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Lan Laboratory

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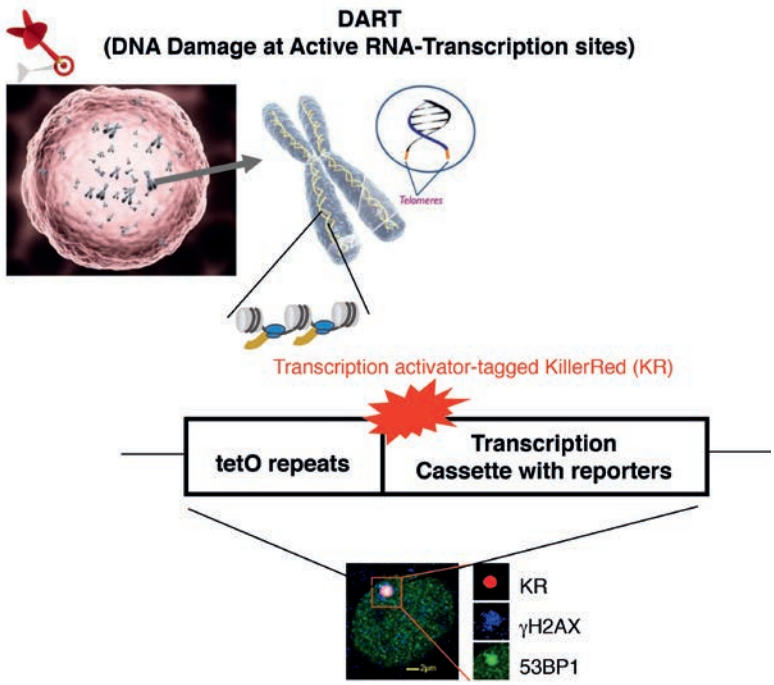
Oxidative DNA damage is a major source of genomic instability during tumorigenesis and aging. The main research interests of **the Lan laboratory** are centered on the mechanisms by which human cells maintain genomic stability against oxidative stress. With a strong appreciation for how human health conditions, especially cancer and neurological maladies, are connected to the loss of genome integrity, ranging from intrinsic genetic predispositions to environmental factors that inflict DNA damage, my lab has developed the first single-cell assay to interrogate the molecular mechanisms of oxidative DNA damage response at specific loci in the genome. By combining this innovative assay with state-of-the-art imaging techniques, we have opened new avenues to understanding the oxidative DNA damage response in different chromosomal environments.

The ongoing research of my lab is focused on transcription-coupled oxidative DNA damage response and cancer. A growing body of evidence suggests that oxidative stress plays an important role in tumorigenesis, aging, and neurodegenerative diseases. Oxidative stress caused by environmental insults and endogenous metabolites induces DNA base modifications and strand breaks. DNA strand breaks have detrimental effects not only on actively proliferating cells, but also on slowly proliferating cells and terminally differentiated cells. At active transcription sites, RNA Polymerase II can bypass DNA base modifications, but not strand breaks. Given the heterogeneity of cancer cells in tumors, it is critical to understand how dividing and non-dividing cells respond to oxidative DNA damage. One of the main research interests of the Lan laboratory is to understand how oxidative DNA damage response is differentially regulated in transcribed and un-transcribed regions, and in dividing and non-dividing cells. We discovered a novel mRNA-dependent and R loop-mediated homologous recombination (HR) mechanism that specifically promotes repair in the transcribed genome. Thus, our work has revealed an unexpected role for mRNA in HR. Importantly, we show that this mRNA-mediated HR mechanism is able to operate even in G0/G1 cells, challenging the current view that HR only occurs during the S/G2 phase of the cell cycle. Our findings may likely lead to a new paradigm in DNA repair, and to a better understanding of how actively proliferating and slowly proliferating cancer cells respond to oxidative damage. In the near future, we plan to address several important questions on this new pathway that we discovered: (1) Whether and how is the RNA-mediated HR pathway distinct from the canonical HR pathway? (2) How is repair "channeled" into the RNA-mediated HR pathway in transcribed regions? (3) Is the RNA-mediated HR pathway important for tumor suppression? In our ongoing studies, we are exploring the function of RNA modifications in the RNA-mediated HR pathway, and are using advanced super-resolution imaging techniques (STORM and PALM) to study DNA-RNA structural changes at specific sites of DNA damage within the genome. We are also using the zebrafish



The Lan laboratory developed the DNA Damage at RNA Transcribed sites (DART) method to precisely introduce oxidative DNA damage at specific transcribed loci in a dose-dependent manner. This is achieved by site-specific positioning of the photo-excitable and ROS-releasing protein KillerRed (KR). This unique method provides a tool to understand how oxidative DNA damage response is differentially regulated in transcribed and un-transcribed regions, and in dividing and non-dividing cells.

model to assess the functional significance of RNA-mediated HR in vivo. Going forward, we would like to expand our studies to investigate the status of this new RNA-mediated HR repair pathway in cancer cells, its potential function in tumor suppression, and its value as a therapeutic target.

A second research priority of my lab is to understand how telomeres respond to oxidative DNA damage. Telomere dysregulation is a major source of genomic instability and a potential target for cancer therapy. Due to G/C-rich telomeric repeats, telomeres are particularly vulnerable to oxidative stress. Interestingly, telomeres are protected by specific "capping" proteins, making DNA damage response at telomeres significantly different from elsewhere in the genome. More specifically, we are investigating whether and how oxidative damage at telomeres triggers telomere attrition, senescence, and the promotion of tumorigenesis. My lab has established a new method to introduce oxidative damage to telomeres in a highly controlled manner, allowing us, for the first time, to specifically follow the oxidative damage response at telomeres. In several projects, we have investigated how HR factors are regulated by shelterin proteins at telomeres during the oxidative damage response. The recruitment of repair factors to telomeres is coordinately regulated by poly-ADP-ribosylation, phosphorylation, SUMOylation, and ubiquitylation of TRF1 to protect cancer cells from telomere damage. Our future goal is to investigate whether and how the mechanisms orchestrating oxidative damage response at telomeres may contribute to the suppression of tumorigenesis and aging, and how we can exploit this specific vulnerability of cancer cells in therapy.

Selected Publications:

Teng Y, Yadav T, Duan M, Tan J, Xiang Y, Gao B, Xu J, Liang Z, Liu Y, Nakajima S, Shi Y, Levine AS, Zou L, **Lan L**. ROS-Induced R Loops Trigger a Transcription-Coupled but BRCA1/2-Independent Homologous Recombination Pathway through CSB. *Nature Communications*. 2018 Oct 8;9(1):4115.

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