Computing the Role of Splicing Dysregulation by SF3B1-SUGP1-DHX15 Axis in Human Cancer

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Aberrations in mRNA splicing contribute to neoplastic transformation, tumor progression and therapeutic resistance. Although mutations in the splicing factor SF3B1 are frequent in cancers, their functional effects and regulatory mechanism are poorly understood. Here, we identify that SF3B1 mutations in CLL alter splicing of a specific subunit of the PP2A to confer post-translational MYC and BCL2 activation. In addition, SF3B1 mutations in breast cancer induce a recurrent pattern of aberrant splicing leading to activation of AKT and NF-kB, enhanced cell migration, and accelerated tumorigenesis. As well, we found MAP3K7 mis-splicing leads to the anemia characteristic of SF3B1-mutated MDS by affecting terminal erythroid differentiation. Moreover, we revealed a critical role for the spliceosomal protein SUGP1 in wild-type SF3B1 splicing. Pan-cancer analyses identified SUGP1 mutations induced use of cryptic 3'ss similar to mutant SF3B1 aberrant splicing. Finally, structural modeling of a trimeric protein complex reveals that the SUGP1-SF3B1 interaction “loops out” the SUGP1 G-patch domain, facilitating its activating interaction with another helicase DHX15. Our study thus provides an unprecedented molecular view of a protein complex essential for accurate 3’ splicing, and reveals that numerous cancer-associated mutations all disrupt the critical SUGP1-SF3B1 interaction.