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NEUROSCIENCE:

Imprinting in the brain

Edwin C. Oh and Nicholas Katsanis

Center for Human Disease Modeling, Duke University, Durham, North Carolina 27710, USA.

Nicholas Katsanis is also in the Departments of Cell Biology and Pediatrics

Nicholas Katsanis: katsanis@cellbio.duke.edu

Abstract

A gene is considered to be imprinted if only the copy inherited from the mother or from the father is expressed throughout life. But one imprinted gene, *Dlk1*, disobeys this rule during postnatal neurodevelopment.

In the adult mammalian brain, neural stem cells continually give rise to new neurons. There is hope, therefore, that these cells might also be of use for treating brain injuries and neurological disorders. Although the molecular signals that establish and maintain neural stem cells are starting to be understood^{1,2}, the roles of genetic determinants and environmental cues in these processes remain largely mysterious. On page 381 of this issue, Ferron and colleagues³ show how one gene, *Dlk1*, is necessary for regulating the numbers of mouse neural stem cells soon after birth and in adulthood.

Multicellular organisms inherit equivalent complements of maternal and paternal chromosomes. Nonetheless, the expression of genes from either the maternal or the paternal copy of a chromosome can be regulated by DNA methylation and post-translational modification of the DNA-associated histone proteins in a heritable process called genomic imprinting⁴. In the brain, more than 1,300 transcripts are imprinted^{5–7} — a feature that is remarkably distinct from other tissue-specific expression profiles and indicates the brain's particular sensitivity to imprinting. *Dlk1*, which also has roles in the regulation of fat tissue, blood cells and skeletal-muscle development, is one such imprinted gene in the mouse brain, as only its paternally inherited copy is expressed⁸.

Given the significance of imprinted genes in the nervous system, Ferron *et al.*³ investigated the role of *Dlk1* in embryonic, postnatal and adult mouse neurogenesis in the subventricular zone (SVZ) of the lateral ventricles. The SVZ is one of two discrete regions in the adult brain where neurogenesis occurs, the other being the subgranular zone in the dentate gyrus of the hippocampus — a structure implicated in learning and memory.

In neurogenic areas, the authors detected *Dlk1* expression both in mouse embryos and after birth, with levels peaking at postnatal day seven (P7) — a transition period between the development of the embryonic and the mature SVZ. However, whereas mice lacking *Dlk1* (*Dlk1*^{−/−} mice) showed no major differences in the number of proliferating cells in their brains' germinal regions at embryonic stages, at P7 they had more proliferating neural stem cells (NSCs) compared with normal mice. Notably, the authors also observed more proliferating NSCs at P7 in mice carrying a non-functional *Dlk1* copy of either maternal or paternal origin — a finding that suggests that imprinting is irrelevant in postnatal neurogenesis.

In the adult brain, loss of *Dlk1* was also associated with a precipitous decline in the number of NSCs and fewer neurons migrating from the SVZ towards their final destination (the

olfactory bulb). These results indicate that disruption of NSC quiescence at early postnatal stages leads to their depletion — and so to depletion of neurons arising from them — in the adult brain.

When stem cells harvested from the brain are maintained in tissue culture, they form spherical clusters called neurospheres⁹. To examine the mechanism by which *Dlk1* might affect NSC maintenance, Ferron *et al.* examined whether the neurosphere yield is different between normal and *Dlk1*^{-/-} mice. Consistent with their *in vivo* data, they observed a transient increase, followed by a decline, in the number of primary neurospheres from the mutant SVZ tissue over time. This result supports the hypothesis that a neurogenic continuum is created at an early postnatal period and is maintained throughout life.

Although the paternal copy of *Dlk1* is typically the one expressed, mice harbouring the non-functional *Dlk1* copy of either maternal or paternal origin developed the neurogenic phenotypes observed in mice lacking both copies of the gene. In search of an explanation for this, the authors demonstrate that, as expected, differentiated neurons in nonneurogenic tissues expressed the paternal copy of *Dlk1*. However, NSCs and their niche astrocytes — cells that are similar to NSCs and are found in the NSC microenvironment — expressed both the maternal and paternal copies of *Dlk1* in P7 and adult animals (Fig. 1). An absence of imprinting in the neurogenic niche is a novel and unexpected concept, because it underscores an underappreciated functional link between epigenetic regulation, in the form of gene imprinting (and the removal thereof), and developmental events such as adult NSC homeostasis.

The precise function of *Dlk1* during neurogenesis remains unclear, but Ferron and colleagues provide some early clues. The DLK1 protein comes in two forms: secreted and membrane-bound. Whereas niche astrocytes preferentially express secreted DLK1, NSCs predominantly express the membrane-bound isoform³. Significantly, loss of membrane-bound DLK1 from NSCs attenuates neurosphere formation in response to soluble DLK1, suggesting that secreted DLK1 stimulates the membrane-bound isoform in NSCs. Previous studies intimated¹⁰ that DLK1 can bind to itself and activate a signal-transduction cascade that is independent of Notch signalling — the pathway in which DLK1 is thought to function. The nature of these alternative signalling cascades is tentative. But at least stem-cell biologists can now differentiate NSCs and niche astrocytes using two additional markers — membrane-bound and secreted DLK1.

This paper³ raises many intriguing questions concerning the role of genomic imprinting and gene dosage during neurogenesis, as well as the potential mechanisms that regulate imprinting within a single organ. For example, do the same principles that underlie regulation of NSC development in the SVZ apply to the subgranular zone? And, if so, does *Dlk1* loss affect learning and memory? Studies involving tissue-specific and developmental-stage-specific loss of *Dlk1* function, as well as behavioural tests, should provide further evidence to support the current study.

More broadly, genomic imprinting serves as an important interface between environment and genes in mature tissues. Determining how *Dlk1* and other imprinted genes operate in concert with signalling cues, as well as discovering the factors that initiate and maintain differential methylation at the genomic region housing *Dlk1*, will lead to a better understanding of adult neurogenesis and brain development. Such knowledge will also inform emerging hypotheses about the role of trans-generational effects (or of their absence in particular processes), in which DNA and histone modifications in the ancestral genetic material affect the phenotypes of subsequent generations¹¹.

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	Embryonic	Postnatal	Adult
<i>Dlk1</i> expression	Varied	SVZ	SVZ, other neurogenic areas
<i>Dlk1</i> imprinting	Maintained	Lost	Lost
Effect on neural stem cells	–	Increased numbers	Decreased numbers

Figure 1. *Dlk1* and development

Ferron *et al.*³ find that *Dlk1* does not behave like a typical imprinted gene. SVZ, subventricular zone.