Hong Wang, PhD
Associate Professor
Physics

Cohesin SA1 and SA2 are RNA Binding Proteins that Localize to RNA Containing Regions on DNA

Dr. Hong Wang obtained her Ph.D from the University of North Carolina at Chapel Hill in 2003 under the supervision of Dr. Dorothy Erie. She received postdoctoral training at NIEHS from 2204 to 2008, and at the Hillman Cancer Center (University of Pittsburgh) from 2008 to 2011 under the mentorship of Drs. Bennett Van Houten and Patricia Opresko. Her graduate and postdoctoral work using AFM imaging and tracking of quantum dot- labeled proteins on DNA revealed how DNA mismatch repair and nucleotide excision repair proteins search and recognize DNA damage at the single- molecule level. In 2009, she received the NIH Pathway to Independent Award (K99/R00) to study protein-DNA interactions at telomeres. She joined the Physics Department at North Carolina State University in 2012. Since then, single-molecule AFM and fluorescence imaging studies from her lab have revealed structures and dynamics of various biological pathways, including telomere maintenance, mitochondrial DNA replication, chromatin structures, epigenetic regulations, and sister telomere cohesion. Currently, her lab's main focus is to understand how the shelterin protein complex modulates higher-order DNA structures at telomeres and how cohesin binds to specific DNA sequences and R-loops.

Abstract: The cohesin complex plays important roles in diverse biological processes including sister chromatid cohesion, DNA double-strand break (DSB) repair, re-start of stalled replication forks, and maintenance of 3D chromatin organization. Since the discovery of the cohesin complex, the long-held view is that cohesin binds DNA through the entrapment of DNA inside the ring subunits (SMC1, SMC3, and RAD21 in humans), and the fourth subunit (SA1/STAG1 or SA2/STAG2) serves supporting roles. Recently, SA2 was identified as 1 of only 12 genes that are significantly mutated in four or more cancer types. Despite the importance of cohesin SA1 and SA2, their biophysical properties are largely unknown. Using single-molecule AFM imaging and tracking of quantum dot-labeled protein on DNA tightropes, we discovered that cohesin SA1 and SA2 are single-stranded (ss) and double-stranded (ds) DNA and RNA binding proteins. SA1 displays similar DNA binding affinities for ds and ssDNA, and binds specifically to double-stranded telomeric sequences mediated through its N-terminal AT-hook domain. Due to SA2's higher binding affinities for ssDNA than for dsDNA,

it recognizes intermediate DNA structures during DNA replication and double-strand break (DSB) repair, such as a dsDNA end, single-stranded overhang, flap, fork, and ssDNA gap. Furthermore, cohesin SA1 and SA2 bind to various RNA containing nucleic acid substrates, including ssRNA, dsRNA, dsRNA with an overhang, RNA:DNA hybrids, a model R-loop substrate, and long ssRNA transcripts. Strikingly, cohesin SA1 and SA2 preferentially localize to regions on dsDNA that contain RNA. These discoveries of previously unknown DNA and RNA binding activities of cohesin SA1 and SA2 open up new directions of research to unravel the mechanisms underlying their diverse cellular functions.