Development of Selective MIZ-1 BTB Domain Inhibitors Targeting HUWE1 E3 Ligase in MYC-Driven Cancers

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Cancer is one of the deadliest diseases around the globe. It has been shown that more than 50% of cancer cases have an overexpression of the MYC oncogene. The main challenge in these cancers is that the MYC oncogene is undruggable. Therefore, targeting the protein repressor of MYC, which is MIZ1, could be a valuable approach in personalized medicine. Thus, the main objective of this study is to prevent the interaction between the MIZ1 BTB domain and the HUWE1 E3 ligase to keep the physiological regulation of the MYC oncogene. To achieve this objective, plasmids containing the MIZ1 transcription factor were transformed into E.coli bacterial cells. After that, the proteins were purified through affinity chromatography and size exclusion chromatography. Then the composition was checked through SDS PAGE and NMR spectroscopy. Finally, the interactions between MIZ1 with HUWE1 WT and mutated peptides were investigated through ITC, DSF, and CD spectroscopy. The findings showed that single amino acid mutations of the HUWE1 peptide have a higher binding affinity than the HUWE1 WT, which indicate that these amino acid residues have a higher effect in the binding. This means that it is possible to prevent the degradation of MIZ1 by using these results to synthesize novel small molecule inhibitors that occupy the protein's binding site. Consequently, the HUWE1 ligase would not bind to MIZ1 and the regulation of the MYC oncogene is restored.

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