CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
R1119

Project Title:
Recruitment of First-Time, Tenure-Track Faculty Members

Award Mechanism:
Recruitment of First-Time, Tenure-Track Faculty Members

Principal Investigator:
Liu, Xin

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

My passion for quantitative biosciences dates back to my childhood years, with inherent curiosity about mathematics cultivated by my parents. While in high school, I became fascinated by chemistry and biology, which led me to choose biochemistry as my major of undergraduate education at Nanjing University, Jiangsu, China. I received my Ph.D. in Chemistry from the University of Pennsylvania, and I did my thesis study with Dr. Ronen Marmorstein at the Wistar Institute, where I learned one of the most important techniques in quantitative biosciences and structural biology, X-ray crystallography. During my time as a postdoctoral fellow in the laboratory of Dr. Roger Kornberg at Stanford University, I continued my training of X-ray crystallography complemented with biochemical reconstitution and electron microscopy, focusing on large macromolecular assemblies.

Collectively, my graduate and postdoctoral research has been concerned with the molecular basis of transcription and transcriptional regulation in eukaryotes. My first research project in the laboratory of Dr. Ronen Marmorstein was to investigate how the retinoblastoma protein (pRb) is inactivated by the E7 viral oncoprotein of human papillomavirus (HPV). pRb was identified as a tumor suppressor to repress the E2F transcription factor that activates cell cycle progression. HPV-E7 was known to inactivate pRb by stimulating the disassembly of the pRb-E2F complex, but the molecular mechanism of this process had not been determined. To that end, I solved the first X-ray crystal structure of HPV-E7. Based on the structure, I made site-directed mutants of HPV-E7, performed in vitro binding studies and E2F-displacement assays, and addressed how two conserved patches on the surface of HPV-E7 are responsible for E2F displacement through direct competition for pRb binding. I then investigated the molecular basis of adenovirus (Ad) E1A protein-mediated pRb inactivation. I determined the structure of pRb in a complex with conserved region 1 of Ad-E1A, and discovered that Ad-E1A uses an unexpected molecular mimicry mechanism to displace E2F. The transcriptional coactivator protein and histone acetyltransferase p300/CBP is another important target for HPV-E7 and Ad-E1A. Although this enzyme activity was long known to influence a wide range of cellular processes including transcription, little was known concerning its structure and catalytic mechanism. To address this gap in our understanding of p300 function, I collaborated with the laboratory of Dr. Philip Cole from Johns Hopkins University to determine the first crystal structure of the catalytic domain of p300/CBP with a specific bisubstrate inhibitor bound, and found that it uses an unusual ‘hit-and-run’ mechanism of catalysis. For all of these findings, I was awarded the Dr. Monica H.M. Shander Memorial Award by the Wistar Institute.

In my postdoctoral research, I have pursued structural and biochemical studies of transcription by RNA polymerase II (Pol II) and associated factors in the laboratory of Dr. Roger Kornberg. I am the recipient of the Jane Coffin Childs Postdoctoral Fellowship since 2008. It is now appreciated that large macromolecular assemblies are responsible for myriad fundamental biological processes, subject to intricate regulation, and therefore objects of great interest for biological studies. Due to their size and complexity, structural analysis of these molecular assemblies presents a formidable challenge. Benefiting from the expertise of the Kornberg lab in structural studies of large protein complexes, I determined a structure of Pol II in a complex with the general transcription factor IIB (TFIIB). The structural analysis, together with modeling and previous biochemical data, shed light on central aspects of the transcription mechanism, including the recruitment of promoter DNA to the Pol II active center, the conformational change from a closed to an open promoter complex, and the transition from the initiation to the elongation phase of transcription. In parallel with this work, I have succeeded in capturing Pol II complexes at early stages in transcription. My results suggest that the widespread and hitherto mysterious phenomenon of abortive transcription may be viewed as promoter proofreading, and the observed structural transitions as checkpoints for promoter control.

As a new faculty member of the Cecil H. and Ida Green Center for Reproductive Biology Sciences at the UT Southwestern Medical Center, I will continue to investigate the molecular basis for transcriptional regulation in the context of three-dimensional genome structure and chromatin environment. The mechanistic insights gained from my proposed studies have the potential to suggest new ways to control gene regulation to block cancer progression.