In silico investigation of nonsynonymous single nucleotide polymorphisms in *BCL2* apoptosis regulator gene to design novel protein-based drugs against cancer

https://doi.org/10.1002/jcb.30330

Abstract:

BCL2 apoptosis regulator gene encodes Bcl-2 pro-survival protein, which plays an important role to evade apoptosis in various cancers. Moreover, single nucleotide polymorphisms (SNPs) in the *BCL2* gene can be nonsynonymous (nsSNPs), which might affect the protein stability and probably its function. Therefore, we implement cutting-edge computational techniques based on the Spherical Polar Fourier and Monte-Carlo algorithms to investigate the impact of these SNPs on the B cell lymphoma-2 (Bcl-2) stability and therapeutic potential of protein-based molecules to inhibit this protein. As a result, we identified two nsSNPs (Q118R and R129C) to be deleterious and highly conserved, having a negative effect on protein stability. Additionally, molecular docking and molecular dynamics simulations confirmed the decreased binding affinity of mutated Bcl-2 variants to bind three-helix bundle protein inhibitor as these mutations occurred in the protein−protein binding site. Overall, this computational approach investigating nsSNPs provides a useful basis for designing novel molecules to inhibit Bcl-2 pro-survival pathway in malignant cells.

KEYWORDS

Bcl-2 apoptosis regulator, cancer, molecular dynamics, nonsynonymous single nucleotide polymorphisms, posttranslational modifications, protein-based inhibitors.