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Houmard J & Drapeau G R. Staphylococcal protease: a proteolytic enzyme specific for glutamoyl bonds. *Proc. Nat. Acad. Sci. USA* 69:3506-9, 1972.
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This paper reports that the extracellular seryl-protease of *Staphylococcus aureus*, strain V8, can specifically cleave peptide bonds on the carboxyl-terminal side of either aspartate and glutamate, or only glutamate residues, depending on the kind of buffer used during the hydrolysis. [The *SCI*® indicates that this paper has been cited in more than 610 publications.]

A Very Welcome Protease

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After my graduation in biochemistry at the Université Paris XI, Orsay, France, in 1970, I crossed the Atlantic to join Gabriel R. Drapeau's group. Back from a postdoc in Charles Yanofsky's lab, he had only recently been appointed as professor in the Department of Microbiology and Immunology. At that time, being on the Faculty of Medicine, Drapeau started a new project for studying the potential relationships that could exist between the numerous extracellular proteins excreted by *Staphylococcus aureus* strains and their pathogenicity.

The method for the purification of one of the proteolytic exoenzymes having been set up, I was asked to study its specificity. Drapeau suggested to me that, instead of using the classical chromophoric substrates designed to test and characterize proteolytic enzymes, I could digest polypeptides of known amino acid sequences, purify the resulting peptides, and determine their amino acid composition. This suggestion turned out to be very wise since we soon had rather strong evidence that our protease was specific for peptide bonds involving acidic amino acids, and thus none of the commercially available substrates would have been hydrolyzed.

At the time, only a limited number of amino acid sequences were known, and the α and β chains of insulin seemed to be the best substrates to start with because of their limited sizes. I do not remember the manufacturer from which we ordered these insulin chains, but he played an important role in my formation as a young scientist.

When I first analyzed the chromatograms from the amino acid analyzer for the purified peptides of the insulin α amino acids to any possible peptides, I first thought that I had a mixture of peptides. Then I realized that I even had some phenylalanine in one of the peptides. So either the insulin was not from the organism for which I had the sequence, or my samples were contaminated. Probably because of previous experiences, Drapeau asked me to check the original product, and it turned out that, despite the high price that we had paid, the insulin α chain was heavily contaminated with β chain. I was then able to easily identify the various peptides that I had purified and to confirm and demonstrate our preliminary conclusions.

Soon after we obtained our results, Andrée Letendre and Samir A. Saheb joined our group. Letendre succeeded in purifying the α-hemolysin and Saheb characterized the metalloprotease from *S. aureus*.[1] Joining our efforts, we could exclude, by comparing the peptides resulting from proteolytic digests of the three proteins, the hypothesis that one of these three proteins could be a precursor of another. However, although a lot of progress has been made, the physiological functions of the large number of proteins excreted by *S. aureus*, as well as their role in pathogenicity, still remain poorly understood.

For the last 10 years, DNA has been more often sequenced than proteins, mainly for technical ease and rapidity. However, the early 1990s might see a new interest in protein sequencing. It has recently been demonstrated that different parts of a single polypeptide can be encoded by genes located on different chromosomes.[2] Molecular biology may thus regain all of its original meaning and not be restricted, as often has been the case, to nucleic acid games.

1. **Saheb S A.** Purification et caractérisation d'une protéase extracellulaire de *Staphylococcus aureus* inhibée par l'E.D.T.A. (Purification and characterization of an extracellular protease from *Staphylococcus aureus* complexed with E.D.T.A). *Biochimie* 58:793-804, 1976. (Cited 5 times.)
2. **Kanno H, Huang I Y, Kan Y W & Yoshida A.** Two structural genes on different chromosomes are required for encoding the major subunit of human red cell glucose-6-phosphate dehydrogenase. *Cell* 58:595-606, 1989. (Cited 15 times.)

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