, M. *et al. J. clin. Invest.* **82**, 1983–1991 (1988).
19. Snyder, F. *Biochim. biophys. Acta* **1254**, 231–249 (1995).

DAEDALUS

# Flash and bang

**A LOT of subtle technology depends on unstable metal compounds. Silver halides, which decompose in light, are used in photographic film; silver and lead azides, which explode on heat or impact, are used to detonate explosives. Both, in effect, are chemical amplifiers. A film and a detonator both take a small amount of energy and use it to initiate a much larger chemical change. Daedalus is now combining the two.**

**He points out that lead and silver azides, and most other metallic detonators, are decomposed by light. There is even a photographic process based on such compounds, carefully diluted and dispersed to stop them exploding. But Daedalus has bolder photochemical plans. He wants them to explode. Intrepid DREADCO chemists are now preparing photographic emulsions, not of silver halide in gelatine, but of silver or lead azide in blasting gelatine. And instead of stabilizing them in an inert matrix, they are doping them with the most active sensitizing dyes known to photography. Their goal is to realize that old chemical joke, the explosive so sensitive that it goes off if you look at it. The faintest glimmer of light will set it off.**

**The immediate market for DREADCO's 'Photoexplosive Film' will be the printing industry. For this purpose, it will be coated onto blank metal plates. The printer merely loads the plate into a special camera, and points it at the image to be printed. When he presses the shutter, the emulsion explodes where the light hits it, and locally indents the metal. The result is an instant printing plate. A dark rinse to remove unexploded emulsion completes the process.**

**Photoexplosive Film will need careful design. If its energy density is too low, it will fail to indent the plate locally; if too high, the excess energy will propagate the explosion sideways and set off the whole emulsion.**

**Once perfected, however, it should soon find wider uses. Many metals can be shaped drastically and deeply by high energy-rate or explosive forming. So a heavy-duty photoexplosive process could forge a massive metal component instantly, directly from its drawing. On a small scale, a tiny sample of photoexplosive film would be the ultimate antitamper device for a container, a safe or a package. The tamperer would not only be badly shaken while automatically raising the alarm: he could be simultaneously photographed into the bargain. For the legitimate consignee, however, a reassuring bang when the package is opened will be the ultimate guarantee of its pristine condition.** David Jones