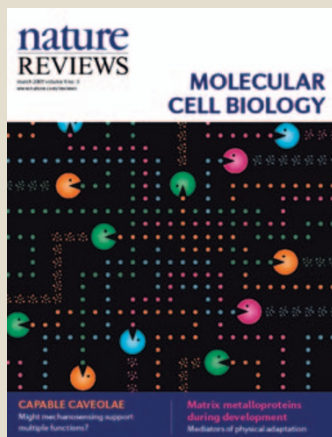




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► **COVER:** 'Proteolysis: the cutting game' by Vicky Askew, inspired by the Reviews on p221 and p245



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Biochemists carefully try to minimize the unwanted effects of proteases in their experiments, as failure to do so can lead to the rapid degradation of the proteins of interest. Ubiquitous protein degradation *in vitro* might give the mistaken impression that proteases cleave non-discriminately. But *in vivo*, proteolysis is in fact highly regulated and selective; proteases only function on a small number of substrates, and cleavage occurs at specific peptide bonds. In the Review on page 245, Christopher M. Overall and Carl P. Blobel discuss the experimental approaches that are used to identify substrates of extracellular proteases. The biochemical characterization of a protease and the validation of substrates in cell-based assays and knockout-mouse models can be used, along with an increasing number of proteomics approaches, to unveil the repertoire of substrates for a protease.

Moving from protease substrates to protease functions, Andrea Page-McCaw, Andrew J. Ewald and Zena Werb (page 221) describe the physiological roles of the matrix metalloproteinases (MMPs) — a family of extracellular enzymes that hydrolyse components of the extracellular matrix to facilitate the growth and remodelling of cellular tissues. They suggest that proteolysis should be considered as a type of post-translational modification whereby proteases do not only inactivate proteins, but can modify their function or cleave inactive substrates to release active signalling molecules. The functional significance of this type of modification is demonstrated by ample evidence that dysregulation of MMPs (and some of the other 566 extracellular proteases that are present in humans) is associated with many diseases, and it is hoped that the study of proteases will elucidate new targets and strategies for therapeutics.

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