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INTERVIEW

The people behind the papers – Madeline Cassani and Geraldine Seydoux

Specification of germ cell fate depends on the asymmetric segregation of germ granules in early embryos. Now, a new paper in Development describes 'germline P-bodies', germ granules in *Caenorhabditis elegans* embryos, which function cooperatively with another condensate, P granules, in germline specification. To find out more, we caught up with first author Madeline Cassani and corresponding author Geraldine Seydoux, Professor at Johns Hopkins University School of Medicine.

Geraldine, can you give us your scientific biography and the questions your lab is trying to answer?

GS: I became interested in germ cells during my postdoc with Andy Fire when we found that germ cell precursors activate mRNA transcription later than somatic cells. This told us that, right from the start, germ cells differ from somatic cells, and I have been interested in the mechanisms that distinguish germline from soma ever since.

Madeline, how did you come to work in Geraldine's lab and what drives your research today?

MC: When I started grad school, I was really interested in studying germ cells because of previous research experience I had working in Zhao Zhang's lab at the Carnegie Institution for Science Department of Embryology. Once I rotated in Geraldine's lab, I fell in love with *Caenorhabditis elegans* as a model organism because of its genetic tractability and how easy it is to image. The Seydoux lab is also asking exciting new questions in biology, which is what continues to motivate me to do research today.

What was known about the role of germ granules in specifying germ cell fate before this work?

GS & MC: Germ granules are prominent RNA-rich granules in germ plasm. In the 1970s, Tony Mahowald showed that germ plasm can induce germ cell fate when injected at an ectopic location in *Drosophila* embryos. The germ cell fate specifying activity was assumed to reside in germ granules. More recent observations in *Drosophila*, *C. elegans*, zebrafish and *Xenopus,* however, have shown that germ plasm contains different condensate types, which raised the question: which condensates specify germ cell fate?

Can you give us the key results of the paper in a paragraph?

GS & MC: We identified 'germline P-bodies', which are condensates in germ plasm distinct from P granules, the *C. elegans* germ granules. Germline P-bodies, like P-bodies found in somatic cells, contain regulators of mRNA decapping and deadenylation, as well as the intrinsically disordered proteins MEG-1 and MEG-2 and the RNA binding protein POS-1, which is required to activate Nanos translation. We found that *meg-1/2* are required to concentrate P-body components in the germline founder cell, activate Nanos translation and specify germ cell fate.

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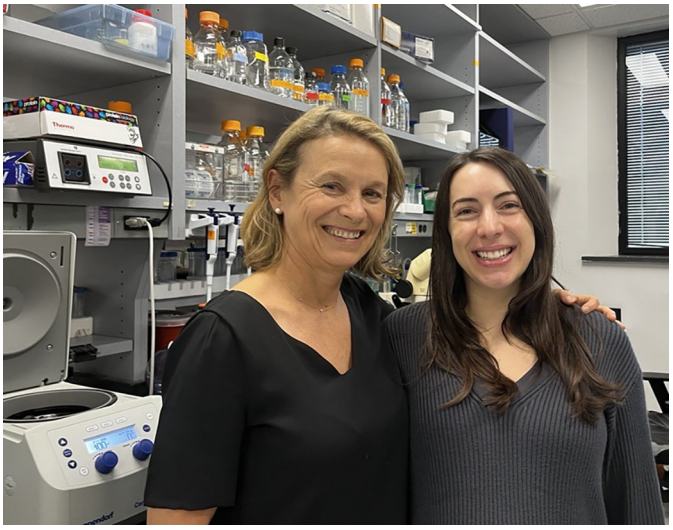

Geraldine Seydoux (L) and Madeline Cassani (R)

Our observations suggest that P granules and germline P-bodies each make complementary contributions towards germ cell fate, with P granules enriching maternal mRNAs in the germline founder cell, and germline P-bodies promoting proper mRNA regulation.

Although able to function independently, P-bodies initially assemble on the surface of P granules and appear to mix in P_4, coincident with the role of MEG-1/2. Do you know how the localisation/mixing of germline P-bodies is regulated and does the close association contribute to efficient functioning of the granules?

GS & MC: The evolving localization of P-bodies and P granules is really interesting, but we don't yet know its significance or how it is regulated. It is tempting to think that the merging of P-bodies and P granules in the germline founder cell is what activates Nanos translation and germ cell fate at that stage. However, Nanos regulation still occurs normally in mutants where P granules do not form and Nanos RNA is always present throughout the cytoplasm. An alternative possibility is that fusion of germline P-bodies to P granules is a consequence, rather than a cause, of binding of P-body proteins to mRNAs in P granules.

Have you tried expressing MEG-1/MEG-2 in somatic cells; do you think this would be sufficient to alter cell fate specification?

GS & MC: That would be a fun experiment! But technically challenging, as we do not yet know how MEG-1/MEG-2 become enriched in germ plasm...

When doing the research, did you have any particular result or eureka moment that has stuck with you?

MC: For a long time, we were really confused about the role of MEG-1/2, because it was always assumed to be part of P granules,

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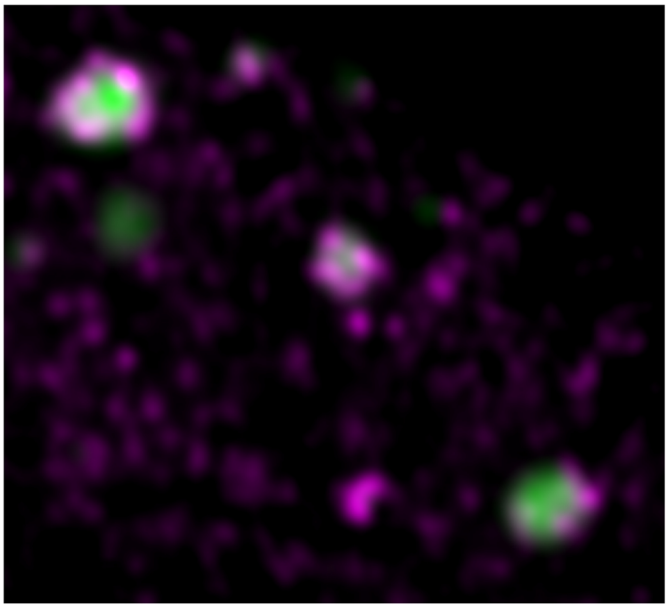

P granules (green, PGL-3) and germline P-bodies (magenta, CGH-1) in the germ plasm of a P_1-stage blastomere. Germline P-bodies are enriched at the surface of P granules, as well as throughout the cytoplasm.

yet there was only a very subtle effect on P granules in *meg-1/2* mutants. When we finally realized that MEG-1/2 are required to stabilize P-body components in the germline founder cell, it really helped to guide our research forward.

And what about the flipside: any moments of frustration or despair?

MC: Yes, there were many times of confusion when we didn't know where the project was going or experiments simply weren't working as expected. One specific moment was when I observed an interesting phenotype when knocking down *meg-1/2* in a strain containing a GFP-tagged protein. After doing many experiments with this strain, it all turned out to be an artefact due to the GFP-tag. Our lab and others have noticed that proteins in condensates are often not fully functional when tagged with fluorescent proteins and that is something to control for in the future.

What is next for you after this paper?

MC: I think it would be exciting to continue to study how P-bodies regulate cell fate transitions, as they have been implicated to in other organisms and tissue types. However, I just graduated and am still in the process of figuring out where I'm going and what I'll be doing next!

Where will this story take your lab next?

GS: Madeline's findings have really changed my view of the role of condensates in germ plasm. Before, I thought that enrichment of mRNAs in P granules was important for their regulation – now, clearly what's more important is regulation by factors in germline P-bodies. The next challenge is to figure out how these factors become activated in the germline founder cell, how they decide which mRNAs to degrade and which mRNAs (like Nanos) to translate, and how does all this regulation impact germ cell fate. I am excited because Madeline's findings give us an opportunity to understand how P-bodies, condensates found in many cell types including germ cells in mammals, contribute to germ cell fate.

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Finally, let's move outside the lab – what do you like to do in your spare time?

MC: In my free time I enjoy reading, trying new recipes in the kitchen and spending time outdoors.

GS: Lately, I have found myself returning to one of my favourite activities in graduate school: travelling! I just came back from a wonderful trip to Cambodia – traveling abroad expands my understanding of the human experience and helps me find space for reflection, gratitude and wonderment.

Reference

Cassani, M. and Seydoux, G. (2022). Specialized germline P-bodies are required to specify germ cell fate in *Caenorhabditis elegans* embryos. *Development* **149**, dev200920. doi:10.1242/dev.200920