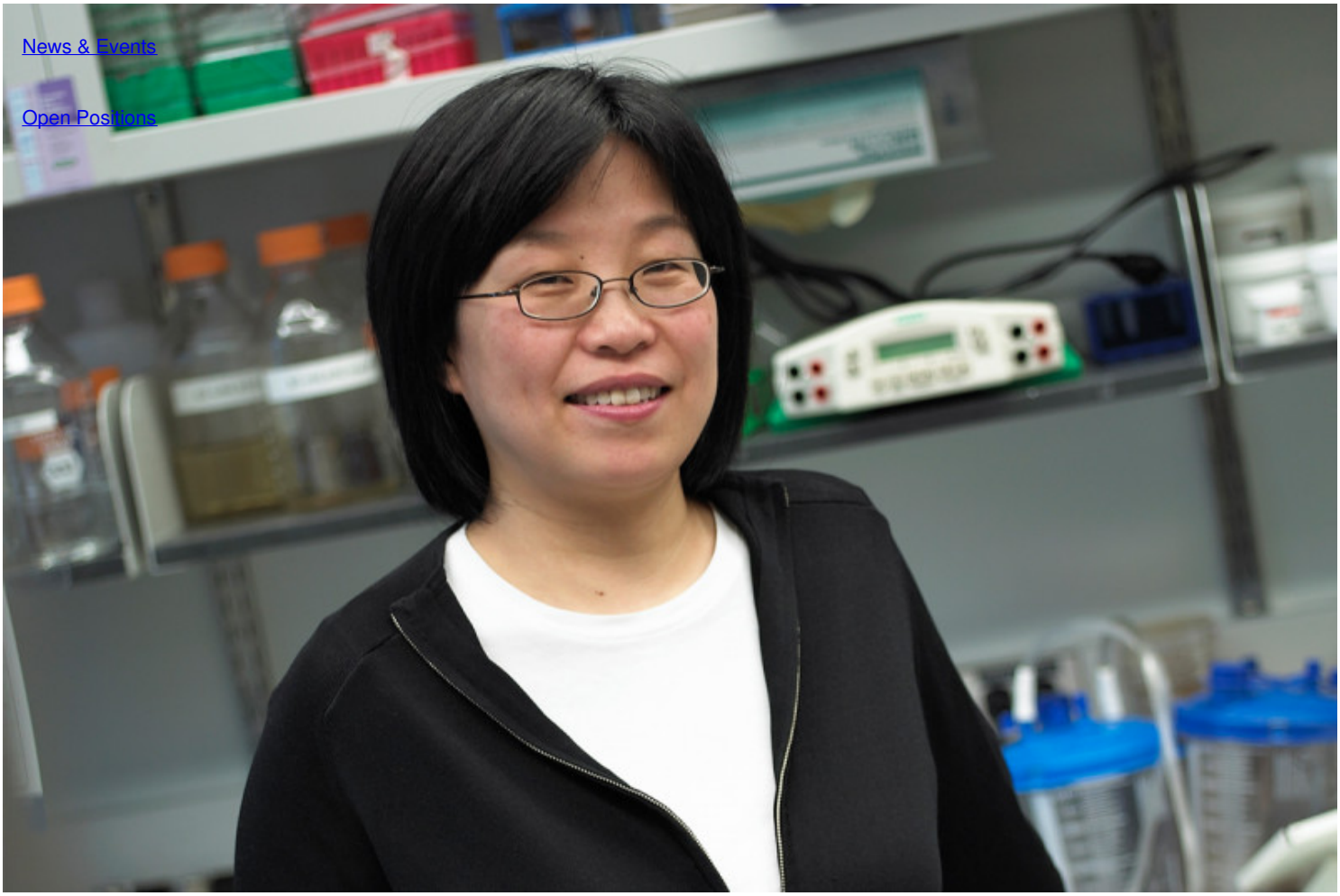
At Work: Molecular Biologist Xiaolan Zhao



Xiaolan Zhao

Molecular biologist Xiaolan Zhao studies chromosomal organization, telomere metabolism, DNA repair, and dynamic protein modification in stable genome maintenance. We spoke with Dr. Zhao shortly after she joined Memorial Sloan Kettering in 2005.

I grew up in a small city near the Great Wall in northern China. When I was a kid, I liked to hike on the Great Wall with friends and it was always exciting to find a different view at the next watchtower.

To explore the world beyond the watchtowers, I applied and was admitted to Peking University. It was during this period I began to appreciate the amazing world inside tiny cells, with all its intricate beauty and unexplored complexity.

During my sophomore year in college, I was fortunate to start working in a molecular plant biology lab led by Zhangliang Chen. For my undergraduate and masters research, I participated in several projects ranging from the regeneration of rice to the investigation of how viruses cause rice diseases. It

was fascinating to learn how cells could regain pluripotency and how viruses could use only a few proteins to change the cellular programs for their own uses.

It was a fun experience in other aspects too. The lab was young and energetic. People in the lab worked closely together, exchanging ideas and sharing experiment tricks. I enjoyed the lab work and lab life so much that I thought of making it my career. With this in mind, I moved on to pursue a PhD in the Department of Genetics and Development at Columbia University.

The Power of Yeast Genetics

My initial plan for graduate study was to understand the cause of cancers. I soon realized that an excellent approach to do so is to use model organisms, such as a fly, a worm, and yeast, because they not only contain the same or similar cellular programs as those altered in cancers but also offer supreme technical advantages over human cells. I did my rotations in labs using different model organisms and eventually stayed in the lab of Rodney Rothstein, whose lab uses yeast to study the function of human disease gene homologs.

Rod is a great mentor and a fun person to work with. He has a lot of interesting ideas, yet is open-minded and supportive of new pursuits. My thesis project started when I discovered that a homolog of the cancer-prone disease genes *ATM/ATR* has an essential function aside from its well-known role in the cell cycle checkpoint.

Using genetic approaches, we found that this essential function is to remove an inhibitor of the ribonucleotide reductase, which is the key enzyme in dNTP synthesis. It turns out that cells carefully regulate dNTP levels so they are balanced and peak in S phase. Such regulation is critical for cell survival and genetic fidelity.

We further determined the regulatory pathway and the molecular mechanisms by which the *ATM/ATR* homolog regulates dNTP levels and consequently genomic stability. This work was very satisfying, not only because we revealed a new function of a human disease protein homolog but also because it showed me just how powerful yeast genetics can be.

As defects in genomic stability are the main causes of cancers and many other human diseases, the in-depth understanding of how cells maintain genomic stability by using model organisms is very important for battling human diseases.

Back to top

How Things Function in Real Cells

While reading literature on genomic stability, I realized that although there is a good body of knowledge of the basic machineries of DNA metabolism, we know very little about the dynamic and spatial organization of chromosomal activities in live cells. Yet it is extremely important that chromosomes carry out specific functions at the right place and the right time. With an influx of new technologies, I thought that this would be a great time to look at these fundamental issues. With this in mind, I joined the lab of Dr. Gunter Blobel at Rockefeller University to pursue my postdoctoral study.

Gunter's lab has been the moving force in several fields and is set up for multidisciplinary research. Gunter was very supportive of my ideas, and we used the nuclear pore complexes as an entry point to probe chromosomal organization and dynamics. We soon realized that one important regulatory mechanism in these processes is a posttranslational modification called SUMOylation.

SUMO is a special protein that can change the properties of many other proteins when covalently linked to them. We found out that cells tightly regulate the machineries of sumoylation by localization and other means. In addition, we identified a novel SUMO E3 ligase and purified an octomeric protein complex that contains this SUMO E3. This complex is quite remarkable, as two of its subunits are members of the chromosomal ATPase family, which can actively tether and/or fold chromosomes.

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> Molecular Biologist

In addition, it contains the particular SUMO E3 that can change properties of other proteins. The functions of the other five subunits are currently not

known, but one is suspected to be involved in ubiquination. In a sense, this complex is like a protein machine that has several whistles and bells and can therefore modulate chromosomal functions using multiple means.

We now know that this complex plays important roles in several chromosomal activities, such as replication, repair, and segregation. Our understanding of this complex is just beginning, but it promises a very exciting journey into the regulation of chromosomal function.

I feel very fortunate to have worked with so many great people, and this is really an exciting part of doing research. I could not have made these discoveries without the generous support of Gunter and Rod, and the valuable help from the students and technicians who have worked with me. I am also grateful to other colleagues who have helped and collaborated with me along the way.

Back to top

Move Across the Road

SKI is a wonderful place to start a new chapter of my research. There are many top labs in chromosomal biology and posttranslational modification fields here at SKI. The Tri-Institutional community and other yeast labs in the City provide a rich environment for collaboration and scientific interaction. New York City is a wonderful place to live and work, and the convenience allows one to strike a good balance between the lab and family.

Currently, my lab is employing genetic, cell biological, and biochemical approaches to reveal the molecular mechanisms of how this new complex contributes to chromosomal replication, repair, and segregation. We are also identifying new players in the SUMO pathway and actively investigating how sumoylation regulates the dynamic and spatial organization of chromosomal activities. These two directions are closely related, and the understanding of one benefits another.

As proteins under study are highly conserved in humans, molecular mechanisms uncovered in our studies will have important implications in the understanding of how human cells work. In addition, since both chromosomal stability and the SUMO pathway are involved in multiple human diseases, we hope that our research will eventually lead to better strategies to prevent and treat these diseases.

Since its beginning in October 2005, the lab has continued to grow and expand. It is great to see that people in the lab enjoy doing science while making real progress. This is one of the biggest joys of being a lab head. Working as a team, we look forward to uncovering many more exciting mysteries inside the nucleus.

Back to top

About Us

Overview

Leadership

Administration

History

Contact Us

Research

Overview

Research programs

Research labs
Core facilities & resources
Education & Training
Overview
Postdoctoral training
Gerstner Sloan Kettering Graduate School
Joint graduate programs
Programs for college & high school students
News & Events
Overview
Seminars & events
Open Positions
Overview
Faculty positions
Postdoctoral positions