Research Roundup

B cells spread to affinity

B cells extend like fishnets to capture and then draw in antigens, according to new research by Sebastian Fleire, Facundo Batista (Cancer Research UK London Research Institute, London, UK), and colleagues. The mechanism allows B cells to discern the affinities of the different membrane-bound antigens they encounter.

The interaction of B cell receptors with antigens gives birth to the immunological synapse, spurring B cell activation and antigen presentation to T cells if the antigen is sufficiently well suited to the B cell receptor. Batista's group examined the cellular changes that accompany the first moments of synapse formation.

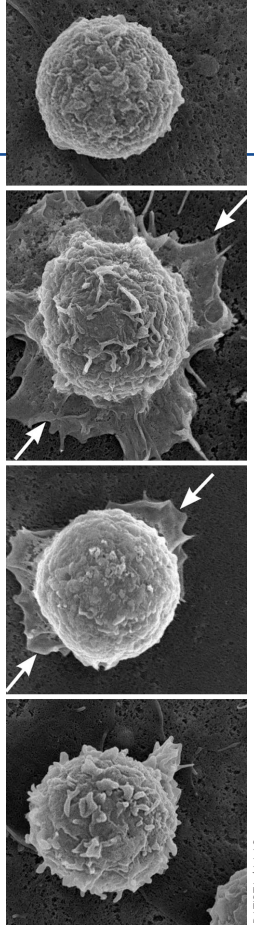
The authors exposed naive B cells to lysozyme antigens with varying affinities for a B cell receptor and watched as the cells first spread, and then contracted inward, drawing in their captured antigens. The degree of B cell spreading depended on two factors: the amount of antigen detected by the B cell and its affinity toward the antigen.

The spread–contract mechanism may help the immune system select for B cells that produce the highest affinity antibodies to a specific antigen. "If you have a high-affinity interaction, you will see higher spreading," says Batista. More antigen will thus be aggregated, which in turn will increase B cell maturation and activation.

The researchers supported their experimental results with a mathematical model in which disabling B cell spreading led to similar amounts of antigen accumulation for both low- and high-affinity antigens. With spreading, however, abundant high-affinity antigens were gathered in higher quantities.

Batista notes that, by spreading and contracting, a B cell improves its chances of eliciting T cell help. More broadly, he says, "this could be a general mechanism by which cells recognize different ligands." T cells, for example, were recently shown to spread in a similar manner. JCB

Reference: Fleire, S.J., et al. 2006. *Science.* 312:738–741.



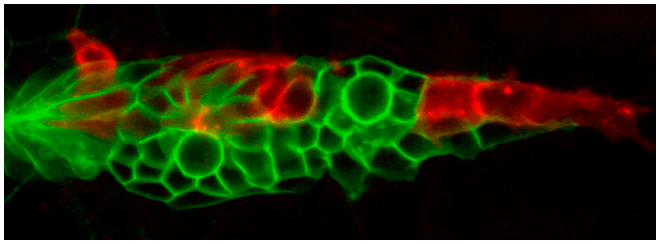
BATISTA/AAAS

B cells spread and contract (top to bottom) to pull in membrane-bound antigen.

Cell clusters follow the leaders

Organogenesis requires the collective movement of large groups of cells during development. According to a new study by Petra Haas and Darren Gilmour (European Molecular Biology Laboratory, Heidelberg, Germany), one such mass transit is directed by a few leader cells that respond to a chemokine signal to guide the trek and keep the marching troops in formation.

The cluster of about 100 cells that forms the posterior lateral line primordium (pLLP), the progenitor of the zebrafish mechanosensory organ, marches down a stripe of the stroma-derived factor 1 (SDF1) chemokine. Time-lapse imaging showed that the tissue's trajectory was controlled by cells that extended filopodia on the leading outer edge of the pLLP. For the column of cells to move, only leader cells required Cxcr4b, the SDF1 receptor; cells on the interior of the pLLP did not need the receptor.



GILMOUR

Migration and shape of a Cxcr4b-deficient cell mass (green) is rescued by a clone of WT cells (red).

Leaders in pLLP migration seem to get appointed to the post, perhaps by having higher receptor activity, says Gilmour. When wild-type and Cxcr4b-lacking cells were combined in genetic mosaic experiments, the wild-type cells quickly took position on the leading edge to restore proper movement.

"We think the job of guiding will be given to those cells that initially sense the most," Gilmour says. "The cluster is extremely unstable. Whenever it has reduced chemokine signaling, it rolls around, and it is this instability that allows sensing cells to get into a position where they can reinstate order." As few as four transplanted Cxcr4b-expressing cells were able to curb the chaos and generate normal movement in mutant tissue.

Solo cell migration is known to be regulated by diffusible gradients of chemokines, but guidance of the pLPP relies more on the self-organization of the cell mass. In mutants with spatially interrupted SDF1 expression, the pLLP made a U-turn where SDF1 ended and reentered the chemokine stripe from the reverse direction. A U-turn would be unlikely in a gradient-controlled situation.

How leader cells coordinate movement is not yet known. One possibility is mechanical pushing and pulling forces among cells. Gilmour believes that the mechanism may apply generally to the migration of cell groups. JCB

Reference: Haas, P., and D. Gilmour. 2006. *Dev. Cell.* 10:673–680.

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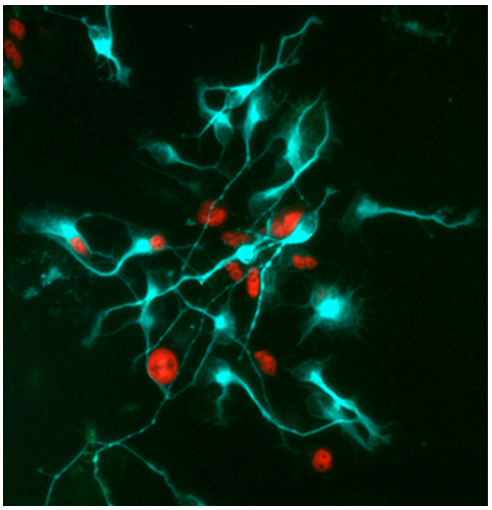


SHEN/ELSEVIER

A clone from a single cortical progenitor contains both early-born (green) and later-born (red) neurons.

Time out for neurons

Neural progenitors have an internal clock that determines the fates of their daughter cells, according to new research by Qin Shen, Sally Temple (Albany Medical College, Albany, NY), and colleagues.

Cortical neurons are born in strict order: subtypes born earliest form layer one and the subplate; consecutively later-born subtypes construct the six cortical layers from the bottom up. The researchers now show that vertebrate neural progenitors maintain this order without extrinsic cues. "In vitro recapitulation of normal timing suggests that there is an internal program," says Shen.

The internal controller seems to be the Foxg1 transcription factor, which was previously linked to the control of timing in neurogenesis. When the researchers knocked down Foxg1, older progenitors reacquired their ability to make younger subtypes. The lab is now looking for changes in gene expression stemming from reduced Foxg1 levels. "If we can identify the genes controlling the timing process," Shen notes, "we may be able to make or suppress a subtype by manipulating these genes."

The findings also sound a note of caution for therapeutic stem cell research. Progenitors from younger mouse embryos could produce the full complement of subtypes, but older progenitors generated only later-born cells. "Stem cells may be limited in their ability to provide different neurons," Shen says, "depending on the stage of extraction." JCB

Reference: Shen, Q., et al. 2006. *Nat. Neurosci.* doi:10.1038/nn1694.

Genome punctuation

The DNA replication process recognizes transcription regulatory elements as punctuation marks at the start and end of genes, according to new research by Ekaterina V. Mirkin, Sergei M. Mirkin (University of Illinois, Chicago), and colleagues.

Because transcription and replication often occur concurrently and share a template, they occasionally collide. Sergei Mirkin and colleagues previously saw that the *Escherichia coli* replication fork slowed considerably during collisions with the moving RNA polymerase. The group now shows that replication also slows down upon colliding with a motionless RNA polymerase.

The stall occurs either just before or just after the coding frame, depending on the direction of the collision. Replication forks coming from the gene's tail end paused at the promoter. When the transcription cassette was flipped to coorient transcription and replication, the fork paused at the terminator instead.

The fork's pause signals are the transcription initiation and termination complexes, depending on the direction. "This polarity," says Mirkin, "assures the replication fork pauses immediately after it passes the coding region, no matter which direction it came from."

Mirkin suggests that these pauses might be a window of opportunity to correct mistakes in the newly replicated DNA. "Imagine a mark for the replication fork that says, 'Look, you just finished copying a very important part of the text. Now slow down and check your work.'" JCB

Reference: Mirkin, E.V., et al. 2006. *Proc. Natl. Acad. Sci. USA.* 103:7276–7281.

ES cells clean house

Malin Hernebring, Thomas Nyström (Göteborg University, Göteborg, Sweden), and colleagues find that mouse embryonic stem (ES) cells do some spring cleaning during differentiation to rid themselves of protein damage.

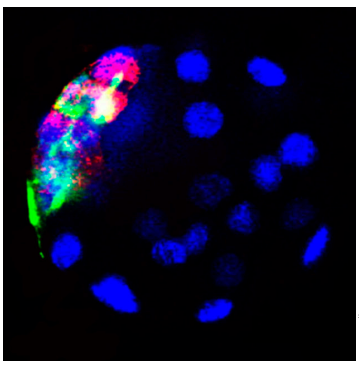
Protein damage is absent in young tissue but accumulates with age. The authors wondered what prevents run-down proteins from being passed via the germline to a newly developing organism.

To address this issue, the researchers measured carbonylation and advanced glycation end product (AGE) formation—two common types of protein damage—in cultured undifferentiated ES cells. "What's been assumed," says Nyström, "is that the [ES] cells would be miraculously kept free of protein damage." But the group was surprised to find levels of these contamination products equivalent to those found in a middle-aged mouse.

After cultured ES cells differentiated, levels of both damage markers dropped dramatically. In blastocysts, too, proliferating cells of the inner cell mass showed damage, but differentiated cells on the outer surface did not.

The elimination of protein damage was accompanied by a threefold increase in the activity of the 20S proteasome, which was previously implicated in degrading oxidative stress products. Nyström posits that this process cleanses the cellular protein slate. The team is now examining how the proteasome's activity is regulated. JCB

Reference: Hernebring, M., et al. 2006. *Proc. Natl. Acad. Sci. USA.* doi:10.1073/pnas.0510944103.



NYSTRÖM/NAS

Undifferentiated cells in the inner cell mass (green) contain proteins damaged by carbonylation (red).