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A FRAMEWORK FOR IDENTIFYING DYSREGULATED CHROMATIN REGULATORS AS MASTER REGULATORS IN HUMAN CANCER

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Chromatin regulators (CRs) are frequently dysregulated to reprogram the epigenetic landscape of the cancer genome. However, the underpinnings of the dysregulation of CRs and their downstream effectors remain to be elucidated. Here, we designed an integrated framework based on multi-omics data to identify candidate master regulator CRs affected by genomic alterations across eight cancer types in The Cancer Genome Atlas. Most of them showed consistent activated or repressed (i.e., oncogenic or tumor-suppressive) roles in cancer initiation and progression. In order to further explore the insight mechanism of the dysregulated CRs, we also developed an R package ModReg based on differential connectivity to recognize CRs as modulators of the transcription factors (TFs) involved in tumorigenesis. Our analysis revealed that the connectivity between TFs and their target genes tended to be disrupted in the patients who had a high expression of oncogenic CRs or low expression of tumor-suppressive CRs. As a proof-of-principle study, 14 (82.4%) of the top ranked 17 driver CRs in liver cancer were validated by literature mining or experiments including shRNA knockdown and dCas9 epigenetic editing. Moreover, we confirmed that chromatin regulator SIRT7 physically interacted with transcription factor NFE2L2, and positively modulated the transcriptional program of NFE2L2 by affecting ~64% of its targets.

Biography

Jiangwen Zhang has graduated from Johns Hopkins University with PhD. He has worked at Harvard University Genome Center as Senior System Biologist for years before joining University of Hong Kong in 2013. He has broad interest in Genetic and Epigenetic Regulation in Development and Diseases. Currently, his lab is focusing on epigenetic regulation of tumorigenesis. His lab employs high through-put Omics assays and large scale computation to dissect the gene regulatory network and signalling pathways involved in oncogenesis.

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