2022 Buck Summer Scholar: Zhixin Zhang

My name is Zhixin Zhang, and I recently graduated from the University of California, Berkeley where I majored in Bioengineering. At my home institute, I'm a member of Dr. Irina Conboy's laboratory that studies aging and rejuvenation. In the Conboy Lab, I worked with Dr. Etsuko Watanabe, Dr. Alexandra Benoni, and Dr. Chao Liu on elucidating the mechanism with which cancer affects muscle protein synthesis to understand cachexia, a muscle wasting syndrome that accompanies many cancers. I'm motivated by my research to continue studying the pathology of age-related diseases and hope to pursue a career developing aging interventions. I was fortunate to join Dr. Judy Campisi's laboratory through the Buck Summer Scholars Program, where I was mentored by Dr. Kohsaku Numa and Dr. Koji Kitazawa. The Campisi Lab studies cellular senescence, a state of permanent cell cycle arrest induced by stress and seeks to understand the drivers of senescence and their relationship to age-related pathologies.

Cellular senescence is maintained by major tumor suppressor pathways as a restraint on uncontrolled cell proliferation in cancer. Even though senescent cells stop dividing, they remain metabolically active and are characterized by altered gene expression and gain of senescence-associated secretory phenotype (SASP), a set of secreted factors that can exert effects on neighboring cells. As senescent cells accumulate in aging tissues, their SASP can promote inflammation locally and even systemically. Chronic inflammation is linked to the pathology of most age-related diseases, including diabetes, Alzheimer's disease, atherosclerosis, and more.

My project in the Campisi Lab looked at how senescent cells in the aging ocular surface at the front of the eye can drive the pathology of dry eye disease (DED). DED is a common age-related disease affecting over 16 million people in the US, causing a decreased quality of life for patients and a substantial economic burden on society. DED is characterized by instability of the tear film and chronic inflammation at the ocular surface. Notably, the prominent pro-inflammatory factors present in dry eye over overlaps with SASP, suggesting that senescent ocular surface cells may mediate the chronic inflammation of DED.

Specifically, I studied whether dipeptidyl peptidase-4 (DPP4) can mediate the pro-inflammatory SASP in DED. DPP4 is a transmembrane protein abundantly expressed on senescent cells and not proliferating cells, and it is a multifunctional protein that can cleave other molecules, has immune costimulatory function, and binds other molecules. Importantly, DPP4 can activate key pathways that are master regulators of SASP, which means that DPP4 may have a role in mediating the chronic inflammation in DED. We hope to clarify the role of DPP4 in the pathology of DED and propose a novel intervention for DED through its inhibition. Currently, the treatment of DED through artificial tear fluid, and immunosuppressive drugs in moderate to severe cases, can only alleviate the symptoms of DED but fail to address the source of the chronic inflammation. If DPP4 proves to be a key mediator of senescent cell secreted factors involved in DED, inhibition of DPP4 could be a powerful therapeutic that addresses the crux of the pathology of the disease.

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