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Q&A

Meet the authors: Joakim Lundeberg and Eva Gracia Villacampa

Joakim Lundeberg and Eva Gracia Villacampa are senior and first authors, respectively, of "Genome-wide spatial expression profiling in formalin-fixed tissues," a Technology article in this issue of *Cell Genomics*. In an interview with *Cell Genomics*, the authors discuss a procedure they developed to perform genome-wide spatial analysis of mRNA in FFPE fixed tissue sections.

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Joakim Lundeberg is a professor in molecular biotechnology at Science for Life Laboratory, KTH Royal Institute of Technology in Stockholm. The current focus of his lab is to develop experimental and bioinformatics protocols to study omics data in tissue sections.

Eva Gracia Villacampa is a PhD student in the division of gene technology at KTH Royal Institute of Technology in Stockholm in the laboratory of Joakim Lundeberg. Her main field of research is spatial transcriptomics method development and its applications in biomedical research.

What motivated you to become a scientist?

JL: Curiosity! My interests have spanned a wide range during my career, initially focused on cloning and then sequencing of genes, and now recently on the spatial localization of genes and the understanding the molecular ecosystem in health and disease.

EGV: I had many different interests but, ultimately, was motivated to take a scientific career path by the goals of expanding our knowledge and improving quality of life through technological and medical developments. Additionally, a career in science gives you a chance to bring positive change to society while it's also a highly regarded and exciting profession.

Eva, what motivated you to join Joakim's lab?

EGV: I joined Joakim's lab right after completing my master's degree in medical biotechnology at the KTH Royal Institute of Technology in 2017. At that time, spatial transcriptomics (ST) was a relatively new technology. I found a high level of expertise, excitement about developing these new technologies, and an excellent atmosphere in Joakim's lab, which is what made me want to pursue a PhD in his lab.

Please tell us about the technology you developed and how this relates to other methods

EGV: We developed an adaptation of ST to be compatible with formaldehyde-fixed tissues. Its objective is to perform unbiased genome-wide spatial analysis of mRNA using spatially barcoded oligo(dT) probes to capture the 3′ end of mRNA molecules in tissue sections combined with high-resolution imaging. It now also relates to the commercial solution for formalin-fixed paraffin embedding (FFPE) samples released by 10x Genomics a few months ago, but in that case, they use probes against the whole transcriptome instead of direct polyA capture.

How did the concept for this technology development work originate? Why did you feel this was worth pursuing in your lab?

EGV: I believe it was very straightforward, mainly due to apparent demand for it. Following the first publication of ST, many people contacted Joakim regarding the compatibility with FFPE samples, as FFPE is the most widespread tissue preservation approach. However, the development of ST methods for FFPE samples was limited by the technical challenges caused

by formalin-induced cross-linking and degradation of mRNA molecules. We wanted to address that challenge by adapting protocols based on commercially available platforms.

Where do you think your methods will have the most significant impact on biomedical research?

EGV: Primarily, these methods will allow for spatial transcriptomic analyses on the rich resources of biobank samples, where fresh frozen samples are the standard for storage of clinical samples. This will promote research on archived biospecimens and allow for ST-informed retrospective and longitudinal studies on biological processes, biomarker discovery, disease progression, immunological responses, and organ development. This method will also bring a positive impact in those areas where there is low availability of fresh frozen samples, including for studies of rare diseases and studies involving pathogens inactivated by formaldehyde treatments.

What other technological challenges are currently a priority for single-cell research?

JL: Integration of additional modalities in a single tissue section—both experimentally and computationally. Multimodality has already proven its impact on single cells, and new results are now emerging for spatial platforms. It will be exciting to explore if the same is true for spatial data as for single cells. It is already clear that antibody stains can provide additional information about cell types to simplify cell segmentation and identification. Still, the power would be combined if protein and RNA data can give a higher order of tissue organization that can be deconvoluted by computational means.

What single-cell research studies do you dream of conducting if there were no budgetary or technical limits? What are the current challenges that need to be overcome?

JL: I dream of simultaneously imaging live tissue and capturing multi-omics data. Temporal aspects will provide an essential new dimension, and the experimental challenge is to capture high-content molecular omics data without tissue destructing. Indeed, we have already shown great value in studying temporal changes in ALS disease in a spatial context (Maniatis et al., 2019). In that study, we identified gene expression changes before morphological changes, with experiments that were only made possible using multiple temporal end-point analyses destroying the sample. There is also some promise that imaging could be performed continuously, in real time on live tissue, to provide RNA data that are spatially extracted without affecting the tissue. Studies using micromanipulation have shown that a portion of cytoplasmic RNA can be retrieved from a cell, which can continue to divide and proliferate. This gives hope that such procedures can be used as a basis for imaging and spatial analyses in live tissue.

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