these and other groups illustrate, the complex physiological regulation of tissue/organ maintenance and function is not only a fascinating biological problem, but it also has implications for many diseases and other conditions that are tightly linked to our endocrine state, including aging.

STEM CELLS, DIET, AND PHYSIOLOGY

Daniela Drummond-Barbosa, *Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States*

Nutrient availability, stresses, and aging affect tissue stem cells in multicellular organisms; yet, the underlying physiological mechanisms in vivo remains largely unexplored. Dr. Drummond-Barbosa pioneered using Drosophila to study the physiology of tissue stem cell regulation. Her laboratory played a major role in delineating how diet, brain insulin-like peptides, and the TOR nutrient sensor control the germline stem cell (GSC) lineage. They also discovered that adipocyte-specific disruption of amino acid transport, other nutrient signaling, and metabolic pathways causes distinct germline phenotypes. They also showed that nuclear receptors act in multiple tissues to affect the GSC lineage through direct and indirect mechanisms. More recently, her group has been exploring how other physiological stresses affect the GSC lineage. Her group's studies point to extensive communication between the brain, adipocytes, hepatocyte-like cells, and the germline, and underscore the complexity of the physiological network that modulates stem cell lineage behavior.

THE IMPACT OF BONE ON THE BIOLOGY OF AGING

Gerard Karsenty, *Columbia University, New York, New York, United States*

We hypothesized that bone may secrete hormones that regulate energy metabolism and reproduction. Testing this hypothesis revealed that the osteoblast-specific secreted protein osteocalcin is a hormone regulating glucose homeostasis and male fertility by signaling through a GPCR, Gprc6a, expressed in pancreatic β bells and Leydig cells of the testes. The systematic exploration of osteocalcin biology, revealed that it regulates an unexpectedly large spectrum of physiological functions in the brain and peripheral organs and that it has most features of an antigeromic molecule. As will be presented at the meeting, this body of work suggests that harnessing osteocalcin for therapeutic purposes may be beneficial in the treatment of age-related diseases such as depression, age-related memory loss and the decline in muscle function seen in sarcopenia.

AGING GERMLINE STEM CELLS IN C. ELEGANS

E. Jane Hubbard, *Skirball/NYU, New York, New York, United States*

Failure to maintain stem cells with age is associated with conditions such as tissue degeneration and increased susceptibility to tissue damage. We use the C. elegans germline stem cell system as a model to study stem cell aging. This system combines a well-established model for aging with an accessible stem cell system, providing a unique opportunity to understand how aging influences stem cell dynamics. The germline stem/progenitor pool in in C. elegans becomes depleted over time. At the cellular level, aging influences both the size of the stem cell pool and the proliferation rate of stem cells. The flux of differentiated cells also affects how aging impacts the pool. This depletion is partially alleviated in mutants with reduced insulin/IGF-like signaling via inhibition of the transcription factor DAF-16/FOXO. In this role, DAF-16 does not act in the germ line, and its anatomical requirements are different from its previously described roles in larval germline proliferation, dauer control, and lifespan regulation. We found that DAF-16/FOXO is required in certain somatic cells in the proximal part of the reproductive system to regulate the stem cell pool. We also find that the degree to which various age-defying perturbations affect lifespan does not correlate with their effect on germline stem cell maintenance. We are investigating additional aspects of aging germline stem cells using this system.

HOSTMICROBE GENETIC NETWORK INTERACTIONS GOVERN THE RESPONSE TO MICROBES

Nicolas Buchon, *Cornell University, Ithaca, New York, United States*

SESSION 6530 (SYMPOSIUM)

CIRCADIAN RHYTHMS, SLEEP, AND AGING: NEW VISIONS ON THE CLOCK, SLEEP, AND AGING

Chair: Amita Sehgal

The symposium will highlight the reciprocal relationship between aging and sleep and circadian rhythms. Circadian rhythms and sleep deteriorate with age, but at the same time, disruptions in these processes can contribute too aging. Presenters will show how work in model organisms is providing insight into this relationship

MOLECULAR AND CELLULAR NETWORKS THAT DRIVE SLEEP

Amita Sehgal, *University of Pennsylvania, Philadelphia, Pennsylvania, United States*

CIRCADIAN REGULATION OF MITOCHONDRIAL UNCOUPLING AND LIFESPAN

Matthew Ulgherait, *CUMC, New York, New York, United States*

Because old age is associated with defects in circadian rhythm, loss of circadian regulation is thought to be pathogenic and contribute to mortality. We show instead that loss of specific circadian clock components Period (Per) and Timeless (Tim) in male Drosophila significantly extends lifespan. This lifespan extension is not mediated by canonical diet-restriction longevity pathways, but is due to altered cellular respiration via increased mitochondrial uncoupling. Lifespan extension of per mutants depends on mitochondrial uncoupling in the intestine. Moreover, up-regulated uncoupling protein UCP4C in intestinal stem cells and enteroblasts is sufficient to extend lifespan and preserve proliferative homeostasis in the gut with age. Consistent with inducing a metabolic state that prevents over-proliferation, mitochondrial uncoupling drugs also extend lifespan and inhibit intestinal stem cell overproliferation due to aging or even tumorigenesis. These results demonstrate that circadian-regulated intestinal mitochondrial uncoupling controls longevity in Drosophila and suggest a new potential anti-aging therapeutic target.