QUANTITATIVE AND SYSTEMS BIOLOGY COLLOQUIUM:

A stress induced genetic program promotes suspended animation and canalization of developmental outcomes in zebrafish gastrulae

Dan Wagner

Assistant Professor, OBGYN and Stem Cell Biology

UCSF

Date:

11/7/2024

Time:

10:30 AM - 11:45 AM

Location:

SSM 104

Notable Honors:

2022 Chan Zuckerberg Biohub Investigator Award, Chan Zuckerberg Biohub

2021 NIH Director's New Innovator Award, NIH-NIGMS

2021 Searle Scholar, Kinship Foundation

2018 2018 Breakthrough of the Year - "Development Cell by Cell", Science Magazine

2017 K99/R00 Pathway to Independence Award (1K99GM121852), NIH-NIGMS

2015 HHMI Postdoctoral Fellowship of the Life Sciences Research Foundation (LSRF)

About the Speaker:

I am a single-cell developmental biologist with fifteen years of experience studying mechanisms of cell fate regulation in models of whole-body tissue regeneration and vertebrate embryogenesis, with expertise in single-cell RNA sequencing, droplet microfluidics, bioinformatics, clonal analysis, in vivo quantitative microscopy, and reverse genetics. The long-term goal of my research is to elucidate genetic mechanisms of cell fate feedback control in developing and regenerating animal tissues. During my Ph.D. in Peter Reddien's lab at MIT, I studied the stem cell system of a planarian flatworm species (Schmidtea mediterranea), which is capable of robust body-wide tissue regeneration. Using a variety of lineage-tracing and molecular approaches, my doctoral thesis established the foundation for our understanding of an adult pluripotent stem cell lineage in planarians (the "cNeoblast"), and its role in driving the regenerative process. In November 2014, I initiated a postdoc in systems biology at Harvard Medical School where I developed high-throughput single-cell transcriptomics and bioinformatics methods to define lineage and transcriptional trajectories of vertebrate cell fate hierarchies. These efforts led to landmark collaborative studies with the labs of Drs. Allon Klein, Sean Megason, Alex Schier, Marc Kirschner, and Olivier Pourquie and revealed systems-level views of whole-embryo developmental fate landscapes, neuronal development, and somite development. In January 2020, I started my own lab as an assistant professor at UCSF to further investigate in vivo mechanisms of cell fate feedback control and the genetic basis of birth defects, using the zebrafish embryo as a model.

Abstract:

Across the animal kingdom, developing embryos possess a widely appreciated capacity to self-regulate precise biological patterns in the face of both intrinsic and extrinsic challenges. The ability to detect, adjust, and respond to developmental perturbations to achieve faithful patterning outcomes, often referred to as "canalization", remains a critical yet poorly understood property of embryonic systems. Zebrafish embryos develop rapidly outside the mother and have adapted their developmental program to withstand a variety of environmental challenges. We have characterized a dynamic and reversible diapause-like state of suspended animation that is accessible to gastrula-stage zebrafish embryos exposed to hypoxic challenge. Embryos subjected to oxygen deprivation, physical crowding, or chemical blocking of cellular respiration pause their developmental progression shortly following the appearance of the embryonic shield (the organizer) at 6 hours post fertilization. Following reoxygenation, embryos that had paused for one or more days could resume normal embryonic and larval development and displayed high survival rates (>80%). We have characterized the molecular dynamics associated with hypoxic pausing (entry, maintenance, and exit) through a combination of in vivo imaging, bulk and single-cell RNA-seq and ATAC profiling. These data revealed significant but reversible alterations to organizer-associated developmental gene expression and cell signaling programs (BMP and Wnt) during hypoxic pausing. In addition, we have identified a set of pausing-induced genetic factors that span several predicted molecular functions (hypoxia response, epigenetic regulation, regulation of mRNA stability), which we hypothesize serve protective roles for cells in the paused state. We have performed a targeted CRISPR loss-of-function genetic screen for several of these factors and characterized phenotypes of reduced survival and/or accumulation of dorso-ventral patterning defects following hypoxia, but not during normal development. We conclude that a protective genetic program expressed and required for faithful embryonic patterning under stress conditions promotes the canalization of developmental outcomes.

For more information, contact: Stefan Materna
smaterna@ucmerced.edu