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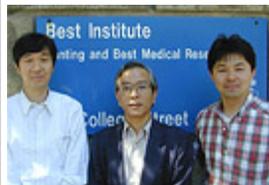
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2009 : December 2009 - Author Commentaries : Masayasu Kojima & Kenji Kangawa

AUTHOR COMMENTARIES - 2009

December 2009



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Ghrelin team: Drs. Kojima, Kangawa, and Hosoda

Masayasu Kojima & Kenji Kangawa

Featured Paper Interview

According to [Essential Science IndicatorsSM](#) from *Thomson Reuters*, the 1999 Nature paper by Dr. Masayasu Kojima and colleagues, "Ghrelin is a growth-hormone-releasing acylated peptide from stomach," (Kojima M, et al., Nature 402(6762): 656-60, 9 December 1999), is ranked at #4 among Highly Cited Papers in Biology & Biochemistry. It has accrued 2,586 citations from its publication to August 31, 2009.

Dr. Kojima's work ranks in the top 1% of the database in the fields of Biology & Biochemistry, Clinical Medicine, and Molecular Biology & Genetics. He is Professor of Molecular Genetics at the Institute of Life Science at Kurume University. His coauthor, Dr. Kenji Kangawa, is in the top 1% in the fields of Biology & Biochemistry and Clinical Medicine. Dr. Kangawa is the Director General of the National Cardiovascular Center Research Institute and Professor at the Kyoto University Graduate School of Medicine.

In this interview, ScienceWatch.com talks with Dr. Kojima about this paper and its impact on the research community.

SW: What factors promoted you and your coauthors to undertake this study?

Our research style is "in the beginning was a novel peptide." We have been searching for novel unknown peptides for almost 30 years. We discovered opioid peptides (a-neoendorphin, etc.), neuromedins, and the natriuretic peptide family (ANP, BNP, and CNP). It is a very exciting experiment to find a novel peptide and explore unknown physiological functions. It is just like a treasure hunt or climbing a virgin peak.

We used several orphan GPCRs as target receptors. Orphan GPCR means that the endogenous ligands have not been identified, and luckily we found the GHS-R ligand, ghrelin. In fact, the GHS-R ligand was the most desired one to be discovered. One reason is that the GHS-R ligand stimulates GH release and seems to be very useful for clinical purposes, such as low GH concentration and anti-aging.

SW: How was it conducted, and what were your findings?

We and all other groups had tried to find the undiscovered GHS-R ligand from the brain, because GHS-R is expressed in hypothalamus and pituitary. However, we discovered the ligand from the stomach. Only our group changed the target tissue and no other groups tried stomach

samples. This was very lucky for us, because content of ghrelin in the stomach was so high that every group should have succeeded in finding the ligand, if only they tried to find it in the stomach.

Please read my essay on the discovery of ghrelin*, in which I describe the story from the beginning of our research to the publication in *Nature*.

SW: How was the paper received by the community?

We had five reviews for accepting our paper to *Nature*. Usually three reviews are enough for *Nature* reviewing. I think that the production tissue (stomach) and the structure (octanoyl modification) of ghrelin were without precedent and the editor of *Nature* wanted assurance that our results were correct.

The endocrinology community was very positive and very excited about our results. However, to my disappointment, my grant for ghrelin research was rejected even after the paper was accepted by *Nature*.

SW: Where have you taken your ghrelin research since this paper's publication?

After the publication of the ghrelin paper, we examined the physiological functions of ghrelin and found that it is a potent orexigenic hormone. This was very exciting too, since ghrelin is a circulating hormone and these results indicated that peripheral injection of ghrelin can be used for treatment of eating disorders, such as anorexia nervosa.

We also created a ghrelin knockout mouse and have been examining what happens if there is no ghrelin. This study is very difficult; however, recently we found interesting phenotypes in these mice. I hope that the results will be published in a high-ranking journal in the near future.

Another interesting subject on ghrelin was the identification of the enzyme, ghrelin O-acyltransferase, which modifies and activates ghrelin. We had searched for the enzyme since the discovery of ghrelin. However, last year two groups reported on the enzyme and we lost. But the results were very surprising and exciting for me, because the enzyme was exclusively specific for acyl-modification of ghrelin.

SW: What makes ghrelin so important?

Since the discovery of leptin in 1994, the importance of humoral factors for regulating appetite has been recognized. Ghrelin is a counter-hormone to leptin not only for its physiological activity but also for its pharmacological functions. It is 10 years since the discovery of ghrelin and even now ghrelin is the only circulating orexigenic hormone. Thus, ghrelin seems to be a good target for developing drugs to regulate appetite or to treat obesity by antagonizing or suppressing its effects.

Finally, please let me talk about my personal pleasure. I am very, very happy and honored to find that "ghrelin" is described in *Lehninger's Biochemistry* and *Stryer's Biochemistry*, which I studied as textbooks in biochemical courses in my college student days. I could not have imagined when I was a young student that my discovery would be included in these textbooks 30 years later. ■

References:

*M Kojima, "The discovery of ghrelin—A personal memory," *Regulatory Peptides* 145(1-3): 2-6, 2008.

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and

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Dr. Masayasu Kojima

[+] enlarge



Dr. Kenji Kangawa

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At Japan Academy Prize: Dr. Kangawa (middle) received the Japan Academy Prize in 2008 for his discoveries of many peptide hormones. He is standing with Dr. Kojima (right) and Dr. Matsuo (left), their teacher and mentor. Dr. Matsuo had worked under Dr. Andrew Schally and helped determine the structure of LHRH, for which Dr. Schally received the Nobel Prize.

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Masayasu Kojima & Kenji Kangawa's current most-cited paper in *Essential Science Indicators*, with 2,586 cites:

Kojima M, *et al.*, "Ghrelin is a growth-hormone-releasing acylated peptide from stomach," *Nature* 402 (6762): 656-60, 9 December 1999. Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

Kenji Kangawa is featured in ISIHighlyCited.com

KEYWORDS: GHRELIN, NOVEL PEPTIDE, PHYSIOLOGICAL FUNCTIONS, GPCR, GHS-R LIGAND, STOMACH, TARGET TISSUE, OREXIGENIC HORMONE, EATING DISORDERS, GHRELIN O-ACYLTRANSFERASE, ACYL-MODIFICATION, APETITE REGULATION, OBESITY, PHARMACOLOGICAL FUNCTION.

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