Proteinase Inhibitors

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Twenty-one chapters from individual authors are combined together in this volume under the editorial direction of Alan Barrett and Guy Salvesen. Previously, Dr Barrett has produced a number of treatises on the topic of proteolytic enzymes and one suspects that these have now assumed 'text-book' status on most library shelves. It seems singularly appropriate and of considerable value, particularly with the current preoccupation with gene technology for the expression of recombinant proteins in foreign cells, to release a companion volume which documents with an authority matching that in its predecessors, the variety and selectivity of inhibitors which regulate the proteolytic enzymes.

All known proteinases may be classified on the basis of their catalytic mechanism into one of only four categories and the first of two preliminary chapters thus introduces the serine, cysteine, aspartic and metalloproteinases. It is accompanied by a valuable, well-written chapter reviewing kinetic procedures for the assessment of proteinase:anti-proteinase interactions. Four articles then ensue in which peptide inhibitors of the four classes of enzyme evolved by nature over thousands of years are considered in turn and evaluated against synthetic analogues devised and synthesised by man within a minute time frame. The successes of such strategies are most impressive.

Ten chapters on individual proteins that are serine proteinase inhibitors (= serpins) reveal the massive amount of information that is now available on what has undoubtedly been the most frequently studied class of enzyme. In more recent years, the discovery of the cystatins, a superfamily of cysteine proteinase inhibitors, has made it possible to have an informative chapter on this subject which has not been previously described elsewhere. The non-conformist inhibitors of cysteine proteinases, the calpastatins, are sufficiently eccentric in their behaviour to warrant the treatment that they receive as a separate topic. The selectivity of these inhibitors is remarkable in that they have no effect whatsoever on any proteinase other than their specific target, the Ca^{2+}-activated cysteine proteinases (or calpains). An even more unusual feature is the ability of one molecule of inhibitor to negate (considerably) more than one molecule of calpain; a fact that has recently been substantiated by the observation of repetition within the (gene) structure of the inhibitor. This leads on to consideration of protein inhibitors of metalloproteinases including the tissue inhibitor of metalloproteinases (= TIMP) that is exported by a number of cells to regulate the degradation of the matrix of connective tissue.

After the detailed scrutiny of all of these naturally-occurring protein inhibitors of serine, cysteine and metalloproteinases, the absence of a chapter on protein inhibitors of aspartic proteinases would seem at first glance to be a glaring oversight. Not so, however, in that very few such proteins actually exist. Nature appears to have evolved different mechanisms (pH; rate of supply of substrate) for the regulation of these enzymes by comparison with the other three classes.

A final chapter focusses attention on the everyday significance of what has gone before in evaluating the importance of proteinase inhibitors as drugs. At just over £100, this volume is on the expensive side but even so, just as with Jeffrey Archer, it would seem destined to become the latest in a series of best sellers.

John Kay