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Perspective

Degradomics: Genomic and Proteomic Approaches to Identify the Protease

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DESCRIPTION

Degradomics is a branch of biology that encompasses all genomic and proteomic techniques devoted to the system-wide study of proteases, their inhibitors, and their substrates. The investigation of protease and protease-substrate repertoires, often known as "protease degradomes," is part of this. These degradomes can be on a cell, tissue, or organism-wide scale. Proteases, the second biggest class of enzymes after ubiquitin ligases and responsible for 2% of all genes in each organism, have prompted biologists to create a discipline devoted to identifying and quantifying their involvement in biology. Degradomics was first reported as relating proteases to substrates on a proteome basis by the Overall Lab in McQuibban in 2000. Dr. Carlos Lopez-Otin and Dr. Chris Overall would subsequently summarise the discoveries of novel protease roles and achievements in protease-substrate discovery, bringing degradomics on a system-wide scale. They compiled a list of existing and emerging methodologies for describing proteolysis.

They highlighted the importance of studying proteases for their functional relevance in processing bioactive compounds by emphasising how proteolysis acts as an additional irreversible way by which cells might gain control over biological processes. Coagulation, complement activation, DNA replication, cell-cycle control, cellular proliferation and migration, hemostasis, immunology, and apoptosis are all regulated by these bioactive chemicals. The degradome was divided into two categories, the first of which refers to the full profile of proteases expressed by a cell, tissue, or organism under specific conditions. The second term refers to a protease's whole substrate repertoire in a single cell, tissue, or organism.

Genomic methods

Yeast two-hybrid screens: Protease-substrate finding has been developed from yeast two-hybrid analyses. Exosites of proteases have been utilised to screen for protease interactions and possible substrates because they play a function in protein-protein recognition and interaction. Protease exosites are used as bait in these protease exosite scanning tests to search a cDNA library for potential interaction partners.

Inactive-catalytic-domain capture is another early adaption of yeast two-hybrid screening in protease-substrate discovery (ICDC). This method tries to get around the problem of protease exosite scanning, which ignores any substrates that don't require exposited recognition before cleavage. Immobilized catalytically inactive mutant protease domains that cannot cleave and release their substrates are used as bait in these studies. The limits of modified yeast two-hybrid screens, valuable in early degradomic research, have led the field to move on to higher-throughput techniques for protease-substrate identification. Their low accuracy, inability to recognise complicated interactions, lack of biological compartmentalization, and failure to account for post-translational modifications required for protein-protein interactions limit their utility. As technology has progressed, proteomic approaches have mostly superseded them.

Proteomic methods

Protease-specific arrays: Beyond transcript expression, a protease specific protein array based on mounted antibodies designed to capture specific proteases from biological materials provides a step up in protein level analysis. Capture antibodies seen on nitrocellulose membranes can capture proteases in complicated mixtures that have been pre-incubated and bound by detection antibodies, allowing for comparative protease level monitoring. In comparison to typical western blots, these arrays allow for parallelization of protein levels. Unfortunately, these assays do not provide information on protease enzymatic action and have the same problems with quantification as western blots.

Gel-based proteomic methods: In the past, two-dimensional Polyacrylamide Electrophoresis gels were used to compare the intensities of protease-treated and untreated sample spots in order to find potential substrates. Fluorescent 2D difference gel electrophoresis, a more recent advancement of this technology, aims to control uniformity between gels for relative measurement. The substrate and cleavage products can be investigated from the fluorescent gel by differently labelling protease-treated and untreated samples with either Cy3 or Cy5, pooling said samples, and evaluating them together by 2D-PAGE. Later, using Mass Spectrometry or Edman Sequencing, the spots matching to possible substrate and cleavage products

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can be identified. The most significant disadvantages of adopting these approaches have to do with the chemistry of the technique and its lack of sensitivity.