Revealing the complex formation/deformation process of anti-tumor suppressor p53 protein complexes in functioning

Duy Tran[1], Akio Kitao[1]
[1] School of Life Science and Technology, Tokyo Institute of Technology, Japan

p53 protein is considered a flexible protein hub in which it is involved in multiple cellular process such as autophagy, cell-cycle arrest, DNA repair, Metabolism antioxidant… In this presentation, we would like to report our recent results on the question that how p53 adapt its conformation to interact with variety biomolecular partners by using enhanced sampling method so-called PaCS-MD. Those include MDM2 (an inhibitor of p53), DNA (for DNA repair), S100B (down-regulator of p53).

1. We have carried out the a/dPaCS-MD [1] to unveil the full picture of complex formation/ deformation of p53 with MDM2 and S100B proteins. Those proteins directly bind to p53 in N-terminal and C-terminal respectively. p53 exhibits the intrinsically disordered property during the complex formation/deformation from non-structural state to structural state.

2. We have carried out the dPaCS-MD to unveil the complex deformation of p53 from its complex with DNA. This process provides the needed step in DNA scanning and repair process. We found that instead of steadily dissociating all p53 monomers at the same time, the p53 dissociates monomer by monomer depending on the DNA sequence they bind to.

3. Perturbing of binding mode of p53 with inhibitor MDM2 by EGCG (compound in tea). We have carried out the high concentration simulation of p53/MDM2 with high concentration of EGCG. We found that the EGCG tentatively hijacks the key interactions of p53/MDM2 complex and lessen the binding affinity of the complex. This gives a hint of answer to the question of aging effect of tea.

Reference

[1] Duy Tran, Akio Kitao, JCTC 16, 2835 (2020)