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651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Multi-Level Control of Myeloma Cell Proliferation and Genomic Instability By the PDZ Binding Kinase (PBK)

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Genomic instability and cell proliferation play important roles in the development and progression of cancer. We identified a six-gene kinase signature that correlated with overall genomic instability in multiple human cancers including multiple myeloma (MM). PDZ Binding Kinase (PBK) was one of the top kinases in this signature. Inhibiting PBK downregulated E2F and FOXM1-related pathways and impacted several members of the DREAM complex, which represses cell cycle genes during quiescence. We further evaluated whether PBK affects entry into mitosis by controlling FOXM1 phosphorylation and affects genome stability.

Using co-immunoprecipitation and chromatin immunoprecipitation assays, we observed that PBK binds to and phosphorylates FOXM1, leading to upregulation of FOXM1 target genes. Overexpression of PBK increased the association of LIN54 (a major component of the MuvB complex) with phosphorylated-FOXM1 and inhibited LIN54 interaction with E2F4 in the DREAM complex. Consistently, PBK knockdown or inhibitor increased the LIN54-E2F4 interaction and inhibited the LIN54 and phosphorylated-FOXM1 interaction. The inhibitor also impaired tumor growth in vitro and significantly increased the efficacy of a chemotherapeutic agent ($P = 0.0011$) in a subcutaneous mouse model of MM. Overall, these data indicate that PBK phosphorylates FOXM1, then FOXM1 interacts with MuvB which is associated with the start of mitosis, dissociating it from E2F4 in the DREAM complex, thus allowing entry into mitosis and subsequent tumor growth.

Given that phosphorylation of FOXM1 also activates the expression of major DNA repair genes (including *RAD51*, *EXO1*), we investigated whether PBK affects genome stability. Surprisingly, we observed that PBK also directly phosphorylates DNA repair/HR genes, such as flap structure-specific nuclease 1 (FEN1), and that PBK inhibition reduces spontaneous and chemotherapy (melphalan)-induced genomic instability ($P < 0.05$). A significant upregulation of PBK has also been observed in MM patient samples at relapse (after melphalan treatment) relative to paired samples collected at diagnosis (GSE19554). To further investigate the consequences of elevated PBK *in vivo*, we transformed the normalized PBK expression into a Z-score and used this to divide patients (in MMRF-COMPASS) into three groups based on PBK expression (i.e., high, medium and low PBK expression groups). Patients with high PBK expression had poor overall survival as compared to those with medium and low PBK expression (P=1.127e−13). DNA replication, mismatch repair, homologous recombination, cell cycle and Fanconi anemia were the top upregulated pathways in patients with high PBK expression. Known drivers of DNA replication, including those involved in the initiation of once-per-cell cycle replication and several DNA repair and HR genes, which are part of different genomic instability signatures (such as RAD51, RAD51C, RAD54B, RAD54L, EXO1, BRCA1, FEN1, ATAD2, CENPA, MAD2L1, TTK), were significantly overexpressed in patients with high PBK expression. Interestingly, FOXM1, which can impact both replication and genome stability was also overexpressed (Log2 Fold change of 1.8; P adj = 1.27E-86).

In summary, we demonstrate that PBK drives DNA replication and genomic instability in MM cells by acting at multiple levels. Therefore, PBK inhibitors investigated here have the potential to impair growth and increase the efficacy of chemotherapeutic agents while reducing spontaneous as well as chemotherapeutic agent-induced genomic instability in MM.

Disclosures No relevant conflicts of interest to declare.

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