Poster Presentation

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The crystal structure of AhRR/ARNT complex

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Aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor, responds to xenobiotics such as dioxin and induces expression of genes involved in xenobiotic detoxication and metabolism. Upon ligand binding, AhR translocates from cytoplasm to nucleus and forms heterodimer with AhR nuclear translocator (ARNT). AhR/ARNT complex interacts with the specific DNA sequence called xenobiotic-responsive element (XRE) to activate transcription. On the other hand, AhR simultaneously induces expression of AhR repressor (AhRR). AhRR also hetrodimerizes with ARNT and interacts with XRE DNA, and thus represses the transcriptional activation of AhR. AhR, ARNT, and AhRR belong to bHLH-PAS family. It typically consists of an N-terminal basic helix-loop-helix (bHLH) domain responsible for DNA binding and tandem Per-Arnt-Sim (PAS) domains (PAS-A and PAS-B) involved in protein-protein interaction and ligand binding. In this study, we aimed to elucidate the transcriptional repression mechanism of AhRR using X-ray crystal structural analysis.
We determined the crystal structure of AhRR/ARNT heterodimeric complex at 2.5 Å resolution. We used human AhRR (bHLH–PAS-A) and bovine ARNT (bHLH–PAS-A–PAS-B) with some flexible loops deleted for crystallization. The crystal asymmetric unit contained one complex of AhRR/ARNT. Overall, AhRR and ARNT interacted with a large contact area of 6308 Å2 in a novel domain arrangement. The bHLH, PAS-A, and PAS-B domains of ARNT wrapped around AhRR PAS-A domain and the inter-domain interactions were not observed in ARNT. Hydrophobic and several electrostatic interactions contributed to the heterodimerization. Each corresponding domain between AhRR and ARNT was similar: a root-mean-square deviation were 0.8 Å and 1.6 Å for bHLH and PAS-A domains, respectively. Structural comparisons of AhRR/ARNT with HIF-2α/ARNT or CLOCK/BMAL1, the other member of bHLH-PAS family, revealed a divergent mechanism of heterodimerization in bHLH-PAS family.

Keywords: crystal structure, transcription factor, intermolecular interaction