

Title: Multipronged Quantitative Proteomics Analyses Indicate Alterations in Kinase Activities as Potential Targets for Circadian Period Altering Drugs in Mammalian Cells

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Drugs or small molecules, which are capable of modulating circadian rhythms, could be useful in developing therapeutic approaches directed towards diverse types of human diseases associated with circadian dysfunctions. In this study, we carried out comprehensive global proteome, phospho proteome, thermal proteome and kinome profilings to decipher the molecular targets of seven potential circadian period modulating drugs in the human osteosarcoma (U2OS) cell line – a robust and well-characterized circadian model system. Luminescence rhythms of Per2-dluc cells indicated that Longdaysin drastically lengthened circadian period. Roscovitine, Purvalanol A, and SP600125 also introduced increase in period length, while treatment with Chir99021, 1-Azakenpaullone, and Indirubin-3′ oxime resulted shorter circadian periods. Intriguingly, differential proteomics analysis revealed increased expressions of kinase inhibitors and reduced levels of cyclin-dependent and other kinases (GSK-3β, JNK and Casein kinases) after treatment with these drugs, which were validated further by kinase enrichment assays. An integrated phosphoproteomics analysis indicated altered phosphorylation levels of several proteins associated with diverse signalling pathways and circadian rhythmicity. Importantly, thermal proteome profiling revealed direct binding of some of these drugs with clock regulatory kinases and their modulators. Our findings reveal that these compounds modulate circadian period through inhibition of multiple kinases and phosphorylation-dependent ubiquitination. We anticipate that this comprehensive study will contribute towards a better understanding of the mechanism of actions of these circadian period altering drugs. This is critical in clearly defining molecular targets in order to modulate daily rhythms for therapeutic benefits.

Biography

Dr. Sandipan Ray is a research associate at the Institute of Neurology, University College London and a visiting scientist at The Francis Crick Institute, UK. He obtained his PhD degree from Indian Institute of Technology Bombay, India. He has substantial expertise in cutting-edge integrated multi-omics research with versatile technical and big-data analysis skills. He has published more than forty peer-reviewed research and review articles in reputed journals and serves as a peer reviewer for several international journals. He is a member of multiple scientific organizations including American Society of Tropical Medicine and Hygiene (ASTMH), Human Proteome Organization (HUPO), and US HUPO.

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