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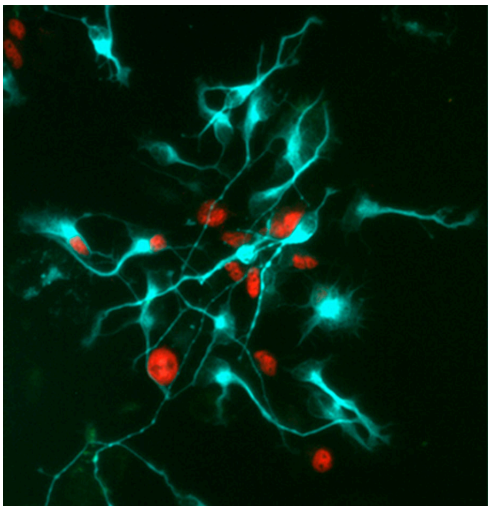


SHEN/ELSEVIER

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.

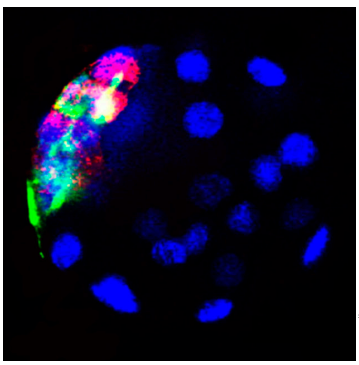
Protein damage is absent in young tissue but accumulates with age. The authors wondered what prevents run-down proteins from being passed via the germline to a newly developing organism.

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).