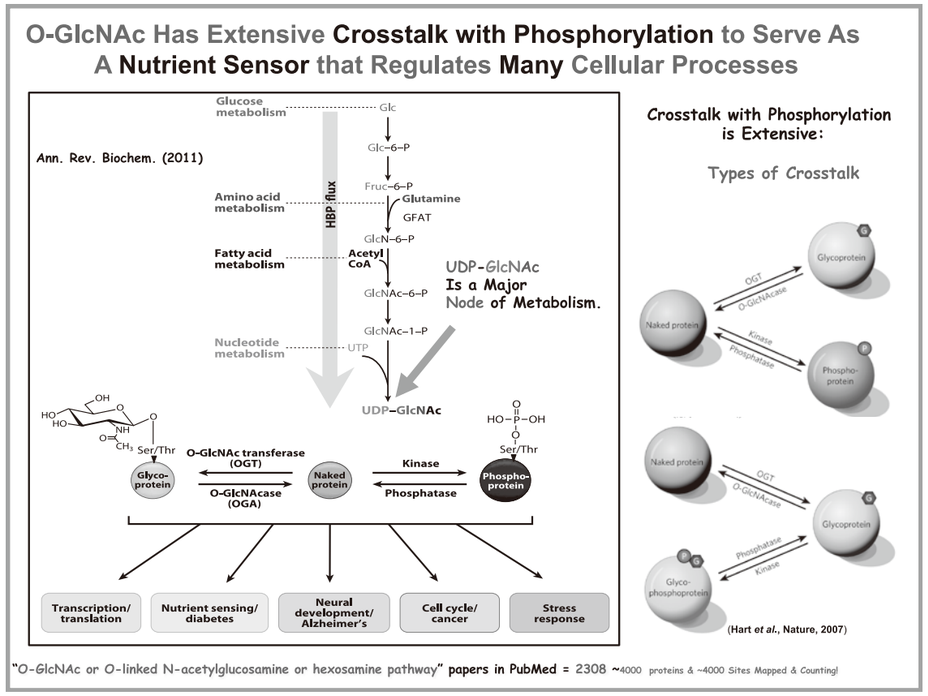
座長：谷口直之　16:20-17:15

山川民夫賞受賞講演

Nutrient Regulation of Signaling and Gene Expression by O-GlcNAc

Gerald Warren Hart, Ph.D.

Gerald Warren Hart, Ph.D. is currently the Georgia Research Alliance William Henry Terry, Sr. Eminent Scholar in Drug Discovery, and Professor of Biochemistry and Molecular Biology at the University of Georgia. He recently served as the Director of Biological Chemistry at Johns Hopkins Medical School for ~21 years. He is an Associate Editor of J. Biological Chemistry and of Molecular and Cellular Proteomics. He founded the journal Glycobiology in 1989, now the leading journal in the field and served as its Editor-In-Chief for 12 years. During his graduate career, he performed some of the earliest studies on cell surface heparan sulfates and on the roles of proteoglycans and sulfotransferases in corneal transparency. During his postdoctoral work, he determined the minimal sequence requirement for N-glycosylation (-Asn-X-Ser-) and showed that corneal keratan sulfate is made via the N-glycan biosynthetic pathway. Hart's laboratory discovered O-GlcNAcylation, he co-led elucidation of GPI anchor biosynthesis with Paul Englund's group, and his lab documented the importance of protein structure for N-glycosylation. His lab discovered the extensive crosstalk between O-GlcNAc and phosphorylation, which regulates transcription and signaling and underlies the etiology of diabetes, neurodegenerative disease, cardiovascular disease and cancer. ~300 publications; Google H-factor = 112; i10-index=304.



O-GlcNAcylation cycles on and off thousands of nucleocytoplasmic proteins and has extensive crosstalk with protein phosphorylation. O-GlcNAc is abundant on nearly all proteins involved in transcription, where it regulates gene expression in response to nutrients. O-GlcNAc also regulates the cycling of the TATA-binding (TBP) protein on and off DNA during the transcription cycle.

Targeted, inducible, deletion of the O-GlcNAc Transferase in αCAMKII positive (excitatory) neurons of adult mice results in a morbidly obese mouse with a satiety defect. Thus, O-GlcNAcylation not only serves as a nutrient sensor in all cells, but also is directly involved in appetite regulation. O-GlcNAcylation also plays an important role in the trafficking of the AMPA receptors in neurons and in the development of functional synaptic spines. Recent studies have shown that more than two-thirds of all human protein kinases are modified by O-GlcNAc and all kinases that have been tested are indeed regulated in some way by the sugar. Abnormal O-GlcNAcylation of CAMKII contributes directly to diabetic cardiomyopathy and to arrhythmias associated with diabetes. Prolonged elevation of O-GlcNAc, as occurs in diabetes, contributes directly to diabetic complications and is a major mechanism of glucose toxicity. Targeted over-expression of OGT to the heart causes severe heart failure in mice, which is reversed when they are crossed with mice having OGA over-expressed in their hearts. Drugs that elevate O-GlcNAcylation in the brain, which prevents hyperphosphorylation, appear to be of benefit for the treatment of Alzheimer's disease in animal models. To date, all cancers have elevated O-GlcNAc cycling, which may play a key role in the regulation of metabolism in cancer cells.

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than research. It is my hobby and

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