Structural basis for the functional regulation of an orphan nuclear receptor

With the support from the National Natural Science Foundation of China, Professors Lin Tianwei and Wu Qiao from the School of Life Sciences, Xiamen University, provided structural insights into the functional regulation of orphan nuclear receptor Nur77 (aka TR3) by chemical compounds, which was reported in *Nature Chemical Biology* (2012, 8(11): 897—904) and *Nature Chemical Biology* (2014, 10(2): 133—140).

Nuclear receptors are essential regulators in the higher eukaryotic cells. These multi-functional transcription factors are typically regulated by physiological ligands, such as hormones. Yet for those so-called orphan nuclear receptors, not only there is no physiological ligand identified up to date, their pockets for binding the ligands were non-existent. A better understanding on the physiological roles of orphan nuclear receptors would be attained by deciphering the molecular mechanism of their functional regulation.

The two groups from Xiamen University carried out the structural investigation based on the path-breaking discoveries that synthetic chemical compounds could regulate the functions of orphan nuclear receptor Nur77 in signaling pathways essential to diabetes and melanoma. It was revealed that the ligand binding domain of Nur77 (LBD) adopted at least two conformations, but only one of the conformations was amenable for binding the functional chemicals. These compounds bind to LBD in the conformation of Structure I (Figure) at sites that are distinct to the classical ligand binding pocket. As such, they can either interrupt or augment an interaction with Nur77 to launch a new molecular event that would lead to a novel biological outcome, be it a downregulation in the blood glucose level or an induction of autophgic cell death in melanoma. It was also shown that a specific function was associated with a specific site in a specific conformation and could be agonized/antagonized by a specific compound. These findings implicate that the functional regulation of orphan nuclear receptors is hinged on the conformational plasticity of LBD and provide a framework for the rational design and development of therapeutics to treat metabolic diseases and cancers.

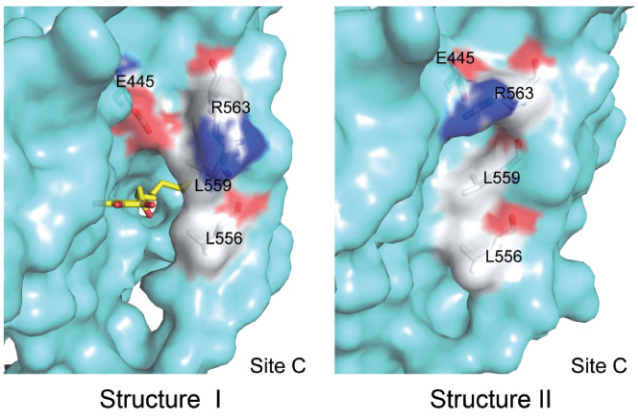

Figure A chemical compound (*yellow*) that steers the cellular fate of melanoma towards autophagic death can only bind LBD in a specific conformation in Structure I but not another conformation in Structure II. This interaction produces an amenable surface for the interaction with downstream factors to activate the autophagic signaling pathway (*Nature Chemical Biology*, 2014, 10(2): 133-140). Each compound identified up to date binds Nur77 at a unique site that is discrete from the classical pocket in typical nuclear receptors for the physiological ligands.