2P05

Study the interaction of p53 with viral oncoprotein LTag, a UA-QCMD approach.

○Shah Rauf[1], Ai Suzuki[2], Hideyuki Tsuboi[1], Nozomu Hatakeyama[1], Akira Endou[1], Hiromitsu Takaba[1], Momoji Kubo[1] and Akira Miyamoto[2, 1]

[1]Grad. Sch. Eng., Tohoku Univ. (6-6-11-1302 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)
[2]NICHe, Tohoku Univ. (6-6-11-1302 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)

【Introduction】

The transformation potential of Simian Virus 40 depends on the activities of large T-antigen (LTag), which interacts with several cellular tumor suppressors including p53. Inhibition of p53 function by LTag is necessary for both efficient viral replication and cellular transformation. We have studied the molecular basis of p53 inhibition by LTag analyzing the protein protein interaction by ultra accelerated quantum chemical molecular dynamics.

【Method】

Our novel UA-QCMD simulator consists of two parts. The first part is our tight-binding (TB) New-Colors and second part is classical molecular dynamics (MD) New-Ryudo program. New-Colors is used for single point quantum calculation which provides the charge and morse potentials. MD simulation with charge and morse potentials obtained from TB calculation is termed as ultra accelerated quantum chemical molecular dynamics, which is 10000000 times faster than the conventional first-principals method and suitable for larger system like protein and DNA.

【Results and discussion】

After QCMD in LTag-p53 interaction (Fig 1) H41 of guanidinium group of ARG280 form hydrogen bond with backbone oxygen O131 of ASP604. The bond distance is 1.75 Å and bond energy is –5.58 kcal/mol. H36 of guanidinium group of ARG280 is hydrogen bonded with side chain oxygen O126 of ASP604. The bond distance is 1.67 Å and bond energy is –8.99 kcal/mol. H37 of guanidinium group of ARG273 is hydrogen bonded with side chain oxygenO130 of ASP604. The bond distance is 1.75 Å and bond energy is –5.68 kcal/mol. H31 of the guanidinium group of ARG273 is hydrogen bonded with O130 of ASP604. The bond distance is 1.79 Å and bond energy is –5.51 kcal/mol. H23 of the N239 is hydrogen bonded with side chain oxygen O124 of GLU601. The bond distance is 1.62 Å and bond energy is –8.49 kcal/mol. Charge of the hydrogen and oxygen atoms, which take part in hydrogen bonding, is redistributed during interaction, as they are significantly different than that are calculated separately in LTag and p53. Our results showed that LTag has strong interaction through ASP604 with ARG273 and ARG280 of p53. ARG273 and ARG280 are the DNA binding residues. They interact with T12 and G13 bases of the DNA and mutations of ARG273 and ARG280 residues induced interaction loss with DNA and are frequently found in many human cancers. Interaction of ARG273 and ARG280 of p53 with ASP604 and GLU601 of LTag interfere p53 to interact with DNA. In conclusion we can say LTag block these DNA binding residues and as a result p53 cannot interacts with DNA and cannot transcript regulatory genes. Ultimately leading to the loss of p53 function and simian virus taking control over cellular transformation.

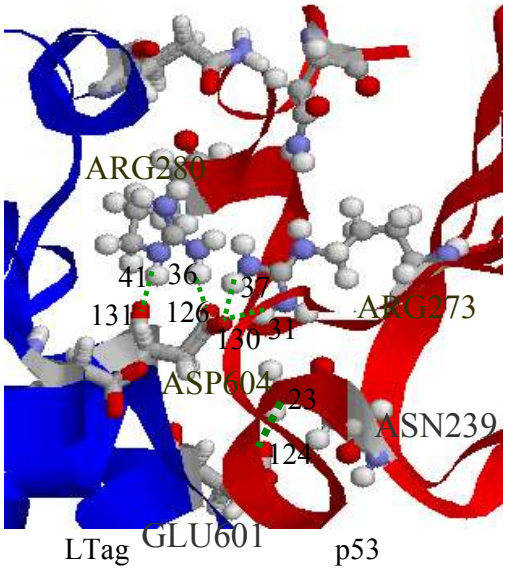

Fig.1 Interaction of LTag with p53 after QCMD calculation. Hydrogen bonds are represented by dash line.