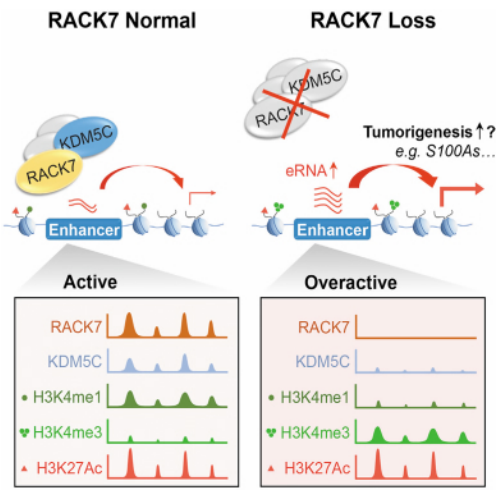
Suppression of enhancer overactivation by RACK7 and KDM5C

Enhancers are important regulatory elements in controlling gene expression, and their activities are properly regulated to ensure normal development and differentiation. Recent cancer genome sequencing projects have identified frequent mutations of enhancer regulators, indicating dysregulation of enhancers may lead to detrimental consequences. New findings from the group led by Dr. Lan Fei (蓝斐) and Dr. Shi Yang from Fudan University revealed a previously underappreciated "overactivation state" of enhancers and a regulatory chromatin complex that suppresses the state. This study was recently published in *Cell* (April 7, 2016, 165: 331—342).

Like "power switches", enhancers set gene transcription at different levels. Four enhancer states marked by different epigenetics modifications have been reported: silent state (OFF, no histone modification and likely with DNA methylation), poised state (pending on additional signal to be ON or OFF, H3K4me1 and H3K27me3), primed state (ready to be ON, H3K4me1), and active state (ON, H3K4me1 and H3K27Ac). A number of epigenetics enzymes and reader proteins work together to regulate the transition among these states. However, after activation, whether enhancers are subjected to further regulation remains unclear. In this study, the authors showed that active enhancers marked by H3K4me1 and H3K27Ac can be further tri-methylated at histone H3K4 residue (H3K4me3), which together with H3K27Ac, marks an overactive state of enhancers. Interesting, a chromatin surveillance system, containing RACK7 (aka ZMYND8, a putative histone modification reader) and KDM5C (a H3K4me3 demethylase), is in charge of tuning down the "volume" of the overactivated enhancer. In cells, the RACK7 interacts with and recruits KDM5C to thousands of active enhancers, and then KDM5C trims two methyl groups from histone H3K4 residue (H3K4me3 to H3K4me1) keeping enhancer activity at the normal level. When the regulation is impaired, a large set ofH3K4me3 marked enhancers arises, accompanied by robust enhancer RNA (eRNA) and further activation of downstream genes. Based on the results, the authors proposed that enhancers with H3K4me3 and H3K27Ac are in an overactivation state.

On the biology side, RACK7-KDM5C complex exerts tumor-suppressive function in part by repressing S100A oncogenes. Loss of RACK7 or KDM5C in ZR-75-30 cells resulted in various cancer phenotypes, including tumor growth and enhanced invasion and migration. Inhibition of S100A in RACK7 KO cells partially reversed the cancer phenotypes. Consistently, RACK7 and KDM5C inactivating mutations have been frequently found in various cancers, and RACK7 levels in tumors anti-correlate with malignancies.



This study provides new sights of enhancer regulation and the connections to cancer. The important questions that remain to answer are how RACK7 is directed to its target enhancers, what the tri-methyltransferase(s) for the overactivated enhancers is, as well as whether the cancer phenotypes resulted from RACK7 or KDM5C mutations could be reversed by pharmacological inhibition of the improperly overactivated enhancers.

Lan Fei was supported by the "Thousand Youth Talents" and grants from NSFC, "973" Program and ISTC. Shi Yang was partly supported by the NIH and Boston Children's Hospital funds.

?1994-2018 China Academic Journal Electronic Publishing House. All rights reserved. http://www.cnki.net