A higher-order configuration of the heterodimeric DOT1L-AF10 coiled-coil domains potentiates their leukemogenenic activity

Xiaosheng Song, Liuliu Yang, Yue Gu, Mingzhu Wang, Buqing Ye, Zusen Fan, Rui-Ming Xu* & Na Yang*[$]

[$]State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin 300353, China. Contact information: yangnaNKU@nankai.edu.cn

Chromosomal translocations of *MLL1* (Mixed Lineage Leukemia 1) yield oncogenic chimeric proteins containing the N-terminal portion of MLL1 fused with distinct partners. The MLL1-AF10 fusion causes leukemia through recruiting the H3K79 histone methyltransferase hDOT1L via AF10's octapeptide and leucine zipper (OM-LZ) motifs. Yet the precise interaction sites in hDOT1L, detailed interaction modes between AF10 and hDOT1L, and the functional configuration of MLL1-AF10 in leukeomogenesis remain unknown. Through a combined approach of structural and functional analyses, we found that the LZ domain of AF10 interacts with coiled-coil domains through a conserved binding mode, and discovered that the C-terminal end of the LZ domain and the OM domain of AF10 mediate the formation of a DOT1L-AF10 octamer via tetramerization of the binary complex. We reveal that the oligomerization ability of the DOT1L-AF10 complex is essential for MLL1-AF10's leukemogenic function. These findings provide new insights into the molecular basis of pathogenesis by MLL1 rearrangements.