Telomeres, the nucleotide repeats that cap the ends of eukaryotic chromosomes, serve critical roles in promoting cell viability and in maintaining chromosomal stability. In humans, telomeres shorten progressively with cell division and aging because DNA polymerase cannot fully replicate the extreme ends of chromosomes. Critical telomere shortening and loss of the protective telomere capping function in cell culture initiates senescence and crisis responses that profoundly alter chromosome stability, cell cycle progression and survival. Expression of telomerase, the reverse transcriptase that synthesizes telomere repeats, is sufficient to lengthen and stabilize telomeres, thus enabling cells to proliferate in an unlimited fashion. Telomerase is expressed in stem cells and progenitor cells in self-renewing tissues, is
downregulated with differentiation and upregulated in the vast majority of human cancers. In the Artandi lab, we are interested in unraveling the molecular and cellular mechanisms according to which telomeres and telomerase modulate stem cell function and carcinogenesis.

TERT and STEM CELLS

Telomerase is comprised of two subunits: TERT, the telomerase reverse transcriptase, and TERC, the telomerase RNA component. In stem cell and progenitor cell compartments, TERT serves a critical role in maintaining telomere length and function to support tissue homeostasis. However, TERT serves an additional function in stem cells, distinct from its role in telomere lengthening and we are actively studying this new role. We have devised new means of identifying telomerase-expressing cells in vivo and we are investigating the location and function of these cells in diverse tissues.

TISSUE REGENERATION AND AGING

Aging in humans and other mammals is associated with impaired proliferative responses in settings of stress, suggesting that altered stem cell function may underlie certain aspects of aging. We are interested in understanding how stem cells self-renew and differentiate and how TERT modulates stem cell function. One major limitation to this understanding is the inability to identify telomerase-positive cells in vivo. We have developed new approaches to solve this problem and are investigating telomerase-positive cells in vivo.

TELOMERASE TRAFFICKING AND ASSEMBLY

Telomerase is a large RNP with complex regulation in human cells. Using IP-MS approaches, we identified a critical new component of the telomerase holoenzyme, TCAB1. TCAB1 is essential for guiding the trafficking of telomerase to Cajal bodies within the nucleus and also to chromosome ends. We seek to understand in molecular detail how telomerase interacts with telomeres and adds telomere repeats in human cells.

TELOMERASE AND DISEASE

Germline mutations in telomerase components underlie several seemingly unrelated disease states, including the bone marrow failure syndrome dyskeratosis congenita, idiopathic pulmonary fibrosis, aplastic anemia and cirrhosis. We are using iPS cell-based approaches to study the mechanisms at play in these diseases with the goal of reversing the life-threatening phenotypes in these patients.

Teaching

COURSES

2017-18
- Current Issues in Aging: GENE 221 (Spr)

2016-17
- Current Issues in Aging: GENE 221 (Spr)

STANFORD ADVISEES

Postdoctoral Faculty Sponsor
Lu Chen, Yuchao Gu

Postdoctoral Research Mentor
Lu Chen, Yuchao Gu

GRADUATE AND FELLOWSHIP PROGRAM AFFILIATIONS

- Biochemistry (Phd Program)
- Cancer Biology (Phd Program)
- Hematology (Fellowship Program)
- Oncology (Fellowship Program)

Publications

PUBLICATIONS

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