Multi-author Review

Proteases as biological regulators

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Proteases as biological regulators. Introductory remarks

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The involvement of proteases in the regulation of intracellular events was neglected for many years. It is true that proteases belong to the first and nowadays best studied class of enzymes in biochemical and physicochemical terms, but only extracellular proteases received this first detailed attention [24]. Involvement of proteases in intracellular control was hard to imagine: Why should a vital class of macromolecules like the proteins, which are assembled at the expense of a lot of energy be broken down by the cell again? Why should the energy-consuming synthesis of peptide bonds be hydrolytically reversed? A first report indicating that most proteins in living cells do not last as long as the cells themselves [32] was forgotten very quickly. Control of metabolism seemed to be performed only on the basis of regulation of enzyme synthesis [4] and through non-covalent [33] and covalent binding [16] of ligands on enzyme proteins. To many earlier researchers, proteases seemed to be boring catalysts present in the cell only to annoy biochemists who wanted to purify proteins.

However, in recent years it became obvious that proteases and proteolysis play vital roles in the biology of all cells. The 'destroying' catalysts, proteases, turned out to function as central control elements. As the interest of the scientific world in proteolysis increased, more and more functions of proteases were uncovered.

The action of proteases might be divided into two different categories: 1) limited proteolysis, in which proteases split only one or a limited number of peptide bonds of a target protein and 2) non-limited, complete degradation of a target protein through hydrolysis of a multitude of its peptide bonds.

While the latter mechanism has its only goal in complete elimination of a certain protein to regulate its intracellular level and recycle the resulting amino acids into the protein synthesis machinery of the cell, limited proteolysis serves different functions. These range from maturation of proteins to gain their biological function to modification and inactivation of proteins, in order to make them alter or lose their biological function. The steadily increasing and at present central interest in proteolysis as an intracellular regulatory tool is documented in the constantly increasing amount of review articles of which some are cited here [1-3, 5-15, 17-23, 25-31, 34-38] and which the reader may consult for special information on a certain subject.

With the articles of this multi-author review on proteases as biological regulators the reader is guided through the cell, and his attention is focused on the function of proteolysis in a variety of cellular events. These events include targeting of proteins destined to function in different cellular compartments, maturation and activation of proteins to fulfill their biological role after they reach their cellular destination, degradation of proteins in hydrolytic vacuoles and in the cytoplasm of the cell to serve a variety of cellular needs, the morphogenesis of cellular parasites, the viruses.

Assembly of the articles on proteolysis in one review for the first time gives the reader a more complete impression of the function of post-translational control through proteolysis in the living cell. One important intracellular proteolytic process is not covered in this Experientia issue: the maturation of peptide hormones. This very central subject will be covered in one of the next issues of Experientia followed by a summary which puts all articles into a frame.

Our knowledge of proteolysis as a control mechanism is rapidly increasing. Thus, to the mosaic of proteolysis as we see it at the moment, we can expect that many new pieces will be added in the future, and we are all excited about the image of the final picture.

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Proteolysis in protein import and export: Signal peptide processing in eu- and prokaryotes

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Abstract. Numerous proteins in pro- and eukaryotes must cross cellular membranes in order to reach their site of function. Many of these proteins carry signal sequences that are removed by specific signal peptidases during, or shortly after, membrane transport. Signal peptidases have been identified in the rough endoplasmic reticulum, the matrix and inner membrane of mitochondria, the stroma and thylakoid membrane of chloroplasts, the bacterial plasma membrane and the thylakoid membrane of cyanobacteria. The composition of these peptidases varies between one and several subunits. No site-specific inhibitors are known for the majority of these enzymes. Accordingly, signal peptidases recognize structural motifs rather than linear amino acid sequences. Such motifs have become evident by employing extensive site-directed mutagenesis to investigate the anatomy of signal sequences. Analysis of the reaction specificities and the primary sequences of several signal peptidases suggests that the enzymes of the endoplasmic reticulum, the inner mitochondrial membrane and the thylakoid membrane of chloroplasts all have evolved from bacterial progenitors.
Key words. Signal peptidase; signal sequence; limited proteolysis; protein traffic; endosymbiont theory; membrane proteins.

Introduction

Numerous proteins in both prokaryotes and eukaryotes have to cross biomembranes in order to reach their destinations within the cell. It is generally accepted that these proteins are distinguished, and consequently sorted, from the bulk of cytoplasmic proteins by virtue of discrete sequence sections, termed signal sequences. A signal sequence is defined as a sequence which contains the information necessary and sufficient to guide a protein