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Perspective

A Better Understanding of Protease Degradomics

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INTRODUCTION

Degradomics is a subfield of biology that encompasses all genomic and proteomic approaches dedicated to the study of proteases, their inhibitors, and their substrates on a system-wide scale. This includes the analysis of the protease and protease substrate repertoire, also called the 'protease degradome'. The extent of these degradomes can span cellular, tissue, and whole-organism scales. Proteases initiate, regulate, and terminate many important cellular functions through highly specific and limited substrate cleavage. This mechanism, called proteolytic processing, enables precise cellular control of several biological processes, including DNA replication, cell cycle progression, cell proliferation, wound healing, immunity, angiogenesis, and apoptosis. The hierarchical importance of proteases in the system, a key point in drug development is influenced by protease specific activity, redundancy, expression levels, spatiotemporal distribution, zymogen activation, protease turnover, and inhibitory properties. Therefore, a tissue-wide degradomics approach (using genomic and proteomics techniques) is required to characterize members of Ca. termed 'substrate degradomes' for each protease. Protease profiling using a DNA microarray chip provides a general view of the protease transcriptome, whereas messenger RNA expression levels are not predictive of protease protein abundance or activity associated with protease-specific and protease-active protein chips.

DESCRIPTION

The substrate chip analyzes the net proteolytic potential of total functional proteolysis against a given substrate without specifying the active proteases involved. This is important information because the net cleavage of a particular substrate determines the biological response. Chemical proteomics makes use of labelled-irreversible protease inhibitors to isolate or discover active proteases in complicated mixtures with the help of Two-Dimensional (2D) gel electrophoresis or with the use of protease-activity chips with Matrix-Assisted Laser Desorption-Ionization-Time-Of-Flight (MALDI-TOF) or MALDI-Quadrupole-TOF (MALDI-Q-TOF) mass-spectrometric identified as captured proteases. *In vivo* programs of inhibitor probes encompass proteases. *In vivo* programs of inhibitor probes encompass dedication of protease feature with the aid of using chemical knockouts or intravital imaging of proteolytic. To discover protease substrates, peptide or inhibitor library processes that determine peptide-bond by evaluation of substrate accumulation in protease-knockout mice, and 2D gel-MALDI-TOF or MALDI-Q-TOF mass-spectrometric evaluation of proteolytic degradation products in protease-handled cell or tissue protein extracts. Yeast two-hybrid strategies of substrate identity with the aid of using exosite-area binding (exosite scanning) and Inactive Catalytic Domain Capture (ICDC) have now been tailored for proteomic displays on columns or chips. The current identity of many bioactive molecules along with cytokines, molecular-adhesion molecules and receptors and intracellular targets (which includes transcription elements and kinases) as new protease substrates which can be exactly processed with the help of proteolytic activity. Upregulation of protease expression and proteolytic activity has been implicated in many pathological conditions such as neurodegeneration, cancer, cardiovascular disease, autoimmune disease and bone degeneration. During the course of disease, various proteases generate characteristic patterns of cleaved proteins and peptides that can influence disease severity and progression. Qualitative and quantitative monitoring of cleaved protease substrates has been shown to provide relevant prognostic, diagnostic, and therapeutic information. The field of degradomics enables global identification of proteolytic events at the organismal level using proteomic approaches and sample preparation techniques that facilitate the detection of proteolytic processing of protease substrates in complex biological samples. Degradomics emerged with the concept that proteolysis represents a specific mechanism for achieving cellular control of critical processes beyond the control of gene expression and translation, and is essential for understanding the complex regulation of biology. Extracellular proteases were thought to degrade the Extracellular Matrix (ECM), but these proteases target process a variety of substrates with different roles, leading to increased protease function. Degradomic studies have also contributed to the Human Proteome Project (HPP) of the Human Proteome Organization (HUPO). The protease-regulated web offers an opportunity to identify new disease biomarkers and targets for drug design.

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CONCLUSION

Contributions of degradomics have identified a number of well-characterized novel protease substrates, speculation continues to grow about previously unknown protease targets. Recently, using N-terminal analysis technique in plasma samples from chemotherapy patients, a proteolytic signature of cell death was discovered. Bioinformatics remains a helpful tool for degradomics due to the increasing complexity of the regulation of cellular processes and the role proteases play in them. Technological advances have accompanied the software, databases, and projects developed for this purpose. A software (CLIPPER) developed by the overall lab statistically evaluates cleavage site candidates determined by a degradative approach.