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The lab focuses on telomeres, protective elements at the ends of chromosomes that are critical for genome integrity and shorten with cell division. de Lange seeks to understand how telomeres are protected from the DNA damage response by a protein complex called shelterin, how they are replicated and maintained, and how telomere shortening contributes to tumor suppression and genome instability in cancer.

Research in the de Lange lab focuses on human and mouse telomeres, which are made up of long arrays of double-stranded TTAGGG repeats that end in a single-stranded (ss) 3' overhang. The lab identified a six-subunit protein complex, which they named shelterin, that specifically binds to telomeres. de Lange and her colleagues determined the fate of telomeres lacking one or more of the six shelterin subunits, showing that cells perceive their natural chromosome ends as damaged DNA when shelterin is compromised.

Shelterin represses six distinct DNA damage response pathways. These include the two main DNA damage signaling pathways, initiated by the ATM and ATR checkpoint kinases, and the DNA double-strand break (DSB) repair pathways involving homology-directed repair (HDR) and non-homologous end joining (NHEJ). Shelterin also protects telomeres from inappropriate resection by nucleases. Shelterin is compartmentalized such that different subunits repress distinct DNA damage response pathways.

de Lange's group aims to determine the mechanism by which each shelterin subunit inhibits its designated pathway. A major mechanistic insight came from the identification of the t-loop structure of telomeres in which the single-stranded overhang is inserted in the double-stranded repeat array of the telomere, thereby hiding the telomere end from the DNA damage response. This structure is formed by the TRF2 component of shelterin. Since TRF2 is responsible for the repression of the ATM kinase pathway and NHEJ, it is likely that the t-loop structure is critical to prevent these two pathways from acting inappropriately on chromosome ends. In addition, the lab showed that POT1 prevents ATR kinase activation. POT1 binds to the telomeric ssDNA, thereby preventing RPA, the ssDNA sensor in the ATR pathway, from gaining access to the telomere end.

In addition to protecting telomeres, shelterin plays a major role in the maintenance of telomeric DNA. Shelterin recruits telomerase, regulates telomere length, and ensures the maintenance of the C-rich strand of telomeres by recruiting the CST (CTC1/STN1/TEN1) complex. CST is a trimeric ssDNA binding complex that is associated with DNA polymerase αprimase. The lab has determined the cryo-EM structure of CST/polα/primase and studies how it is recruited by shelterin to mediate fill-in synthesis of the telomeric C-strand. They also have revealed an important role for CST/polα/primase fill-in synthesis in the repair of DSBs.

The lab also aims to understand how telomere shortening limits cancer development and how telomere dysfunction can lead to genome instability in cancer. Recent data on cancer-prone families with excessively long telomeres showed that telomere shortening is a powerful tumor suppressor mechanism that prevents cancer formation. However, in checkpoint-deficient cells, telomeres can shorten to a point where they become a substrate for NHEJ and form dicentric chromosomes. By modeling this so-called telomere crisis in vitro, the de Lange lab showed that dicentric chromosomes lead to chromothripsis and kataegis, two extreme forms of mutational alteration observed in cancer.

EDUCATION

Doctoraal examen, 1981
University of Amsterdam and National Institute for Medical Research

Ph.D. in biochemistry, 1985
University of Amsterdam and The Netherlands Cancer Institute

POSTDOC

University of California, San Francisco, 1985–1990

POSITIONS

Assistant Professor, 1990–1994
Associate Professor, 1994–1997
Professor, 1997–
Associate Director, Anderson Center for Cancer Research, 2006–2011
Director, Anderson Center for Cancer Research, 2011–
The Rockefeller University

AWARDS

Paul Marks Prize, 2001

NIH Director's Pioneer Award, 2005

The Rockefeller University Distinguished Teaching Award, 2007

Massachusetts General Hospital Cancer Center Prize, 2008

Research Professor Award, American Cancer Society, 2010

AACR G.H.A. Clowes Memorial Award, 2010

Vilcek Prize, 2011

Vanderbilt Prize, 2012

Rosalind Franklin Award, National Cancer Institute, 2012

Dr. H.P. Heineken Prize, 2012

Breakthrough Prize in Life Sciences, 2013

Katharine Berkan Judd Award, 2013

Jill Rose Award, 2013

Canada Gairdner International Award, 2014

Outstanding Investigator Award, National Cancer Institute, 2016

Lewis S. Rosenstiel Award, 2017

Bert and Natalie Vallee Award in Biomedical Science, 2018

Mike Hogg Award, 2019

Karl Friedrich Bonhoeffer Award, 2022

NCI Outstanding Investigator Award, 2024

Pezcoller Foundation-AACR International Award, 2024

HONORARY SOCIETIES

Foreign Associate, National Academy of Sciences

National Academy of Medicine

American Academy of Arts and Sciences

American Association for the Advancement of Science

Associate Member, European Molecular Biology Organization

Royal Netherlands Academy of Arts and Sciences

Royal Holland Society for Sciences and Humanities

Foreign Member, The Royal Society

SELECTED PUBLICATIONS

Cai, S.W. et al. Cryo-EM structure of the human CST–Polα/Primase complex in a recruitment state. *Nat Struct Mol Biol* 29, 813–819 (2022).

Schmutz, I. et al. TINF2 is a haploinsufficient tumor suppressor that limits telomere length. *ELife* 9, e61235 (2020).

Mirman, Z. et al. 53BP1-RIF1-shieldin counteracts DSB resection through CST- and Pol α-dependent fill-in. *Nature* 560, 112–116 (2018).

Maciejowski, J. et al. Chromothripsis and kataegis induced by telomere crisis. *Cell* 163, 1641–1654 (2015).

Doksani, Y. et al. Super-resolution fluorescence imaging of telomeres reveals TRF2-dependent t-loop formation. *Cell* 155, 345–356 (2013).