BIOGRAPHICAL SKETCH

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NAME: Utz Herbig

eRA COMMONS USER NAME (credential, e.g., agency login): UTZHERBIG

POSITION TITLE: Associate Professor of Microbiology, Biochemistry & Molecular Genetics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Munich, LMU, Germany	B.Sc.	1991	Chemistry
University of Munich, LMU, Germany	M.Sc.	1995	Chemistry/Biochemistry
Vanderbilt University, Nashville, TN	Ph.D.	1999	Molecular Biology
Vanderbilt University, Nashville, TN	Postdoc	2000	Molecular Biology
Brown University, Providence, RI	Postdoc	2006	Molecular Biology

A. Personal Statement

In recent years, as new and unexpected roles for cellular senescence have emerged, the field of cellular senescence has gained a tremendous amount of momentum. It is now evident that cellular senescence plays critical roles in suppressing cancer development, promoting aging and age-associated diseases, facilitating wound healing, and regulating embryonic development in mammals. My research, which is geared towards understanding the biological role of ***telomere***-based senescence responses and their impact on human health, not only has contributed significantly to these advances, but also is at the forefront of this field. I have developed and now optimized the technique to visualize dysfunctional telomeres in mammalian cells on a single cell level and, consequently, was able to demonstrate, for the first time, the presence of senescent cells with dysfunctional telomeres in mammalian tissues. Being one of only very few laboratories with demonstrated ability to efficiently detect cells that had undergone telomere dysfunction-induced senescence (***TDIS***) in tissue, my group has provided strong evidence that TDIS is critical for human health. We were first to demonstrate a biological role for telomere based senescence responses during aging in long lived mammals (a), provide strong evidence that TDIS suppresses malignant cancer development in humans (b) and uncover a role for TDIS in tissue repair, wound healing, and fibrosis (c). My group continues to study TDIS, as well as the effects of the senescence associated secretory phenotype (SASP), during cancer development, tissue repair, and aging.

More recently, studies in my laboratory have shifted towards analyzing the contribution of immune-cell senescence to aging and the development of age-related diseases. In a collaborative study with the Fitzgerald-Bocarsly lab, we have developed a novel method to accurately identify, isolate, and characterize senescent immune cells from human peripheral blood and from tissue. We discovered that healthy human donors increasingly develop T lymphocytes with high senescence associated beta-galactosidase and other characteristics of cellular senescence with advancing age. We proposed that cellular senescence of T lymphocytes is a major contributing factor to the observed decline of immune cell function with age and age associated disorders and that immune cell senescence, therefore, plays a significant role in aging and the increased susceptibility of the elderly to age- associated diseases (d).

a. Herbig, U., Ferreira, M., Carey, D. & Sedivy, J.M. 2006. Cellular senescence in aging primates. **Science** 311: 1257

b. Suram, A., Kaplunov, J., Patel, P.L., Ruan, H., Cerutti, A., Boccardi, V., . . . Herbig, U. 2012. Oncogene-induced telomere dysfunction enforces cellular senescence in human cancer precursor lesions. **The EMBO Journal** 31: 2839-2851 (2012)

c. Razdan, N., Vasilopoulos, T. & Herbig, U. 2018. Telomere dysfunction promotes transdifferentiation of human fibroblasts into myofibroblasts. **Aging Cell** 17: e12838

d. Martínez-Zamudio R*, Dewald H*, Vasilopoulos T, Fitzgerald-Bocarsly, P** and Herbig U.** 2021. Senescence Associated β-Galactosidase Reveals the Abundance of Senescent CD8+ T Cells in Aging Humans. **Aging Cell**. e13344 *co-first authors. **co-senior authors.

Ongoing projects that I would like to highlight Include:

R01 CA136533
Herbig (PI)
2/1/2017-1/31/2022 (NCE until 1/31/2024)
Deciphering the Code For Senescence Escape During Cancer progression in Humans

R21 AG067368
Herbig and Fitzgerald-Bocarsly (mPI)
5/1/20-4/30/2022 (NCE until 4/30/2023; additional NCE will be requested)
Causes of Immune Cell Senescence in Aging Humans

R21AG067368-S1
Herbig and Fitzgerald-Bocarsly (mPI)
8/21-4/23 (Additional NCE will be requested)
The impact of Alzheimers Disease neuropathology on immune cell senescence in older African Americans.

Rutgers Facility Grant
Herbig (PI)
6/22-6/23
Center for Advancer Proteomic Research to analyze the SASP of senescent human CD8+ T cells

Rutgers Bridge Grant
Herbig (PI)
3/23-2/24
RBHS bridge funding support to study functional defects of senescent human CD8+ T cells

B. Positions, Scientific Appointments and Honors

2013-present Associate Professor, Dept. of Microbiology, Biochemistry and Molecular Genetics and The Center for Cell Signaling, RBHS, Rutgers The State University of NJ
2011-present Member of the Cancer Institute of New Jersey
2006-2013 Assistant Professor, Dept. of Microbiology and Molecular Genetics and NJMS-UH Cancer Center, UMDNJ

Honors

2010 American Cancer Society Research Scholar Grant Award
2007 New Scholar Award; The Ellison Medical Foundation
2000 University Central Intramural Discovery Grant; Vanderbilt University

C. Contribution to Science

1. **Mechanisms of initiation of DNA replication:** My early contributions to science were centered around understanding the mechanisms and identifying protein factors involved in the initiation of eukaryotic DNA replication, a process that is deregulated in cancer. Using the DNA replication model system of Simian Virus 40, I contributed to identifying novel regulatory mechanisms that suppress viral replication origins and activate these in a timed fashion. I co-identified and cloned the human DNA replication initiation factor Cdc6 and characterized the functional significance of the ATPase and phosphorylation sites of this factor.

a. Herbig, U., Weisshart, K., Taneja, P., and Fanning, E. 1999. Interaction of the Transcription Factor TFIID with Simian Virus 40 (SV40) Large T Antigen Interferes With Replication of SV40 DNA In Vitro. **J. Virol.** 73:1099-1107. PMID: 9882311

b. Herbig, U., Marlar, CA., and Fanning, E. 1999. The Cdc6 Nucleotide Binding Site Regulates Its Activity in DNA Replication in Human Cells. **Mol. Biol. Cell** 10: 2631-2645. MID: 10436018

c. Herbig, U., Griffith, JW., and Fanning, E. 2000. Mutation of cyclin/cdk phosphorylation sites in HsCdc6 disrupts a late step in initiation of DNA replication in human cells. **Mol. Biol. Cell** 12: 4117-4130. PMID: 11102512

2. **Telomeres and cellular senescence during aging.** At Brown University and Rutgers, my studies shifted towards understanding the causes and physiological consequences of telomere initiated cellular senescence, particularly in aspects of aging, aging associated diseases, and wound healing. I discovered that the reason for growth arrest in cells that had reached the end of their proliferative lifespan was because their telomeres, the physical tips of our chromosomes, had become critically short and dysfunctional, resulting in the activation of a stable G1 DNA damage checkpoint arrest. Having additionally discovered specific markers for Telomere Dysfunction Induced cellular Senescence (TDIS), I tested the long standing hypothesis that TDIS promotes organismal aging by progressively depleting our tissues of functional cells that are required for tissue homeostasis. My studies revealed that senescent dermal fibroblasts displaying dysfunctional telomeres indeed increased exponentially in the dermis of aging baboons, reaching levels of over 20% in very old animals. Our study was the first to demonstrate replicatively senescent cells in vivo, and additionally provided first evidence of the potential pro-aging properties of replicative senescence in long lived animals. More recently, we discovered that in addition to activating cellular senescence, generation of dysfunctional telomeres also can lead to a gain-of-function phenotype. Specifically, we discovered that telomere dysfunction is a cellular event that is critical for transdifferentiation of fibroblasts into myofibroblasts and that telomere dysfunction, therefore, plays an important role during wound healing and tissue repair in humans. In addition, in a collaborative effort with the Fitzgerald-Bocarsly laboratory we recently developed a novel method to accurately identify, quantify and isolate senescent and SA-βGal expressing immune cells from peripheral blood and discovered a dramatic increase in senescent CD8+ T cells in aging humans.

a. Herbig, U., Jobling, WA., Chen, BPC, Chen, DJ., and Sedivy, JM. 2004. Telomere shortening triggers replicative senescence of human cells through a signaling pathway involving ATM, p53 and p21CIP1 but not p16INK4a. **Molecular Cell** 14: 501-513. PMID: 15149599

b. Herbig, U., Ferreira, M., Condel, L., Carey, D., and Sedivy, J.M. 2006. Cellular Senescence in Aging Primates. **Science** 311: 1257 PMID: 16456035

c. Razdan, N, Vasilopoulos, T., and Herbig, U. 2018. Telomere Dysfunction Promotes Transdifferentiation of Human Fibroblasts Into Myofibroblasts. **Aging Cell**, doi: 10.1111/acel

d. Martínez-Zamudio R*, Dewald H*, Vasilopoulos T, Fitzgerald-Bocarsly, P** and Herbig U.** 2021. Senescence Associated β-Galactosidase Reveals the Abundance of Senescent CD8+ T Cells in Aging Humans. **Aging Cell**. e13344 *co-first authors. **co-senior authors. PMID: 33939265

3. **Telomeres and cellular senescence during cancer development.** My studies have additionally contributed significantly to 1) revealing the tumor suppressing functions of TDIS and 2) characterizing the causes of telomere dysfunction and erosion in mammalian cells. Testing the decades-old hypothesis that replicative senescence evolved as a tumor suppressing mechanism in humans, we demonstrated that the vast majority of cells in early neoplastic human lesions - but not cells of their malignant cancer counterparts-, display hallmarks of TDIS. Our data were the first to provide evidence that a telomere initiated senescence response suppresses cancer growth in humans. For many years it was thought that telomere erosion and dysfunction is primarily a consequence of the “end replication problem”, the inability of the replicative polymerase to completely duplicate linear chromosomes. Our work, and that of others, recently changed this dogma. We contributed to revealing that double stranded DNA breaks (DSBs), induced by drugs, endonucleases, or ionizing radiation, are in fact irreparable. As a consequence of genotoxic stresses that also cause telomeric DSBs, telomeres become dysfunctional and rapidly trigger cellular senescence. In addition, we demonstrated that telomere dysfunction observed in tissue culture, as well as in tumor tissue, primarily is a result of telomeric DNA replication stresses triggered by BRCA2 deletion, drugs, oncogene expression, inactivation of the telomere specific DNA replication factor hStn1, or elevating the levels of reactive oxygen species. Our data therefore uncovered a novel and unexpected function for telomeres: that of acting as a molecular trigger of cellular senescence in response to a large number of stresses that place a cell at risk for malignant transformation. We further discovered that cellular senescence, activated by oncogene expression, is not always stable which causes cells to escape from senescence after a period of apparent inactivity. Our studies identified two cell autonomous mechanisms of senescence escape: 1. epigenetic derepression of hTERT expression and 2. POU2F2 dependent activation of cell cycle re-entry.

a. Suram A, Kaplunov J, Patel PL, Ruan H, Cerutti A, Boccardi V, Fumagalli M, Di Micco R, Mirani N, Gurung RL, Hande MP, d'Adda di Fagagna F, Herbig U. 2012. Oncogene-induced telomere dysfunction enforces cellular senescence in human cancer precursor lesions. **The EMBO Journal**. 31: 2839-51. PMID: 22569128

b. Boccardi V, Razdan N, Kaplunov J, Mundra JJ, Kimura M, Aviv A, Herbig U. 2015. Stn1 is critical for telomere maintenance and long-term viability of somatic human cells. **Aging Cell**. 14: doi: 10.1111 PMID: 25684230

c. Patel PL, Suram A, Mirani N, Bischof O, Herbig U. 2016. Derepression of hTERT gene expression promotes escape from oncogene-induced cellular senescence. **PNAS**. 113:E5024-33. PMID: 27503890

d. Martínez-Zamudio, R.I., Stefa, A. Nabuco, JA., Vasilopoulos, T., Simpson, M., Doré, G., Roux, PF. Galan, MA, Chokshi, RJ., Bischof, O. and Herbig, U. 2023. Escape from Oncogene-Induced Senescence is Controlled by POU2F2 and Memorized by Chromatin Scars. **Cell Genomics.** 3, 100293

Complete List of Published Work in MyBibliography: https://www.ncbi.nlm.nih.gov/pmc/?term=herbig+u