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Computational study on halogen bonding interaction of MDM2 inhibitors

Yujing Zhou and **Ming Wah Wong**
National University of Singapore, Singapore

p53, as "guardian of the genome", plays a very important role in cells. It acts as a transcription factor and more importantly as a tumor suppressor protein. High level of wild-type p53 shows growth-inhibitory properties. The level of p53 in cells is negatively regulated by MDM2 via an auto regulatory feedback loop. However, in many tumor cells, MDM2 is overexpressed and highly impair the function of p53 to suppress tumor. Thus design and development of effective inhibitors to block p53 and MDM2 interactions offer a novel strategy to conquer cancer. Since most of the research up to now lacks the understanding of the nature chemistry of the binding, this study is focused on better understanding the chemistry of the interaction between MDM2 and its inhibitors, especially the halogen bonding interaction. From our docking studies of ligand RG7112, a nutlin derivative inhibitor for MDM2 in clinical trial phase one, using the Molecular Operating Environment, a group of key residues, Lys51, Phe55, Gly58, Tyr67, Val93 and His96, were identified to serve as pharmacophore and provides useful information for future design and optimization of potent ligands. Among the key residues, His96 was observed to provide two important interactions, which are halogen bonding between phenyl-chloride atom and His96 backbone oxygen atom, and CH-π interaction between the phenyl ring and His96 histidine ring. From the comparison docking of a group of chlorinated and non-chlorinated MDM2 ligands, the docking scores were shown to be better for chlorinated inhibitors than non-chlorinated. In addition, the docking poses of all non-chlorinated inhibitors solidified our hypothesis, as for non-chlorinated ligands, the binding towards receptor were quite loose, and the inhibitors may not even be maintained in the pocket region. Furthermore, a set of docking studies of chlorinated, brominated and iodinated RG7112 fragments was done. Space filling model of the best poses showed close contact between inhibitors and His96 groups, with distance between halogen atoms and His96 oxygen 3.6-4Å, with a score following halogen bonding strength trend I>Br>Cl, In addition, the phenyl rings of the inhibitors and the His96 histidine ring were identified in a good orientation to form CH-π interaction which may also contribute to the binding efficiency, and this finding prove by a set of docking for non-benzyl RG7112 fragments, showing that without the phenyl rings, the inhibitors were still bounded within the pocket region, but would not be deep enough into the pocket and with worse docking scores. Thus we may make the conclusion that the halogen bonding between the phenyl-halogen atoms and His96 backbone oxygen helps the ligands bind to the pockets, and the CH-π interaction between phenyl rings and His96 histidine ring helps to refine the pose orientation, to produce tighter binding. The two key interactions above contribute together and are critical for the binding of ligands towards MDM2 receptor.

a0047225@nus.edu.sg