B·DEBATE International Center for Scientific Debate BARCELONA

CRG Centre for Genomic Regulation

ALI SHILATIFARD

CV

PARTICIPANT AT:

CODING AND NON-CODING FUNCTIONS OF THE GENOME
BARCELONA CONFERENCE ON EPIGENETICS AND CANCER

October, 29th-30th, 2015, Barcelona

Ali Shilatifard, Professor in Biochemistry and Molecular Genetics at Northwestern University, Chicago, USA

Dr. Ali Shilatifard is a biochemist/molecular biologist with an immense interest in understanding the molecular mechanism of the regulation of gene expression. As a Jane Coffin Childs postdoctoral fellow, Shilatifard made a seminal contribution to the field of leukemia biology by identifying the first function of any of the MLL translocation partners. Shilatifard identified ELL as a RNA Polymerase II (Pol II) elongation factor. Since its inception in 1997, the central theme in the Shilatifard laboratory has been the identification of the molecular properties of both MLL and ELL and why their translocations result in leukemogenesis. ELL is the first and best molecularly and biochemically characterized MLL partner in leukemia. In addition to his studies on ELL, within the past 15 years, Shilatifard's laboratory identified the yeast homologue of MLL, the Set1 protein in a complex named COMPASS, capable of methylating histone H3K4. Based on these fundamental yeast studies, we now know that MLL is also found in a COMPASS-like complex functioning as an H3K4 methylase. Shilatifard's laboratory also identified and demonstrated that many of the MLL partners in leukemia are found with ELL within the Super Elongation Complex (SEC) regulating the transcription of the MLL-chimera target genes. Most recently, Shilatifard's laboratory has demonstrated that Pol II elongation factors play a diverse role in regulating gene expression including the marking of both poised and inactive enhancers in the embryonic state and in the priming of future developmental gene expression patterns. Dr. Shilatifard has been recognized and funded by the Leukemia and Lymphoma Society, the American Cancer Society, and through three grants from the National Institutes of Health, and recently was selected as the inaugural recipient of the Outstanding Investigator Award from the National Cancer Institute. He serves as a Senior Editor for the journal Science, a Deputy Editor for Science Advances, Editor for Molecular and Cellular Biology, and also serves on the Scientific Advisory Boards of Genentech, the Max Planck Society, and Cell Signaling Technology.

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ABSTRACT

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Enhancer Malfunction in Cancer

Why certain point mutations in a general transcription factor are associated with specific forms of cancer has been a major question in cancer biology. If enhancers are the reason that there are multicellular organisms, then recent studies suggest that enhancer malfunction through point mutations in either the regulatory elements or the factors modulating enhancer-promoter communication could be the cause of tissue-specific cancer development. I will discuss recent findings in regards to the identification of cancer-related enhancer mutations and the role of Drosophila Trr and its human homologues, the MLL3- and MLL4/COMPASS-like complexes, as enhancer histone H3 lysine 4 (H3K4) monomethyltransferases functioning in enhancer-promoter communication. Recent genome-wide studies in the cataloguing of somatic mutations in cancer have identified mutations in intergenic sequences encoding regulatory elements, and in MLL3 and MLL4, in both hematological malignancies and solid tumors. We have proposed that cancer-associated mutations in MLL3 and MLL4 exert their properties through the malfunction of Trr/ MLL3/MLL4-dependent enhancers. I will also discuss recent findings from our laboratory regarding the role of chromatin and chromatin modifiers in enhancer-promoter communication in development and during disease pathogenesis.

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