BIOGRAPHICAL SKETCH

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NAME: Gao, Yang

eRA COMMONS USER NAME (credential, e.g., agency login): YANGGA

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
University of Science and Technology of China, Hefei, Anhui	B.S.	05/2007	Life Science
Iowa State University, Ames, IA	PH.D.	05/2013	Biochemistry
Iowa State University, Ames, IA	POSTDOC	02/2014	Biochemistry
National Institutes of Health, Bethesda, MD	POSTDOC	06/2019	Biochemistry

A. Personal Statement

Genome replication and maintenance play fundamental roles in both tumorigenesis and cancer treatment. The overarching goals of my research are to investigate the molecular mechanisms of genome replication and maintenance processes, how they work under normal and stress conditions, how their abnormalities lead to mutations, genome rearrangements and cancer, and how they selectively protect cancer genome integrity during cancer treatment. My proposed research aims to illustrate the molecular mechanisms of the unique activities of DNA polymerase θ in genome maintenance and tumorigenesis. I will combine biochemical, biophysical and structural biological techniques in my research. I have acquired adequate expertise to successfully perform the proposed work. I was educated as a structural biologist and biochemist since the beginning of my career. During my PhD studies I employed experimental and computational techniques to characterize structure and mechanism of proteins in glucose metabolism. My journey on enzymes in nucleic acid metabolism started with my first postdoctoral position in 2013. Subsequently, I have studied double strand break repair nuclease complex Mre11-Rad50, translesion DNA polymerases η and v, and DNA replisome from bacteriophage T7. At my independent lab at Rice University, my research continued to focus on the mechanism of DNA polymerase synthesis and inhibition. Using the time-resolved crystallography, we have recorded the molecular movies of mismatch incorporation process at atomic resolution (Accepted at Nature Commun.). We also collaborated with XPose Inc to perform structural based inhibitor screening for new cancer drugs. In addition, we have reconstituted the mitochondrial replication and maintenance system in test tubes and are investigating the mechanism of DNA replication and error generation in mitochondria. We recently determined the first structure of twinkle helicase from mitochondrial and elucidated the mechanism of DNA loading and translocation of twinkle with cryo-electron microscope and high-speed atomic force microscope (manuscript under review). My past work has led to 21 publications, including two first-author articles in the prestigious journal Science.

1. Gao Y, Cui Y, Fox T, Lin S, Wang H, de Val N, Zhou ZH, Yang W. Structures and operating principles of the replisome. Science. 2019 Feb 22;363(6429) PubMed Central PMCID: PMC6681829.
2. Gao Y, Yang W. Capture of a third Mg^{2+} is essential for catalyzing DNA synthesis. Science. 2016 Jun 10;352(6291):1334-7. PubMed Central PMCID: PMC6320252.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2019 -	Assistant Professor, Rice University, Houston, TX
2014 - 2019	Postdoctoral Fellow , National Institute of Health (NIH), Bethesda, MD
2013 - 2014	Postdoctoral Fellow, Iowa State University, Ames, IA

Honors

2019 – 2023 CPRIT Award for First-Time Tenure Track Faculty Member, Rice Univ.
2013 – 2013 Teaching Excellence Award, Graduate College, Iowa State Univ.
2010 – 2010 Graduate Student Teaching Award, Iowa State Univ.
2007 – 2007 Undergraduate Research Excellence Award, Univ. of Sci. and Tech. of China

C. Contribution to Science

1. Mechanism of DNA synthesis. DNA polymerases replicate genomic DNA with the assistance of divalent metal ions. It was proposed for decades that two metal ions were required and sufficient for polymerase catalysis. However, the conclusion was mainly based on static crystal structures of polymerases prepared under inhibitory conditions and the dynamic catalytic process was not directly visualized. I investigated the polymerase catalysis with a novel diffusion-based time-resolved crystallography method. By collecting over a hundred crystal structures during polymerase catalysis under different conditions, I for the first time proved that DNA polymerase with well aligned DNA, dNTP and two metal ions are not adequate for the chemical reaction (publication "d"). Only upon the arrival of a third metal ion the reaction proceeds. The third metal ion is present transiently and not directly coordinated by the polymerase, explaining why it escaped from detection for decades. My finding not only illustrated the chemical mechanism of polymerase reaction but also revolutionized how people think about enzyme catalysis. We suspect that the transient bound metal ions play essential roles in all divalent metal ion dependent enzymes in nucleic acid metabolism. To facilitate the research in the field, we summarized our diffusion-based time-resolved crystallography method in great detail in a method paper (publication "c"). DNA is subject to endogenous or environmental consults and specialized translesion DNA polymerases are evolved to bypass various DNA lesions. I have collaborated with an undergraduate student to investigate how a translesion DNA polymerase adds nucleotide against oxidative lesion 8,5′-cyclopurine-2′-deoxynucleosides, which will obstruct replication and transcription if not dealt properly (publication "a"). Our structures and biochemical experiments elucidated how the backbone distorting lesion can be tolerated in polymerase active site in a metal ion dependent manner. Lastly, I have reviewed the common themes in polymerase catalysis and the diverse mechanisms of polymerase bypassing various types of lesions (publication "b").

    a. Weng PJ, Gao Y, Gregory MT, Wang P, Wang Y, Yang W. Bypassing a 8,5'-cyclo-2'-deoxyadenosine lesion by human DNA polymerase η at atomic resolution. Proc Natl Acad Sci U S A. 2018 Oct 16;115(42):10660-10665. PubMed Central PMCID: PMC6196489.
    b. Yang W, Gao Y. Translesion and Repair DNA Polymerases: Diverse Structure and Mechanism. Annu Rev Biochem. 2018 Jun 20;87:239-261. PubMed Central PMCID: PMC6098713.
    c. Samara NL, Gao Y, Wu J, Yang W. Detection of Reaction Intermediates in Mg^{2+}-Dependent DNA Synthesis and RNA Degradation by Time-Resolved X-Ray Crystallography. Methods Enzymol. 2017;592:283-327. PubMed Central PMCID: PMC6097844.
    d. Gao Y, Yang W. Capture of a third Mg^{2+} is essential for catalyzing DNA synthesis. Science. 2016 Jun 10;352(6291):1334-7. PubMed Central PMCID: PMC6320252.

2. Structural basis of replisome operation. Since DNA was established as the genetic material and the DNA double-helical structure was proposed, the mechanism of DNA replication has been a central subject in molecular biology research. However, the structural basis of DNA replication was not resolved due to the complexity of DNA replication. To determine replisome structures, I reconstituted the simplest replisome from Bacteriophage T7 and adapted the cutting-edge cryo-electron microscope technique. By solving nearly 20 structures of T7 replisomes on its relevant DNA substrates, I illustrated the mechanism of helicase translocation, helicase-leading strand polymerase coupling and primase-lagging strand polymerase coordination (publication "c"). Based on the first structure of a replisome, I consolidated many years of biochemical data and pointed out the potential mechanisms of replication coupled repair (publication "b"). In addition, I summarized mechanisms of different helicases specialized in different processes of DNA metabolism (publication "a"). In summary, my work provided a scaffold in understanding structural basis of DNA replication.

a. Gao Y, Yang W. Different mechanisms for translocation by monomeric and hexameric helicases. Curr Opin Struct Biol. 2020 Apr;61:25-32. PubMed Central PMCID: PMC7156327.
b. Yang W, Seidman MM, Rupp WD, Gao Y. Replisome structure suggests mechanism for continuous fork progression and post-replication repair. DNA Repair (Amst). 2019 Sep;81:102658. PubMed Central PMCID: PMC7467748.
c. Gao Y, Cui Y, Fox T, Lin S, Wang H, de Val N, Zhou ZH, Yang W. Structures and operating principles of the replisome. Science. 2019 Feb 22;363(6429) PubMed Central PMCID: PMC6681829.

3. Allosteric communication mechanisms of Mre11-Rad50 (MR) complex. MR complex play pivot roles in DNA double-strand break. The MR complex contains endo- and exo-nuclease activity to initialize DNA recession, ATPase activity to drive DNA translocation, and a several hundred Angstrom long coiled-coil domain that can potentially bridge different DNA strands. How different activities are coordinated within MR complex are not well understood. I have worked with Dr. Nelson for nine months and characterized the allosteric communication of MR complex from bacteriophage T4. I showed that the nuclease activities of Mre11 is autoinhibited by its C-terminal domain and Rad50 binding to the C-terminal domain of Mre11 relieves its autoinhibition (publication “d”). I participated in studying how the long coiled-coil domain mediate MR complex function (publication “c”). In addition, I collaborated with two undergraduate students and investigated the allosteric communication with evolutionary analysis (publication “b”) and characterized the role of Rad50 C-terminus unstructured region in DNA binding (publication “a”). Collectively, my work revealed the working mechanism of the highly conserved MR complex.

   a. Streff HE, Gao Y, Nelson SW. Functional evaluation of the C-terminal region of bacteriophage T4 Rad50. Biochem Biophys Res Commun. 2020 May 28;526(2):485-490. PubMed PMID: 32238267.
   b. Gao Y, Meyer JR, Nelson SW. A network of allosterically coupled residues in the bacteriophage T4 Mre11-Rad50 complex. Protein Sci. 2016 Nov;25(11):2054-2065. PubMed Central PMCID: PMC5079247.
   c. Barfoot T, Herdendorf TJ, Behning BR, Stohr BA, Gao Y, Kreuzer KN, Nelson SW. Functional Analysis of the Bacteriophage T4 Rad50 Homolog (gp46) Coiled-coil Domain. J Biol Chem. 2015 Sep 25;290(39):23905-15. PubMed Central PMCID: PMC4583041.
   d. Gao Y, Nelson SW. Autoinhibition of bacteriophage T4 Mre11 by its C-terminal domain. J Biol Chem. 2014 Sep 19;289(38):26505-26513. PubMed Central PMCID: PMC4176212.