Mapping Molecules of an Unsung Brain Cell

In a first, Fred Hutch researchers create a gene-expression map of glial cells in tiny worms. Here's why that matters.

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An estimated 86 billion neurons in the average human brain govern our body's functions and conjure — somehow — the human mind.

To better understand how those billions of cells talk to each other across a vast network comprising trillions of connections, researchers study the nervous system of a tiny worm called Caenorhabditis elegans, an organism that shares many features with human biology and has yielded insights leading to Nobel prizes in 2002, 2006, 2008 and 2024.

C. elegans has 302 neurons in one sex and a few more in the other. Scientists have charted which genes in those neurons are turned on to make which proteins, the building blocks cells need to do their jobs. They've also diagrammed how those neurons connect and communicate.

But those maps leave out the other major cell type of the nervous systems of both worms and humans — glial cells — which is like making a globe that shows only continents but no oceans.

In a study published recently in the journal Developmental Cell, researchers at Fred Hutch Cancer Center present an atlas of gene expression in C. elegans glial cells, including differences across sexes, that fills in the gaps and makes some scientific history.

A cell atlas of all glia of an animal, which includes a public website to visualize the data — wormglia.org — is a first for any organism.

When combined with existing neuron atlas and network maps for C. elegans, it completes the first detailed molecular and cellular map of the entire nervous system of a multicellular adult animal. This now provides researchers a powerful and complete cell-by-cell, gene-by-gene view inside the brain of an animal.

Why does this matter? Although glial cells comprise half the number and volume of cells in the human brain, historically they haven't received the same scientific attention as neurons.

It was originally assumed that that glial cells didn't warrant as much scrutiny because they serve passive, supporting roles — holding neurons together, delivering nutrients, cleaning up after them and helping them talk to each other efficiently — while neurons call all the shots.

"We are really starting to appreciate a lot more the active role that glial cells play in helping neurons decide who they can talk to, who they don't talk to and how they connect, how long they can communicate," said the study's lead author, Aakanksha Singhvi, PhD, of Fred Hutch's Basic Sciences Division. "The story has entirely flipped on its head in the last two decades, so we're very happy to have been part of that change."

She works at the forefront of efforts to better understand what glial cells are, what they do and how they contribute to brain diseases such as epilepsy, Parkinson's and Alzheimer's when they malfunction. But it's still early days for such research.

"In general, we know very little about glial cells," Singhvi said. "They're really the black box in the black box that's called the brain."

To better navigate this uncharted territory, she teamed up with Manu Setty, PhD, a computational biologist in the Basic Sciences Division.

Making a map by feeling their way through the dark required "wet lab" sequencing techniques to figure out the gene expression patterns in each glial cell, combined with "dry lab" computational modeling to make sense of the enormous dataset they generated.

"We would have these group meetings together where we would brainstorm and say, 'OK, this is the biology we are after and this is the data,'" Singhvi said. "We would go back and forth and come up with a plan that was both rooted in the computational aspects as well as the wet lab aspects, each of us knowing the limitations of our technique and the strengths that we can bring to the table."

Glial cells provide more than support

Singhvi's lab has helped pioneer the use of C. elegans worms, which are about 1 millimeter long, to study glia and understand the fundamental biology of brain cells.

Her team has discovered that glial cells also orchestrate neural activity and influence behaviors as varied as sensory perception, learning and memory and aging of the nervous system.

Historically, glial cells have been categorized by their anatomy, but this study found that even glia that are anatomically identical may vary significantly, turning on different genes to make different cellular building blocks called proteins with different functions.

"Molecularly, two different things that look anatomically similar may not do the exact same thing, and they may have different functions to play," she said. "Just because it looks like a round circle

doesn’t mean it’s always an eye, right?”

Glial cells may also vary by sex, though the evidence is limited.

That’s why the field needs an atlas of gene expression to tell glial cells apart.

Counting transcripts in individual cells

Every cell of our bodies contains the same DNA, but skin cells and lung cells and brain cells all turn on different genes within that DNA, which provide the specific sequences of nucleotides needed to make the proteins each type of cell needs to do its job.

Think of genes like pages of a book that can never leave the DNA library of the cell’s nucleus.

Instead, the sequence needed to make a protein is copied or transcribed from the gene into messenger RNA.

That mobile copy — called an mRNA transcript — delivers the sequence out of the library and into one of the cell’s many molecular factories. There, the copied sequence of nucleotides is translated into a sequence of amino acids, punching out a chemical ribbon that folds into a 3-D shape defining its function.

To understand the gene expression of a single cell — which genetic sequences in the library are getting copied and how often — researchers must work backwards by identifying all the transcripts that cell’s nucleus is cranking out.

A map tracing the gene expression of an entire class of cells, such as glia, is called a transcriptome.

A single-cell transcriptome exists for the neurons in C. elegans as well as a connectome mapping all the worm’s neural connections.

But constructing a transcriptome for glial cells was difficult because so little is known about them on the molecular level. It was like figuring out all the ingredients of a cake without a recipe.

Instead, Singhvi’s team, led by postdoctoral research fellow, Maria D. Purice, PhD — first author on the study — had to reverse-engineer the dessert after it was baked to figure out what made it delicious.

They used an RNA sequencing method that extracts transcripts from inside the individual nuclei of glial cells across both sexes and works backward to determine which genes were copied and how often.

The sequencing produced a huge dataset, but they needed some computational help to transform that big list of ingredients into meaningful recipes for each type of glial cell.

“We have to kind of go from this really noisy, messy data to something that actually makes sense,” Singhvi said.

Predicting what makes glial cells similar and distinct

Setty’s team used various computational techniques to organize the cells into groups based on shared ingredients — chocolate cakes in one group and cheesecakes in another group, for example.

Just as cakes may look similar, but each has a distinct flavor, glial cells differ from each other in significant ways that affect their function.

“Every glial cell, whether or not it looks the same, has its own unique combination of molecules that makes it different from the next glial cell,” Singhvi said. “Not every glial cell will do the exact same work because their combination of things they have in their portfolio is different.”

They grouped the cells by the ingredients they shared with other cells, a process that revealed a surprising variety of distinct groups.

Out of 50 glial cells, they identified 32 distinct clusters.

“First of all, we are all surprised that there are so many clusters,” Setty said. “But when you have clusters, it just says these cells belong to a group. It doesn’t necessarily tell you what the properties are that define the group.”

To identify the properties of each group, they first needed to find a minimal set of genes — a signature — that distinguishes glial cells from non-glial cells. Then they looked for other signatures that distinguish types of glial cells from each other as well as how glial cells differ across sexes.

Setty trained a machine-learning computer model on the gene expression data so that it could make accurate predictions about which genes most likely comprise those different signatures.

Given a list of ingredients but no recipe, could the model predict the type of cake?

“Everything we do in computation is just a prediction, right? Nothing is a validation,” Setty said.

Purice, with help from many other researchers in the Singhvi lab, then tested those predictions in real life with real worms.

She would try to find some glial cells in the entire worm nervous system that matched the same properties as a signature predicted by the model.

They repeated the cycle of “dry lab” prediction and “wet lab” validation several times, which revealed each cell’s molecular recipe with unusual clarity, making it possible to gain “deep mechanistic insights into glial biology brain-wide,” according to the study.

They found, for example, that a core set of six genes could tell glial cells apart from non-glial cells. They also tested predictions about what genes define distinct glial cell classes and how signatures differ across sexes.

“Very few atlas studies do this level of extensive validation, going back in the animal and making sure,” Singhvi said. “That’s really important. This dataset is now telling us that glial cells in the back of your brain and in the front of your brain are very different and are doing different things — it’s that level of distinction that we have been able to glean out of this careful analysis, which is very important when you’re thinking of how the whole brain is working.”

Opening a new can of worms

Glial cells in worms perform the same function in worms as they do in humans, such as the glial cells that regulate neuron activity and shape.

“Most functional genes in the glial cell, the business end of the glial cell, are conserved and are exactly the same between C. elegans and humans,” Singhvi said. “There’s some variations, which makes sense because the poor worm has only 50 glial cells, but it’s doing most of the functions that the 86 billion glial cells in a human brain are doing.”

The glial cell gene expression atlas makes it possible to explore in more depth how glial cells work in both species.

“It really opens up a lot of questions about how glial cells develop in different parts of the brain, how they develop in different sexes, and what makes glial cells the same or different,” Singhvi said. “I mean, it really opens up an entire can of worms, literally, about glia biology.”

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