Deciphering the Brain Glycocode

Xing Chen*

*College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China*
E-mail: xingchen@pku.ecu.cn

The human brain accounts for ~2% of the body weight, but consumes as high as 20% of glucose. As a result, the brain possesses the highest level of glycosylation, such as sialylation and O-GlcNAcylation, among all the organs. The glycans in the brain have been implicated in neural connectivity and neurodegenerative diseases. Aiming to elucidate the functional roles of brain glycosylation, we have developed chemical tools for glycan labeling, imaging, and glycoproteomics. To enable in vivo visualization of the sialoglycans in the mouse brain, we used stealth liposomes to shuttle azidosugars into the brain for metabolic labeling of brain sialoglycans, followed by click-labeling with imaging probes. Termed liposome-assisted bioorthogonal reporter (LABOR), this strategy, for the first time, enables click-labeling and imaging of brain sialoglycans in living mice. Furthermore, to implement expansion microscopy (ExM) for brain glycan imaging, we developed click-ExM, which integrates click labeling into ExM to enable super-resolution fluorescence imaging of glycans. We demonstrated click-ExM imaging of sialoglycans in cultured neurons and in brain tissues with super-resolution. Finally, we performed glycoproteomic analysis of protein O-GlcNAcylation in primary neurons, which revealed that O-GlcNAc is enriched at the synapses and regulates synapse activation.

References

01. Xie, R.; Dong, L.; Du, Y.; Zhu, Y.; Hua, R.; Zhang, C.; Chen, X.* "*In Vivo* Metabolic Labeling of Sialoglycans in the Mouse Brain By Using A Liposome-Assisted Bioorthogonal Reporter Strategy" *Proc. Natl. Acad. Sci. USA* 113, 5173-5178 (2016).
02. Sun, D.; Fan, X.; Shi, Y.; Zhang, H.; Huang, Z.; Cheng, B.; Tang, Q.; Li, W.; Zhu, Y.; Bai J.; Liu, W.; Li, Y.; Wang, X.; Lei, X.; Chen, X.* "Click-ExM Enables Expansion Microscopy for All Biomolecules" *Nat. Methods* 18, 107-113 (2021).
03. Lv, P.; Du, Y.; He, C.; Peng, L.; Zhou, X.; Wan, Y.; Zeng, M.; Zhou, W.; Zou, P.; Li, C.; Zhang, M.; Dong, S.*; Chen, X.* "O-GlcNAcylation modulates liquid–liquid phase separation of SynGAP/PSD-95" *Nat. Chem.* 14, 831-840 (2022).
04. Fan, X.; Song, Q.; Sun, D.; Hao, Y.; Wang, J.; Wang, C.; Chen, X.* "Cell-Type-Specific Labeling and Profiling of Glycans in Living Mice" *Nat. Chem. Biol.* 18, 625-633 (2022).
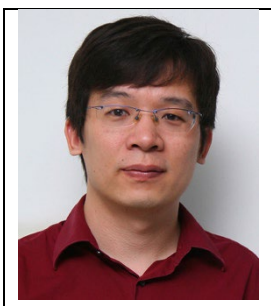
Xing Chen. Tsinghua University (BS, 2002), University of California, Berkley (Ph.D., 2007, Advisor: Carolyn Bertozzi), Harvard Medical School (Postdoc, 2007-2010, Advisor: Timothy Springer), Peking University (professor, 2010-present). The current research interest focuses on chemical glycobiology. Some of recent awards include Zhang Shuzheng Award for Outstanding Achievements in Glycoscience (2021), ACS Horace S. Isbell Award (2021), Xplore Prize (2010), Tan Kah Kee Young Scientist Award (2020), CCS-RSC Young Chemist Award (2018), and ACS David Y. Gin New Investigator Award (2016).