CC/NUMBER 10
MARCH 9, 1992

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Kirschke H, Langner J, Wiederanders B, Ansorge S, Bohley P & Hanson H. Cathepsin H: an endoaminopeptidase from rat liver lysosomes. *Acta Biol. Med. Germ.* 36:185-99, 1977.
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We found a cysteine proteinase in lysosomes of rat liver with the remarkable properties to hydrolyze both aminopeptidase and endopeptidase substrates. The main proofs of the endoaminopeptidase nature of cathepsin H was the competitive inhibition of the enzyme activity by amino- and endopeptidase substrates among one another and the uniform inhibition or activation of the endopeptidase as well as the aminopeptidase activity by various effectors. [The *SCI*® indicates that this paper has been cited in more than 155 publications, making it the most-cited article published in this journal.]

Cathepsin H: One of the Lysosomal Cysteine Proteinases

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In the early 1970s when all of us had finished our doctoral theses, we decided to continue the work on cellular proteolytic enzymes initiated in Halle by Emil Abderhalden (1877-1950). This idea was strongly promoted by his follower Horst Hanson (1911-1978), who was at that time the director of the Institute of Physiological Chemistry at the Martin-Luther-University in Halle. All of us had different intentions to come to this field. The main aim was, however, to identify the proteinases that are important for the selective breakdown of intracellular proteins. Because of the high proteolytic capacity of lysosomes, we expected to find proteinases in this organelle with the properties of cleaving preferentially either short- or long-lived cytosolic proteins.

Only lysosomal cathepsins D and B were known at that time. We identified two further cysteine proteinases in lysosomes: cathepsin L[1,2] (EC 3.4.22.15) and cathepsin H[1] (EC 3.4.22.16). Although these enzymes, as we saw later, could not be responsible for the selectivity of the intracellular protein breakdown, because of their broad specificity on proteins as substrates, they are certainly important enzymes, ubiquitous in mammalian cells, for the overall degradation of proteins in lysosomes. Herein, cathepsin H may mainly act as an aminopeptidase with broad substrate specificity. Other aminopeptidases have not been identified in lysosomes yet.

Interest in this enzyme grew for several reasons. By comparison of the amino acid sequences, cathepsin H[3] showed a close relationship not only to lysosomal cysteine proteinases, such as cathepsins L and S, but also to papain, aleurain, and proteinases of the cellular slime mould *Dictyostelium discoideum.*[4] Cathepsin H seems to be an important link in the evolution of plant and animal cysteine proteinases from a common ancestral protein.

In case of leakage from lysosomes or secretion from cells, cathepsin H enters an environment of about pH 7.1, where it is irreversibly inactivated. In addition, cathepsin H has been found to react very quickly with endogenous inhibitors of cysteine proteinases, the cystatins,[5] occurring in the cytoplasm and extracellular fluids of mammals. The K_1 values for inhibition of cathepsin H by the cystatins are about one or two orders of magnitude lower than for inhibition of cathepsin B (except by cystatin C). This is surprising in terms of the high aminopeptidase and low endopeptidase activity of cathepsin H and its inactivation at neutral pH. We do not yet know the physiological significance of the rapid reaction of cathepsin H with the cystatins. Transformed cells have been shown to secrete procathepsins B and L and mature cathepsin S. Cathepsin H or its precursor have never been observed among the secreted cysteine proteinases, although their processing in normal cells is very similar.[6]

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Received January 17, 1991