Name: Raymond Chien
PI Name: Ying-Xian Pan

Email: rc1268@njms.rutgers.edu
PI Email: yx.pan@rutgers.edu

Investigating the Molecular Mechanisms Underlying Morphine Tolerance Using Tandem Mass Tag-Based Phosphoproteomics/Proteomics

Raymond Chien[1], Ayma F. Malik[1], Jin Xu[1], Guoan Zhang[2], Ying-Xian Pan[1]

[1]Department of Anesthesiology, Rutgers New Jersey Medical School, Newark, NJ, 07103;
[2]Protomics and metabolomics Core Facility, Weill Cornell Medicine, New York, NY 10021 USA

Mu opioids, including morphine, fentanyl, and oxycodone, remain in the mainstream for moderate-to-severe pain management in the clinic despite their adverse side-effects. Particularly, mu opioid tolerance can promote other adverse effects, such as addiction and respiratory depression, which significantly contribute to the development of opioid use disorder, a main cause of the worldwide opioid epidemic and opioid overdose deaths. However, molecular mechanisms, especially at the posttranslational level, underlying mu opioid tolerance remain exclusive. In the current study, we developed a long-term morphine tolerance model with twice daily administration (10 mg/kg, subcutaneously) for 6 weeks in C57BL/6J (B6) male mice. The results revealed that morphine tolerance increased in a linear fashion over the first 3 weeks and was sustained with a slight decrease as continuous dosing after 3 weeks, a scenario that reconciles clinical observation that with extended dosing, morphine tolerance is progressively developed at the beginning and then stabilized for a relatively long time in cancer patients. Using tandem mass tag-based phosphoproteomics proteomics, we unbiasedly mapped morphine-induced changes of global protein phosphorylation in five brain regions under this morphine tolerance paradigm. Our results showed that morphine can induce changes of many phosphoproteins, some of which were time-dependent or region-specific. Pathway analysis of the differentially expressed phosphoproteins showed many shared and unique signaling pathways and identified several upstream regulators or key molecular targets, such as protein kinases and ion channels, which likely are the casual factors for morphine tolerance. These results provide novel insights on the molecular mechanisms of morphine tolerance.