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Watching DNA polymerases incorporate drug molecules and bypass an oxidative lesion

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DATE	**: 26 November 2015, Thursday** ***(including Q & A session)***
TIME	**: 1630 – 1800**
VENUE	**: SCM809**
LANGUAGE	**: English**
FACILITATOR	**: Dr. ZHANG Ge**

Abstract

Topic one: *Although lamivudine and emtricitabine, two L-deoxycytidine analogs, have been widely used as antiviral drugs for years, it is structurally unknown how they are bound and incorporated by any DNA polymerases or reverse transcriptases. To fill the void, we solved 12 high resolution ternary crystal structures of human DNA polymerase lambda, DNA, and L-dCTP or the triphosphates of lamivudine and emtricitabine. The structures of these 12 ternary complexes reveal that relative to natural D-dCTP in the canonical ternary structure, these L- nucleotides all have their ribose rotated by 180°. Among the four ternary complexes with a specific L-nucleotide in each asymmetric unit, two are similar and show that the L-nucleotide forms three Watson–Crick hydrogen bonds while in the remaining two similar ternary complexes, the L-nucleotide surprisingly interacts with the side chain of a conserved active site residue R517 through one or two hydrogen bonds. Our mutagenic and kinetic studies further demonstrate that the side chain of R517 is critical for L-nucleotide binding and incorporation..*

Topic two: *One common oxidative DNA lesion, 8-oxoG, is highly mutagenic in vivo due to its anti-conformation forming a Watson-Crick base pair with correct dCTP and its syn-conformation forming a Hoogsteen base pair with incorrect dATP. Here, we utilized time-resolved X-ray crystallography to follow 8-oxoG bypass by human DNA polymerase β (hPolβ). In the 12 solved structures, both Watson-Crick (anti-8-oxoG:anti-dCTP) and Hoogsteen (syn-8-oxoG:anti-dATP) base pairing were clearly visible and were maintained throughout the chemical reaction. Additionally, a third Mg(II) appeared during the process of phosphodiester bond formation and was located between the reacting α- and β-phosphates of the dNTP, suggesting its role in stabilizing reaction intermediates. Our "three-metal-mechanism" overthrows the dogma of "two-metal-mechanism" in the field of polymerases. After phosphodiester bond formation, hPolβ reopened its conformation, pyrophosphate was released, and the newly incorporated primer 3'- terminal nucleotide stacked, rather than base paired, with 8-oxoG. These structures provide the first real-time pictures of how a polymerase correctly and incorrectly bypasses a DNA lesion.*

Speaker

Dr Zucai SUO *received BS / MS degrees in the Chemistry / Physical Chemistry from Fudan University, and the Ph.D. degree in the Chemistry from Pennsylvania State University, USA, and then served as Postdoc in the Biological Chemistry from Harvard Medical School, Boston, USA. From 2007, he was an Associate Professor in the Department of Biochemistry of the Ohio State University, and then a full Professor. Since 2014, he has also been an Adjunct Professor in School of Chinese Medicine, Hong Kong Baptist University. His research area is mainly on DNA polymerases. In recent years, he published over 84 SCI journal papers in the area of DNA polymerases.*

****Welcome****