QCB Evenings

Thursday, March 6th • 5:00 – 6:30 PM • SI001

Free pizza and drinks! All students and postdocs are welcome!

Testing the Role of Discoidin Domain Receptors in Nociception | Victoria Lopez, Tracey Lab

Nociception is the sensory process that detects noxious, or potentially tissue-damaging stimuli. Using Drosophila larvae as a model, we are investigating the functions of the *smoke alarm (smal)* and *discoidin domain receptor (ddr)* genes. The Tracey lab previously identified the smal gene for its role in nociception behavior and nociceptor morphology. Both smal and ddr encode homologs for mammalian Discoidin Domain Receptors (DDRs). Mammalian DDRs are receptor tyrosine kinases that are activated by binding collagen. Analysis of *smal* and *ddr* coding sequences in flies suggest that only proteins encoded by the *ddr* locus contain an intracellular kinase. To determine the relationship between *smal* and *ddr*, we are investigating three alternative hypotheses: (1) DDR signals through Smal via cross phosphorylation, (2) Smal negatively regulates DDR, and (3) Smal and DDR signal independently of each other. To investigate these hypotheses, we generated a *smal ddr* loss-of-function double mutant in order to compare to *smal* and *ddr* single mutants. We observed the dendrite morphology of larval nociceptors in this double mutant and in *ddr* single mutants. Based on the nociceptor morphology of these mutants, we hypothesize that *ddr* mutants will phenocopy *smal ddr* double mutants. In addition, RT-PCR data shows that *ddr* is overexpressed in our *smal* null mutant, which has reduced dendrite branching in nociceptors. Interestingly, we also found that overexpression of *ddr* in larval nociceptors is sufficient to reduce dendrite branching. Our evidence suggests that *ddr* functions with *smal* to reduce dendrite branching in larval nociceptors. Further analysis of the double mutant compared to *smal* mutants and *ddr* mutants will allow us to understand epistatic relationships and the role of these genes in nociception and neural function.

The role of the paraspeckles in EWS activated cancers | Renee Kinne, Hollenhorst Lab

The ETS family of transcription factors become aberrantly activated in multiple cancers. This activation is dependent on the co-activator EWS in both prostate cancer and Ewing sarcoma, an adolescent bone cancer. In prostate cancer, EWS is a binding partner necessary for oncogenic ETS, primarily ERG, activation. In Ewing sarcoma, the intrinsically disorder region (IDR) of EWS is fused to ETS members, primarily FLI1, and promotes aberrant expression and activation. The IDR of EWS promotes liquid-liquid phase separation (LLPS) and acts as a transcriptional activation domain. In cells, EWS is found in phase separated bodies called paraspeckles. Paraspeckles are nuclear bodies that have a role in transcriptional regulation, but their role in cancer is not well understood. NEAT1, the essential RNA scaffolding of the paraspeckle, has a role in tumor progression in prostate cancer and I have shown that both ERG and EWS/FLI1 interact with NEAT1. Prostate cancer and Ewing sarcoma lines showed paraspeckle presence through NEAT1 RNA-FISH. Knock down (KD) of two necessary paraspeckle components, NEAT1 or FUS, in Ewing sarcoma cells reduce paraspeckle presence, colony growth, and EWS/FLI1 activity at the transcriptional level. KD of FUS and NEAT1 also increased migration, which is consistent with EWS/FLI1 loss. I have shown that ERG colocalize with EWS granules in a purified protein droplet assay. This suggests that oncogenic ETS can participate in EWS LLPS. I have performed ChIP RT-qPCR and seen that ERG and SFPQ, a necessary paraspeckle protein, can be found at the same genomic region. Taken together these data suggest that the paraspeckle has a role in EWS/FLI1 activity in Ewing Sarcoma and that components of the paraspeckle interact with ERG. Because ERG and FLI1 are homologous, there is potential that the paraspeckle acts as a mechanism of oncogenic transcription in prostate cancer as well as Ewing sarcoma.