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Molecular dynamics simulation on the low sensitivity of Y352H, I310N mutants of NEDD8-activating enzyme (NAE) for MLN4924 inhibitor as a cancer drug

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MLN4924 is a experimental cancer drug that inhibits the NEDD8-activating enzyme (NAE). This anti-tumor candidate, which is a small-molecule selective inhibitor of NAE, is conjugated to cullin protein on Cullin-RING ligases (CRLs). This covalent modification activates cullin complex to recruit an ubiquitin-charged E2 and leads to downstream target protein polyubiquitination and proteasomal degradation. MLN4924, which can form a covalent adduct with NEDD8, and block NAE at the first step in this pathway, has shown anti-tumor activity in many kinds of cancer cell lines and xenograft models, including lung cancer, colon cancer, melanoma and lymphoma. The anti-tumor activity of MLN4924 results from inactivation of CLRs, which causes DNA re-replication and inhibition of nuclear factor (NF)- κ B signaling, thus leading to cancer cell death. A mutation can reduce the enzyme's sensitivity for MLN4924. Verma et al. in 2013 studied on molecular dynamics simulation of a mutant A171T and consequently found out that this mutation reduce MLN4924 interaction with DNA Binding site of enzyme as a result of reduction of enzyme affinity to ATP. A year later, in 2014, Wei Xu et al. carried out a research on inhibitor resistant cell lines and revealed that a couple of mutations so called Y352H and I310N leads to enzyme resistance to MLN4924 inhibitor, interestingly, the cause reported was the increase of enzyme affinity to ATP. Whereas; in Wei Xu et al experiment the molecular dynamics simulation was not considered, this study is conducted to identify mutation mechanism in enzyme using Gromacs software.

Key words : MLN4924 , NEDD8-activating enzyme (NAE), Y352H, I310N, Mutation, Drug Discoveries

Biography

Experienced biotechnologist with certifications, 4.5 years experience as a senior Microbiologist and Specialty Service Director of Iranian Biological Resource Center (IBRC) under the authority of Academic Center for Education, Culture and Research (ACECR) and additional 5 years working as Microbiology technologist at medical laboratory in addition to premier research background and a MSc. degree in Microbiology from Karaj Islamic Azad University (IAU).

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