

miR-9a reduced the expression of the reporter gene by 70%. So, in cells that are not destined to become SOPs, *miR-9a* inhibits residual *sens* expression by binding its 3' UTR, thereby preventing proneural gene expression and SOP development.

But, it seems unlikely that *miR-9a* functions as an absolute switch; only a proportion of *miR-9a*-deficient flies developed additional sensory organs. The authors propose that *miR-9a* functions to fine-tune *sens* expression and the proneural gene feedback loop, thereby ensuring the precision of the production of SOPs. Intriguingly, *miR-9a* is 100% conserved from flies to humans, and *miR-9a* is highly expressed in neurogenic regions in the developing and adult mammalian brain. Perhaps, the authors note, *miR-9a* is also involved in mammalian neurogenesis.

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ORIGINAL RESEARCH PAPER Li, Y. *et al.*

MicroRNA-9a ensures the precise specification of sensory organ precursors in *Drosophila*. *Genes Dev.* **20**, 2793–2805 (2006)

FURTHER READING Cohen, M. S. *et al.*

Denoising feedback loops by thresholding — a new role for microRNA. *Genes Dev.* **20**, 2769–2772 (2006)

According to the linear model of PCP, morphogen gradients, such as Hedgehog (Hh) in the abdomen or Wingless (Wg) in the eye, control polarity by establishing gradients of the Ds system, which then functions through the Stan system. But, if these two systems are independent, how does Hh signalling function? Constitutive activation of the Hh pathway in clones reverses the polarity of nearby hairs in both *ds⁻* and *stan⁻* flies, but not in *ds⁻ stan⁻* flies, which indicates that Hh polarizes cells through both the Ds system and the Stan system.

From these findings, the researchers propose a radical new model that the Ds system and the Stan system each uses an independent mechanism to polarize cells and to propagate polarity from cell to cell.

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ORIGINAL RESEARCH PAPER Casal, J. *et al.*

Two separate molecular systems, Dachous/Fat and Starry night/Frizzled, act independently to confer planar cell polarity. *Development* **133**, 4561–4572 (2006)

BIOENERGETICS

Turn up the heat

PGC1 transcriptional co-activators are important regulators of mitochondrial biogenesis and respiration. Two new studies from the Spiegelman laboratory now shed light on the role of PGC1 in several disease aetiologies. PGC1 α and PGC1 β are implicated in oxidative-damage-related neurodegeneration by suppressing the generation of reactive oxygen species (ROS). Moreover, PGC1 α is associated with defective energy homeostasis associated with Leigh syndrome French Canadian variant (LSFC), a genetic disorder that is characterized by neurodegeneration and severe liver defects.

Given that the mitochondrial electron-transport chain is the main producer of ROS, the authors examined the role of PGC1 α and PGC1 β in ROS metabolism. Following exposure to oxidative stress, the expression levels of *Pgc1 α* , and to a lesser extent *Pgc1 β* , were increased, as were those of several genes encoding components of the ROS defence system including several ROS-detoxifying enzymes. RNA-interference-mediated knockdown of either one or both co-activators reduced the basal gene-expression levels of components of the ROS defence system, and the induction of gene expression following an oxidative challenge was practically abolished. Cells from *Pgc1 α* -null mice showed reduced gene expression of components of the ROS defence system and increased sensitivity to oxidative stress. Spiegelman and co-workers therefore concluded that PGC1 α and PGC1 β regulate the basal and induced gene-expression levels of the ROS defence system.

By challenging the brain of *Pgc1 α* -knockout mice with oxidative stress, Spiegelman and colleagues observed increased neuronal damage, which occurred with excessive oxidative stress. By contrast, overexpression of PGC1 α in neuronal cells that were subsequently exposed to oxidative stress resulted in increased survival. This protective effect was associated with increased gene expression of ROS-detoxifying enzymes.

These findings imply that PGC1 α “may serve as an adaptive set-point regulator” that allows the stimulation of mitochondrial electron transport without causing self-inflicted oxidative damage. In other words, PGC1 α can turn up the heat safely.

In a second study, the Spiegelman group purified the PGC1 α holoenzyme complex and identified the LRP130 protein, which is mutated in patients with LSFC, as one its components. The authors showed that LRP130 regulates the



transcription of the *Pgc1 α* gene, which, in turn, regulates many genes. They found that LRP130 is required for the regulation of certain PGC1 α target genes that are required for gluconeogenesis and mitochondrial electron transport. The significance of these findings was tested *in vivo* by treating mice with *Lrp130* small interfering RNA, and the mice were subsequently either fed or starved. The expression of several gluconeogenesis genes was strongly induced in control mice that had been starved, but this induction was blocked in *Lrp130*-knockdown mice. Glucose and ATP production were also significantly reduced in these mice compared with control mice. Together, these data link LRP130 and PGC1 α to defective hepatic glucose and energy homeostasis in patients with LSFC. Whether the neurodegeneration phenotype of LSFC is linked to a sensitivity to oxidative stress remains to be determined.

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ORIGINAL RESEARCH PAPERS St-Pierre, J. *et al.* Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* **127**, 397–408 (2006) | Cooper, M. P. *et al.* Defects in energy homeostasis in Leigh syndrome French Canadian variant through PGC-1 α /LRP130 complex. *Genes Dev.* **20**, 2996–3009 (2006)

WEB SITE

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