Mutation in MCL1 predicted loop to helix structural transition stabilizes MCL1-Bax binding interaction favoring cancer cell survival

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Abstract

Myeloid cell leukemia-1 (MCL1), an anti-apoptotic BCL-2 family protein plays a major role in the control of apoptosis as the regulator of mitochondrial permeability which is deregulated in various solid and hematological malignancies. Interaction of the executioner proteins Bak/Bax with anti-apoptotic MCL1 and its cellular composition determines the apoptotic or survival pathway. This study highlighted the deleterious MCL1-Bax stabilizing effect of the mutation V220F on MCL1 structure through computational protein-protein interaction predictions and molecular dynamics simulations. The single point mutation at V220F was selected as it is residing at the hydrophobic core region of BH3 conserved domain, the site of Bax binding. The molecular dynamics simulation studies showed increase in stability of the mutated MCL1 before and after Bax binding comparable with the native MCL1. The clusters from free energy landscape found out structural variation in folding pattern with additional helix near the BH3 domain in the mutated structure. This loop to helix structural change in the mutated complex favored stable interaction of the complex and also induced Bax conformational change. Moreover, molecular mechanics based binding free energy calculations confirmed increased affinity of Bax towards mutated MCL1. Residue-wise interaction network analysis showed the individual residues in Bax binding responsible for the change in stability and interaction due to the protein mutation. In conclusion, the overall findings from the study reveal that the presence of V220F mutation on MCL1 is responsible for the structural confirmational change leading to disruption of its biological functions which might be responsible for tumorigenesis. The mutation could possibly be used as future diagnostic markers in treating cancers.

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