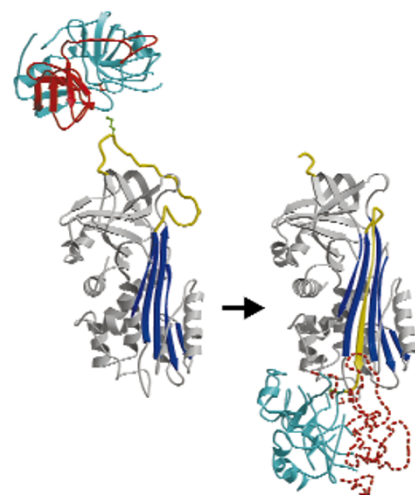# The 'serpin'ator

Life is a balancing act. Within all organisms protein molecules are continuously being made and destroyed. The levels of important structural proteins, enzymes, and regulatory proteins depend on the careful control of the rates of synthesis and degradation. Thus, complex and highly regulated mechanisms have evolved to carry out proteolytic degradation. It is well known that unregulated proteolysis can destroy normal cells and tissue and contribute to diseases such as heart attack, stroke, arthritis, emphysema and cancer.

The question then is how are the proteases regulated? Many proteases are controlled by a group of proteins called serpins (SERine Proteinase INhibitors). Serpins act as 'bait' by presenting part of an exposed, flexible, ~20 amino acid long peptide loop (the reactive center loop). Once the target protease 'bites', or attempts to, it becomes irreversibly locked in a stable complex. The serpin–protease complex is then cleared from the system.

Thus, serpins act as 'protease sinks', removing proteases before they damage surrounding cells or tissue.

While a number of lines of evidence suggest that a major conformational change plays an important role in the mechanism of inhibition by serpins, many different models have been proposed. Now, the structure of a serpin–protease complex shows an unexpected degree of conformational disorder induced in the protease (Huntington, J.A., Read, R.J. & Carrell, R.W. *Nature* **407**, 923–926, 2000).

By comparing the structures of trypsin and antitrypsin alone and in complex Huntington *et al.* propose the following scenario. The serpin (lower molecule on the left) reacts with the protease (upper molecule on the left) *via* the reactive center loop (yellow). The active site serine of the protease is covalently linked to the reactive center loop of the serpin. This cleaves the reactive center loop which then inserts into the β-sheet of the serpin

(blue). This movement swings the protease 71 Å to the opposite end of the serpin. The part of trypsin that becomes disordered upon complex formation is in red. Thus, inhibition occurs by a kind of 'one, two punch' — by disrupting the active site and effectively "crushing the protease against the body of the serpin". Clearly, inhibition by serpins is not for the faint of heart. *Boyana Konforti*

Catching rays

In the early days of protein and nucleic acid crystallography, diffraction data were collected on X-ray films. But these X-ray films are inherently insensitive and it could take weeks or even months on a laboratory X-ray source to record an entire data set of sufficient quality for structure calculation. Moreover, additional processing steps — film development and digitization — are time consuming and require human intervention, thus making it difficult to automate the data collecting process.

To shorten the data collection time, several detectors with high sensitivity have been developed over the past three decades. One of these designs — the X-ray imaging plate — took advantage of a certain type of phosphor that can store the energy of the impinging X-ray photons in a latent form; upon stimulation by a laser, the energy is re-emitted as phosphorescence. A plate coated with this phosphor can be used to capture the x-ray diffraction patterns.

An early application demonstrated the utility of the imaging plate: the diffraction

patterns from a contracting muscle placed in a synchrotron radiation beam were recorded[1]. Both the strong and weak diffraction lines from the muscle were clearly visible after <10 s of exposure, compared to the five to ten minutes usually required to record an image of similar quality on an X-ray film. Moreover, the short exposure time allowed the measurements of changes in diffraction intensities during muscle contraction, which reflected the changes in the structure of the actin filament during this process.

Like X-ray films, data recorded on the imaging plates can only be retrieved offline, introducing dead time in the data collection process. This is not desirable, especially when used with synchrotron radiation where the beam time is valuable, and particularly in the field of structural genomics where high throughput is key (see the accompanying Structural Genomics Supplement). An electronic X-ray detector based on the charge-coupled device (CCD), which was developed

in parallel with the imaging plate, is superior in this respect and is gaining popularity since its introduction into the synchrotron radiation beam lines for macromolecular crystallography.

Interestingly, both the imaging plates and CCD were originally developed for applications other than crystallography — the imaging plates were designed for diagnostic radiography[2] whereas the CCD was developed as an information storage device[3,4]. Both have also been widely adapted to other areas of science — the CCD has become an essential component in astronomical observatories while the imaging plates have been routinely used in molecular biology research for quantifying radioactive bands in gels. These devices are examples of technology transfer between disciplines and demonstrate that progress in one area of science can have a profound influence on other branches. *Hwa-ping Feng*

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