CHEMICAL REVIEWS

Volume 102, Number 12

Introduction: Proteases

Whether as paradigms of enzyme catalysis and structure, targets for drug development, or reagents for green chemistry, proteases have long commanded the rapt attention of biochemists. The ubiquity and consequence of proteases in nature are almost unrivaled. Approximately 2% of the genes in most organisms are proteases, second in number only to transcription factors, and proteases are involved in virtually every physiological process. This issue of *Chemical Reviews* contains 15 articles chosen to give the reader an appreciation for the depth and variety of the chemistry of proteases, including mechanism, structure, specificity, inhibition, folding, organic synthesis, and design.

Historically, proteases are sorted into four mechanistic classes: aspartate proteases, cysteine proteases, serine proteases, and zinc proteases, and this issue of *Chemical Reviews* initially follows this format. Dunn reviews the pepsin family of aspartate proteases, calling attention to newly discovered members and summarizing the recent advances in structure, mechanism, and inhibition. Brömme and colleagues discuss mammalian cysteine proteases of the papain family. These proteases were once believed to be nonspecific digestive enzymes, but are now recognized to have well-defined physiological roles. Denault and Salvesen review another family of cysteine proteases, the caspases. Originally discovered in cytokine processing, caspases are now more recognized for their role in the protease cascade of programmed cell death. Serine proteases with the classic Asp−His−Ser triad are the largest class of proteases, including digestive enzymes with minimal specificity and processing enzymes with exquisite substrate recognition. Hedstrom reviews mechanism and specificity in the chymotrypsin family, while Fuller and colleagues discuss how kex 2 and related members of the subtilisin family meet the challenge of specificity in hormone processing.

The textbook organization of four mechanistic classes is now woefully inadequate. The MEROPS database (http://www.merops.co.uk/) recognizes 42 different clans of proteases, i.e., 42 evolutionarily distinct protease structures. With these structures come several new mechanisms: novel serine proteases with His/Ser and Lys/Ser dyads, two metal proteases, and membrane bound proteases with undefined active sites. This incredible display of convergent evolution can probably best be appreciated by considering the variety of proteases that perform a particular physiological task. Dalbey and colleagues examine signal peptidases, which include novel serine proteases as well as aspartate and metalloproteases. The N-terminal processing of proteins is critical for cell function and Lowther and Matthews review a new class of metalloproteases that use either one or two metal ions to perform this reaction. Viral proteases include a surprising array of different structures and mechanisms. Tong discusses these important chemotherapeutic targets. The realization that many growth factors and receptors are shed from the cell surface ignited a race to isolate the responsible proteases. Arribas and Borroto discuss the proteases of ectodomain shedding, which includes novel membrane bound enzymes.

Chemists and nature share a common interest in controlling protease activity. Powers et al. have comprehensively surveyed irreversible inhibitors of serine, cysteine, and threonine proteases, where clever chemistry subverts the normal catalytic reaction. Nature is even more resourceful; serpins are "spring-loaded" inactivators of serine and cysteine proteases. As discussed by Gettins, serpins undergo an extensive conformational change when they react with their target proteases, deforming the protease active site to form a stable covalent adduct. Nature also regulates protease activity by synthesizing inactive precursors that are processed into mature enzymes. Bryan discusses how the prodomains catalyze the folding of protease structure. Both serpins and prodomains challenge the idea that protein structure is thermodynamically controlled.

The Protease thematic issue ends with three articles discussing current efforts to harness the catalytic power of enzymes for synthetic applications. Bordusa surveys issues and applications of proteases in organic synthesis. Evans and Xu describe inteins and protein splicing, a remarkable system that both cleaves and synthesizes peptide bonds. Lastly, Tanaka updates the state of efforts to create proteases de novo using catalytic antibody methodology.

We are very grateful to the authors for their effort and cooperation in producing this issue. It is our hope that the keen insight and excellence of scholarship of these articles will make this issue an invaluable resource for many years to come.

Lizbeth Hedstrom
Department of Biochemistry
Brandeis University

CR0101712

10.1021/cr0101712 CCC: $39.75
Published on Web 12/11/2002