Abstract

MDM2 is a key regulatory partner of p53 protein, a tumour suppressor protein that facilitates the cancer cell death via apoptosis. Intracellular levels of both the proteins are tightly regulated via a negative feedback loop. MDM2 overexpression causes degradation of p53 which is linked to several human cancer diseases including sarcoma, glioblastoma, breast carcinoma, melanoma, and leukemia. Several small molecules are being developed to inhibit the interactions between p53 and MDM2. However, previous studies suggest occurrence of G-quadruplex in the promoter as an alternative anti-tumour therapy due to the comparative advantage over protein targets. The present study verifies the G-quadruplex formation in the P2 promoter of the MDM2 using in silico and in vitro methods. We use QGRS Mapper tool to predict the quadruplex forming sequences. We perform circular dichroism spectroscopy and polymerase stop assay to verify the G-quadruplex formation, and fluorescence displacement assay to evaluate the G-quadruplex ligand affinity. We found a G-quadruplex forming sequence between -414 to -390 with a G-score of 108. The G-quadruplex structures conforms to anti-parallel topology. The Ligands stabilize G-quadruplex structure which then impedes the Taq DNA polymerase movement. We found TMPyP4 as a better stabilizing ligand than Quarfloxin. The present study suggests MDM2 quadruplex as a novel therapeutic target for cancer diseases involving MDM2 overexpression.