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Abstract Book

GSA GENETICS G3 Genes | Genomes | Genetics

1 **Welcome and Opening Remarks from Conference Chairs** *Barbara Conradt and Piali Sengupta*

2 **GSA Welcome** *Jane Hubbard* 1) NYU Grossman School of Medicine.

3 **CGC and tribute to Don Moerman** *Ann Rougvie* 1) University of Minnesota.

4 **The diversity of data in Wormbase; how to find it and use it** *Paul Sternberg*

5 **Roles of miRNAs in *C. elegans* development** *Luisa Cochella*[1] 1) Research Institute of Molecular Pathology.

6 **Worms frozen in time** *Oded Rechavi*[1] 1) Tel Aviv University.

7 **Worm Health Organization: Understanding the pandemics facing *C. elegans*** *Emily Troemel*[1] 1) University of California, San Diego.

9 **Rewiring quality control in *C.elegans* meiosis using a new chemically-induced proximity system** *Chenshu Liu*[1,2], Abby F. Dernburg[1,2] 1) University of California, Berkeley, CA; 2) Howard Hughes Medical Institute, Chevy Chase, MD.

During the extended meiotic prophase, homologous chromosomes must pair, culminating with the assembly of synaptonemal complex (SC) along their lengths (synapsis). Synapsis is essential for crossover formation between homologs, and thus for their accurate segregation. In *C.elegans*, defects in synapsis are monitored by a quality control program called the synapsis checkpoint, as one or more pairs of unsynapsed chromosomes lead to a cell cycle delay and can eventually trigger apoptosis. Previous work from our lab revealed that the synapsis checkpoint requires the presence of unsynapsed pairing centers (PCs), special regions on each chromosome that promote homolog pairing and synapsis. However, how cells detect defects in SC assembly remains unknown. In *C.elegans*, the Polo-like kinase PLK-2 shows dynamic subnuclear localization during meiotic prophase: it is first recruited to PCs during early prophase, and following synapsis it relocalizes to the SC. This suggests that the localization of PLK-2 might be part of the signal that triggers the synapsis checkpoint.

To test this idea, we deployed a new chemically-induced proximity (CIP) system that we engineered by modifying a core component of the auxin-inducible degradation system. We engineered mutations into the F-box protein TIR1 to prevent it from interacting with other ubiquitin ligase components. By fusing one protein to this TIR1 sequence and another to a “degron” peptide, we can induce proximity between the two tagged proteins using the small molecule indole acetic acid (auxin). With this system, we successfully targeted PLK-2 to specific chromosomal/nuclear structures. We found that ectopic targeting of PLK-2 to X-chromosomal PCs following synapsis was sufficient to induce apoptosis. Importantly, such induced apoptosis did not require HUS-1, an essential component of the DNA damage checkpoint, but was abrogated by mutation of PCH-2, an essential component of the synapsis checkpoint. By combining this CIP system with various meiotic mutants, I will also discuss about how PLK-2 coordinates with other meiotic kinases and the nucleoskeleton during meiotic quality control and cell cycle progression. Together, we have developed a simple, versatile CIP system and leveraged it to better understand the mechanisms underlying meiotic progression and quality control. This CIP system will enable a wide variety of new experiments in *C. elegans* and other model organisms.

10 **R-loop-induced irreparable DNA damage in *C. elegans* meiosis**

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Most DNA-RNA hybrids are formed naturally during transcription and are composed of a nascent RNA strand hybridized to DNA as part of R-loops. The accumulation of these structures in S-phase can result in replication-transcription conflict, an outcome which can lead to the formation of double strand breaks (DSBs). While R-loops’ role in mitotically dividing cells has been characterized, there are only a handful of studies describing the effect of R-loops in meiosis and these studies present a complex picture of the outcome of R-loop formation on germ cells. Here we show that DSBs formed by R-loops trigger an altered cellular response to DNA damage.

RNase H is an enzyme responsible for degradation of the RNA strand in DNA-RNA hybrids and plays an essential role in preventing this outcome and its deleterious consequences. Using null mutants for the two *Caenorhabditis elegans* genes encoding for RNase H1 and RNase H2 (hereby *rnh* mutants), our studies explore the effects of replication stress-induced DNA-RNA hybrid accumulation on meiosis. As expected, *rnh*∫mutants exhibit an increase in R-loop formation. Consequently, an elevation of DSBs in germline nuclei is evidenced by the accumulation of RAD-51 foci. Despite no repair mechanism abrogation, *rnh* mutants fail to repair all DSBs generated, leading to a fragmentation of chromosomes in diakinesis oocytes. By

stresses through its ability to activate multiple stress response pathways, but that chronic ATFS-1 activation is detrimental for longevity.

1084A The microbiome-muscle connection: Native microbiota affect muscle ageing and motility

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Large-scale human metagenomic sequencing has identified associations between gut microbiome composition and host physiology, including immunity, nervous system function, and ageing. New findings in humans and model organisms suggest that the gut microbiome affects healthy ageing, and that the microbiome could be used to develop interventions to improve the way we age, but underlying mechanisms are not understood.

To define host-microbiome interactions affecting ageing we have established a new model system consisting of the nematode *C. elegans* combined with an experimental microbiome of 11 bacterial isolates representing the most abundant genera of *C. elegans* in the wild. Cultivation with the experimental microbiome preserves age-related motility, an effect that requires components of the p38 MAP kinase pathway, including *nsy-1* and *pmk-1.* The experimental microbiome also induces mitochondrial fragmentation in body-wall muscle in a non-*pmk-1* dependent manner, suggesting multiple routes of communication by which the experimental microbiome may modulate age-related motility.

In a transgenic proteotoxicity model expressing human Aß$_{42}$ in muscle, age-associated paralysis is suppressed by the experimental microbiome. Cell-free supernatant from the experimental microbiome suppresses paralysis and reduces Aß$_{42}$ aggregation *in vitro*, suggesting secretion of microbial bioactive compounds capable of abrogating Aß$_{42}$-associated toxicity. Together these findings show that molecular host-microbiome interactions modulate muscle function, mitochondrial dynamics and proteostasis during ageing to delay age-related decline in motility.

1085B Tyramine modulates the systemic stress response by stimulating the release of intestinal insulin like-peptides (ILPs)

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Multicellular organisms trigger a complex and coordinated response against systemic stress. We have recently shown that in *C. elegans*, the neural stress-hormone tyramine supplies a state-dependent neural switch between acute flight- and long-term environmental-stress responses (De Rosa et al, 2019). Tyramine release during the flight response, stimulates the DAF-2/Insulin/IGF-1 signaling (IIS) pathway and precludes the nuclear translocation of the DAF-16/FOXO transcription factor through the activation of an adrenergic-like receptor TYRA-3 in the intestine. We hypothesize that tyramine stimulates the release of agonist ILPs from the intestine which acts as an autocrine and/or paracrine signal to systemically activate the DAF-2/IIS pathway. To test this hypothesis we are screening ILPs mutants for their resistance to environmental stressors (oxidative and thermal stress). The *C. elegans* genome encodes 40 ILPs, 28 of which expressed in the intestine. We performed a screening of intestinal peptides described as strong DAF-2 agonist, by silencing individual intestinal ILPs and testing worm resistance to environmental stressors (oxidative and thermal stress). Thus, so far we found that *ins-3* and *ins-7* mutants are resistant to environmental stress, like tyramine-deficient and *tyra-3* mutants. We are further testing whether tyramine directly stimulates the release of these ILPs from the intestine through a Gq-protein mediated signaling pathway. These studies will provide insight into how a neurohormone coordinates systemic cellular stress responses.

1086C Host-microbiome interactions with age on *Caenorhabditis elegans* reproduction

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Interactions with and alterations of the gut microbiome with age can have a dramatic impact on our physiology. Changes in the membership of the gut microbiome can dictate levels of immunity, stress resistance and vitality across systems. Linking changes in the microbiome to microbial factors that may influence them has been a challenge in many systems due to the complexity of the microbiomes and intractability of following these interactions over an individual's lifespan.

To address this gap, we leveraged recent advances in characterization of the natural microbiome of *C. elegans* to examine both the gut microbiome on the aging process in *C. elegans* and vice versa. First, we utilized a 64-member microbiome (BIGbiome) and asked whether microbiome membership changed as animals age. Compared to *E. coli* OP50 controls, the BIGbiome