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Neuroscience: Sibling neurons bond to share sensations

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Abstract

Two studies show how electrical coupling between clonally-related neurons in the developing cerebral cortex might help them link up into columnar microcircuits that process related sensory information.

A pioneering set of experiments in the 1950s and 1960s inspired generations of neuroscientists to explore how the anatomy of the brain gives rise to its function^{1–3}. When researchers lowered electrodes into the cerebral cortex of cats and monkeys, they found that neurons lying above and below each other form ‘functional columns’ — that is, they respond in a similar way to certain stimuli, such as the touch on different parts of the skin or the orientation of an elongated visual stimulus. Even though such cortical columns have long been considered exemplars of basic computational units of cortical organization, the precise relationship between their anatomy and function has been difficult to define and remains debated^{4–5}. This is particularly true in rodents, whose cortex seems to lack functional columns almost entirely. What is common to rodents and other mammals, however, is a highly specific organization of cortical connections, which link neurons across layers in the cortex to relay and process related sensory information^{6–8}. On pages XXX and XXX of this issue, Yu *et al.*⁹ and Li *et al.*¹⁰ reveal some of the developmental events that may give rise to such precisely arranged functional circuits.

It has long been known that during embryonic development of the cortex, neuronal progenitor cells give birth to daughter cells that migrate towards the brain surface to form strings of neurons that span the cortical layers (Fig. 1a). These radially aligned clones, referred to as radial units or ontogenetic columns, have been proposed to constitute the basis for the functional columns in the mature brain⁹. However, a direct link between cellular lineage, microcircuit development and sensory preference of neurons had not been demonstrated.

Yu and colleagues¹⁰ used viruses to label sibling neurons with a fluorescent protein in the developing cortex of mouse embryos, and then recorded the cells’ electrical activity to learn how they were interconnected in brain slices obtained soon after the animals were born. They showed that gap junctions — small pores that couple adjacent cells electrically by bridging their membranes — formed transiently between sibling neurons within the same radial unit, very early in development (Fig. 1b). Gap junctions were previously observed

between clusters of excitatory neurons in the developing cortex and were suggested to contribute to the establishment of neuronal assemblies¹², but the ancestry and significance of such cell clusters were unknown. Nonetheless, it has been shown that, later in development, neurons in radial clones preferentially connect to each other in a different way, through chemical synapses¹³ mediated by neurotransmitter molecules (Fig. 1c). Now Yu *et al.* report that the transient electrical coupling is essential for the subsequent establishment of chemical synapses between sibling neurons, as the inactivation of their gap junctions abolished the formation of such synapses.

In the related paper, Li and colleagues¹¹ applied the same method to label radial clones and then used a microscopy technique (two-photon calcium imaging¹⁰) to monitor the activity of sibling neurons in the cortex of live mice in response to different visual stimuli. The authors observed that clonally related neurons, when compared with a random subset of neighbouring cells, were much more likely to respond to stimuli of the same orientation in the animals' visual field (Fig. 1d). Moreover, the blockade of gap junctions eliminated the shared preference for stimulus orientation, which further supports the role of electrical coupling between sibling neurons in influencing the functional organisation in the cortex.

The two studies are intriguing because they support a role for genetic lineage in the assembly of precise columnar circuits in the cortex. An extreme interpretation of the authors' results would be that ontogenetic columns constitute an elementary unit of functional organization in the cortex, that is, a basic circuit that is repeated and comprises excitatory neurons that process related sensory information. However, the relevance of ontogenetic columns for sensory processing is still unclear; an excitatory neuron in the mammalian cortex receives inputs from at least a thousand others, but only a handful of the connections are from sibling neurons. So it will be important to address how much the connections between siblings actually contribute towards shaping their sensory responses.

The small size of ontogenetic columns in mice, as described by Li *et al.* and Yu *et al.*, may explain why functional columns had not previously been described in the visual cortex of rodents, where neurons with different sensory preferences seem to be locally intermixed^{15,16}. But the authors' findings also raise the question of whether there is any relation between ontogenetic columns and the much larger functional columns in the cortex of non-rodent mammals such as cats or primates. Large functional columns could form as aggregates of multiple ontogenetic 'minicolumns', or from larger radial clones containing many more neurons than in rodents, or by a different mechanism altogether.

Regardless, the two studies demonstrate that at least some of the connection specificity in cortical microcircuits is established intrinsically by clonal lineage. They also show that cellular lineage may influence how neurons develop a similar sensory preference during early postnatal development — but how might this be achieved? Yu and colleagues' results suggest a close interplay between clonal lineage and early neuronal activity. Electrical coupling is likely to influence the formation and/or stabilization of chemical synapses between neurons that share gap junctions, as it is known that synapses can grow stronger or weaker if the cells' electrical activities are correlated or uncorrelated, respectively (a process known as synaptic plasticity). It is tempting to speculate that the sensory preference of these

subnetworks might then be developed by similar mechanisms: electrically coupled neurons could select and stabilize a common set of sensory inputs, which would endow these cells with a shared preference for certain sensory features. Future experiments are required to determine the developmental events that define how non-sibling neurons with similar stimulus preference become connected to each other in the cortical circuit.

Other important questions remain unanswered. To what extent is the electrical coupling between cortical neurons necessary for the establishment of stimulus selectivity? In other words, did the early blockade of gap junctions between sibling neurons result in a fundamentally altered visual cortex? Li and colleagues' results indicate that gap-junction blockade does not prevent the emergence of orientation preference, but more subtle features (such as the range of orientations that a neuron detects) may depend on gap junction connectivity.

Another issue relates to the fact that, during embryonic development, clonally related neurons not only migrate radially towards the cortical surface, but some also become distributed tangentially. The connectivity and functional fate of these 'displaced' sibling neurons remains undetermined. Do they also establish functional subnetworks with their siblings, or do they connect locally with non-sibling neighbours? How does the interplay between sensory input and synapse plasticity link up neurons from different ontogenetic columns with similar sensory preference to form larger functional assemblies? And do 'displaced' sibling neurons have a role in this process? Whatever the answers to these questions may be, the current studies show the fascinating way by which neurons emerging from the same progenitor cell are destined to share functional properties, and thus how the earliest developmental events influence the elaborate functional circuitry of the brain.

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Figure 1. A link between neuronal lineage and sensory preference.

a, During embryonic development, newly born neurons migrate towards the surface of the cortex and form clones of sibling neurons that span the cortical layers. Yu *et al.*¹⁰ and Li *et al.*¹¹ used viruses that expressed a green fluorescent protein to label neurons derived from a single progenitor cell. **b,** Yu *et al.* show that, early in development, sibling neurons are preferentially connected by small pores (gap junctions) that allow electrical currents to pass directly between them. **c,** They also found that, as development proceeds, gap junctions disappear, and chemical synapses are preferentially established between sibling neurons. **d,** Li *et al.* describe that, in a later phase, sibling neurons respond to similar sensory features, such as the orientation of visual stimuli.