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Orexin neuron induction through epigenetics and hexosamine biosynthesis pathway in human and mouse pluripotent stem cells

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Glucose is metabolized through several pathways; glycolysis, pentose phosphate pathway, and hexosamine biosynthesis pathway (HBP). Orexin system plays a central role of integration of sleep/wake in broad spectrum of neural-metabolic physiology. Orexin-A and -B, are produced from prepro-orexin encoded by HCRT/Hcrt gene. Despite enormous efforts, authentic methods successfully used to induce other hypothalamic peptide neurons could not generate the orexin neurons from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). We succeeded in generating functional orexin neurons from mouse ESCs and human iPSCs by adding ManNAc, an intermediate of HBP. The induced orexin neurons were sensitive to glucose, and possessed the ability to respond to neurotransmitter and peptides such as GABA, TRH, ghrelin, and leptin. CpGs of the Hcrt genome locus was hypomethylated, which was associated with H3/H4 higher acetylation. Concomitantly, histone acetyltransferase, p300, CBP and Mgea5 (O-GlcNAcase) were colocalized at the Hcrt gene locus in the orexin neurons. In the orexin non-expressing cells, hypoacetylation of H3/H4 and hyper O-GlcNAc modification were observed at the Hcrt gene locus, which were occupied with Ogt and Sirt1. Therefore, stream of HBP is sensed in the epigenetic mechanism to switch the Hcr gene from inactive state to active state. These results indicated that the multi-layer epigenetic regulation in the generation of orexin neurons. The established method will be useful for development of orexin neurons for regenerative medicine, and the induced orexin neurons will provide a strong tool for the development of medical applications for diseases related to the orexin system.

Biography

Kunio Shiota is a professor in the Laboratory of Cellular Biochemistry at The University of Tokyo. He obtained Bachelor of Science/Doctor of Veterinary Medicine from Miyazaki University in 1973, and his PhD from the University of Tokyo in 1979. He joined the Central Research Division of Takeda Chemical Industries Ltd., as a research fellow. After a decade of service at Takeda, he returned to The University of Tokyo in the Laboratory of Cellular Biochemistry and rose to his current position of Professor in 1988.

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