1P20

Study on small-molecule inhibitor of the p53 suppressor HDM2 using ultra accelerated quantum chemical molecular dynamics

○Shah Rauf[1], Ai Suzuki[2], Riadh Sahnoun[1], Michihisa Koyama[1], Hideyuki Tsuboi[1], Nozomu Hatakeyama[1], Akira Endou[1], Hiromitsu Takaba[1], Carlos A. Del Carpio[1], Ramesh C. Deca[2], Momoji Kubo[3], 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. (6-6-10 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)
[3]FRI, Grad. Sch. Eng., Tohoku Univ. (6-6-11-701 Aoba, Aramaki, Aoba-ku, Sendai 980-579)

[Introduction]

The mouse double minute protein2 (MDM2) also known as for humans is widely known due to its biological role as a negative regulator of the tumor suppressor activity of p53 protein. The binds o the HDM2 tumor suppressor protein p53 and increases its degradation thus blocking the transcriptional activity of p53 thus results in tumor suppressor. Targeting the interfaces between proteins has huge therapeutic potential, but discovering small-molecule drugs that disrupts protein protein interactions is an enormous challenge. We have studied one small molecule Nutlin by quantum chemical molecular dynamics simulation to see how it mimics the p53 and acts as anticancer drug. According to our result the Nutlin-3 interacts with the p53 binding sits Q72 and V93, which may be more favorable than the interaction of p53 with the HDM2.

[Methods]

We have developed ultra accelerated quantum chemical molecular dynamics program, which is the combination of two programs: New-Colors and New-Ryudo. New-Colors are used for single point quantum calculation. New-Ryudo is used for dynamics calculation. Combination of two programs is used for quantum chemical molecular dynamics simulation, which is 10000000 times faster than the conventional first principal method. We used the program to study the protein-protein and protein drug interaction at quantum point of view.

[Results and Discussion]

In this study we use one of the compound Nutlin-3 and study the interaction with p53 binding pocket of HDM2 protein. According to our result the compound forms hydrogen bonds to O72 and V93 of HDM2 protein (Fig. 1), which may be more stable than thep53-HDM2 interaction, thus mimics the natural interactions of p53 with HDM2. in comparison with p53-MDM2 interaction. The compound forms hydrogen bonds to Q72 and V93, (fig. 1) which may mimics the natural interactions of p53 with MDM2. The binding energy between H of Nutlin-3 and O of HDM2 is calculated -4.08 kcal/mol and charge of H is 0.0583 and O is –0.7244 respectively. Whereas binding energy between H of HDM2 and O of Nutlin-3 is –5.87 kcal/mol and charge of H is 0.0764 and the O is –0.4895 respectively. More result will be shown in the presentation.

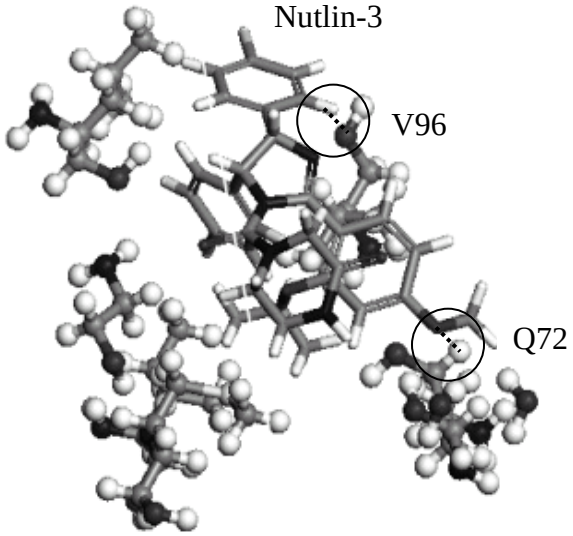

Fig. 1 Interaction site of Nutlin-3 (stick) with HDM2 (ball and stick). Hydrogen atoms are colored white and oxygen atoms are black in the circle.