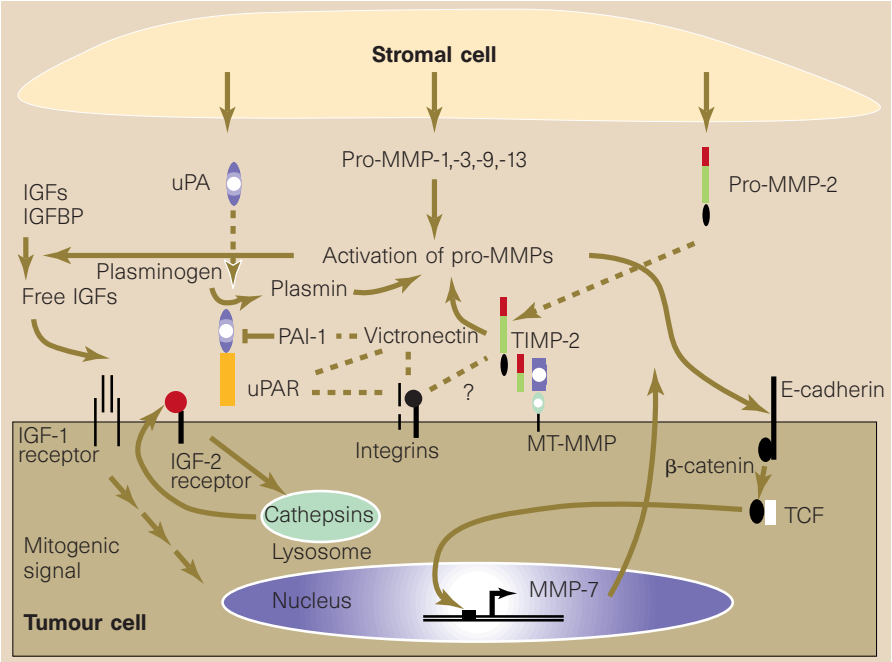

Figure 1 **Interactions between tumour and stromal cells, and the regulation of proteases and protease inhibitors. The two main protease systems are the urokinase plasminogen activator (uPA)/uPA receptor (uPAR)/plasminogen network, and the matrix metalloproteinases (MMPs). IGF, insulin-like growth factor; TCF, T-cell factor.**

derbilt Univ., Nashville), loss of E-cadherin function allows transcriptional activation of MMP-7 (Fig. 1), which sets in motion further remodelling events. Mice that lack another MMP, MMP-9, show failures of vascularization and apoptosis in the skeletal growth plate early in development[6]. When these mice are crossed with animals in which expression of MMP-9 coincides with activation of an angiogenic switch during tumour formation, loss of MMP-9 suppresses tumorigenesis (Z. Werb). This is exciting evidence to link MMP-9 causally with angiogenesis.

The idea that some proteases mainly affect tumour growth rather than invasion may also apply to the cathepsins (H. Rochefort, INSERM, Montpellier). Cathepsins are aspartyl or cysteine proteases that are found within lysosomes in normal cells, but are released in high levels by many types of cancer cell. Cathepsins interact with the mannose 6-phosphate/insulin-like growth factor (IGF)-2 receptor, which is subsequently internalized. This prevents the receptor from acting as a sink for IGF-2, so the cell-proliferative actions of IGF-2 can proceed via the signalling IGF-1 receptor. The IGF signalling pathway may also be the target for the actions of MMPs and tissue inhibitors of metalloproteinases (TIMPs) on tumour growth. Overproduction of TIMP-1 suppresses T-antigen-induced hepatocellular carcinomas, possibly by preventing MMP-mediated degradation of IGF-binding proteins and, thus, reducing the local availability of IGF-2 (R. Khokha, Ontario Cancer Inst., Toronto).

What does all of this mean for cancer therapeutics? At least six synthetic MMPIs are now undergoing clinical trials, with phase I/II data published for marimastat (P. Brown, British Biotech, Oxford). This drug shows good safety and tolerability, although reversible musculo-skeletal toxicity is the main side-effect[7]. The preclinical data showing suppression of tumour invasion, metastasis and angiogenesis are impressive, and, with phase III trials continuing for at least another year, the problems at British Biotech seem to have more to do with management tactics than with marimastat itself.

Clearly, we need to know a lot more about the basic biology of proteases and inhibitors. By identifying the key 'weapons' at specific tumour sites, and their precise functions, the next generations of selective antagonists can be developed. The potential of combination anti-protease strategies using MMPIs and promising synthetic uPAR antagonists (S. Rosenberg, Chiron Corp., Emeryville) needs to be studied, as does the integration of protease inhibition with conventional chemo- and radiotherapies. The era of protease and angiogenesis inhibitors in cancer therapy has only just begun. □

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Daedalus

Smokeless powder

Smoking delivers nicotine to the smoker. Nicotine is pleasurable, which is why he smokes. However, smoking harms him, and annoys those around him. But nicotine is addictive, so he can't give up. This dismal reasoning underlies one of the fiercest public debates of our time. A new finding (M. L. Pianezza, E. M. Sellers & R. F. Tyndale *Nature* 393, 750; 1998) offers a way out. Nicotine is largely oxidized in the liver to cotinine. People whose livers perform this reaction badly are much less likely to become addicted to smoking. Daedalus has three possible explanations of this finding, each with a useful twist.

If nicotine cannot go to cotinine in the body, it will go instead to nicotine *N*-oxide. Being very similar to nicotine, the *N*-oxide may be its antagonist — sitting on and blocking its receptors but failing to trigger their pleasure. This should protect the smoker from addiction. If so, it could form the basis of a splendid new anti-smoking treatment.

Alternatively, it may be that nicotine is the pleasurable agent of smoking, but it is cotinine that is addictive. Blocking the reaction to cotinine (by a suitable enzyme inhibitor) would then convert smoking from a degrading addiction to a voluntary pleasure. It would also prolong that pleasure. Deprived of its fastest degradation route, nicotine would last longer in the body. The smoker would be satisfied with fewer cigarettes.

Or cotinine might turn out to give both the pleasure and the addiction of smoking. This is the most revolutionary possibility of all. For smoking is a clumsy, annoying, inefficient ingestion process. It survives because nicotine is unstable in air; it cannot easily be packaged as a drink (like caffeine or alcohol) or a pill (like amphetamine). It must be thermally liberated from a stable precursor, and breathed in at once, before it degrades.

But cotinine is stable in air. So nicotine could be extracted from tobacco, converted to cotinine, and sold as a pill or a beverage. Smokers by the million would happily abandon their smelly habit, and satisfy their craving by a product that could be drunk or chewed. Their risk of lung cancer (triggered by all that tarry smoke) would plummet. So might their risk of heart disease, which is blamed on nicotine itself. Cotinine, a product of the body's detoxification mechanisms, should be far less cardiotoxic. The commercial possibilities are limitless. If Joe Camel doesn't do it, DREADCO will.

David Jones