



## How Many Cell Types Does It Take to Wire a Brain?

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type (J2a) rather than an mtDNA type, and its immigrant status is suggested by its presence at 10 to 20% frequency in high castes, both in Indo-European speakers and farther south among Dravidian speakers, and its near-absence in lower castes or “tribals” (8).

Perhaps the most striking example of sex-biased language change comes from a genetic study on the prehistoric encounter of expanding Malayo-Polynesians with resident Melanesians in New Guinea and the neighboring Admiralty Islands (9). The New Guinean coast contains pockets of Malayo-Polynesian-speaking areas separated by Melanesian areas. The presence of Malayo-Polynesian mtDNA (at local frequencies of 40 to 50%) is similar in these areas regardless of language, whereas the Malayo-Polynesian Y chromosome correlates strongly with the presence of Malayo-Polynesian languages. Mirroring the situation in the Indian upper castes, the presence of immigrant Malayo-Polynesian Y-chromosome DNA is modest, at frequencies of 10 to 20%, in the Malayo-Polynesian pockets, but this figure is still an order of magnitude higher than in the non-Malayo-Polynesian areas.

In Europe, a genetically researched proto-historic case of language dominance is the

colonization of Iceland from 874 C.E. by Scandinavian Vikings and abducted women from the British Isles (10, 11). Icelandic mtDNA today is mainly British, while the Y chromosome is predominantly Scandinavian, as indeed is the Icelandic language. A contrasting case is found in Greenland, where both the mtDNA (12) and the language today are nearly pure Eskimo, while half the Y chromosomes are European (13), evidently from contact with male European whalers over the centuries. The Greenlandic and Dravidian cases suggest that a Y-chromosomal signal may be a necessary factor, but not a sufficient one, as a predictor of language.

If the emerging correlation is confirmed, there should be underlying causal factors of a social nature. It may be that during colonization episodes by emigrating agriculturalists, men generally outnumbered women in the pioneer colonizing groups and took wives from the local community. When the parents have different linguistic backgrounds, it may often be the language of the father that is dominant within the family group. It is also relevant that men have a substantially more variable number of offspring than do women, as has been recorded both in prehistoric tribes such as the 19th- and 20th-century Polar

Eskimo from Greenland (14) and in historic figures such as Genghis Khan (1162 to 1227 C.E.), whose Y chromosome is presumed to be widespread across his former Mongol empire and is carried by 0.5% of the world's male population today (15). Prehistoric women may more readily have adopted the language of immigrant males, particularly if these newcomers brought with them military prowess or a perceived higher status associated with farming or metalworking.

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## NEUROSCIENCE

# How Many Cell Types Does It Take to Wire a Brain?

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Microglia, highly mobile immune cells that reside in the central nervous system, are traditionally viewed as “barometers” of the brain because they rapidly respond to cellular damage caused by injury and disease by engulfing and cleaning up debris (1). Imaging studies, however, have revealed that microglia are also ceaselessly active in healthy brains, and other studies have shown that this activity is often associated with synapses, which move signals between neurons (2–4). Despite these intriguing observations, the function of microglia at healthy synapses has been elusive. On page 1456 of this issue, Paolicelli *et al.* (5) help pin it down. They demonstrate that microglia are

involved in the development of brain wiring in newborn mice and that disrupting microglia-synapse interactions delays the maturation of synaptic circuits. The finding offers insight into the mechanisms underlying synapse maturation and into brain diseases in which synaptic connectivity is altered.

In the brain, microglia are the only cells that express the fractalkine receptor CX3CR1; it specifically binds the chemokine fractalkine CX3CL1, which is expressed by neurons (6). Fractalkine signaling often modulates the activation of microglia response to injury or disease (7, 8). In genetically modified knockout (KO) mice unable to produce the fractalkine receptor (*Cx3cr1*<sup>KO</sup>), there is a transient decrease in microglial density in several developing brain regions, including the hippocampus, a region critical for learning and memory. To determine whether this decrease affects the development of hippo-

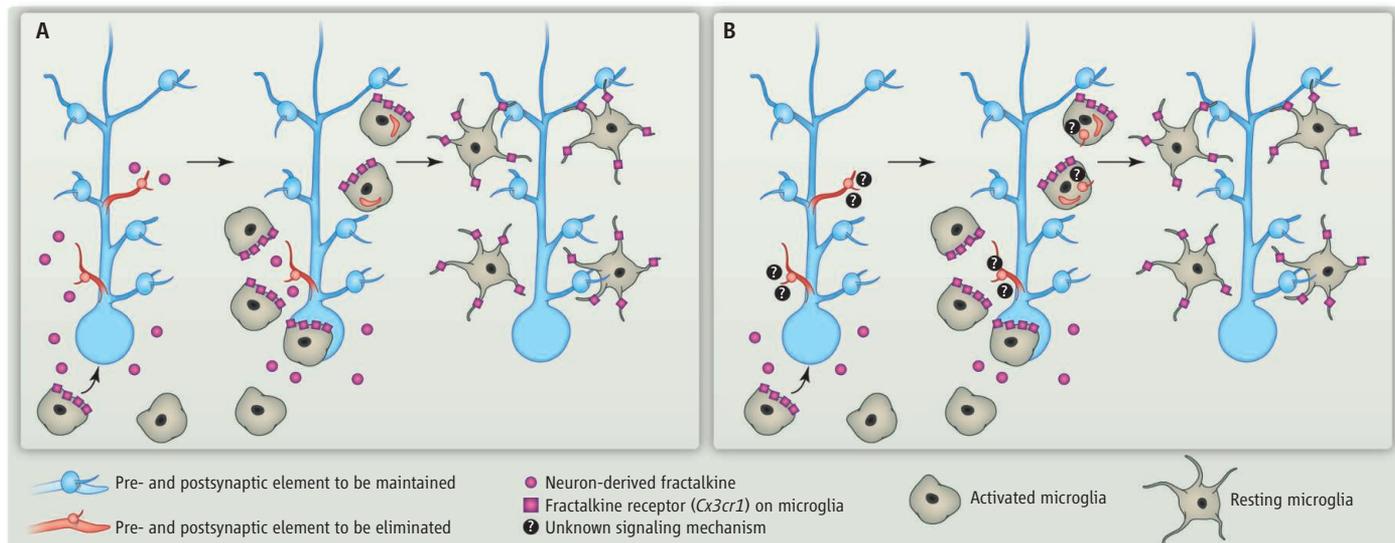
Microglia play an important role in the maturation of synaptic circuits in newborn mice.

campal synapses, the researchers compared *Cx3cr1*<sup>KO</sup> mice with age-matched controls, looking for anatomical, electrophysiological, and behavioral abnormalities associated with disrupted synaptic maturation.

They observed that newborn *Cx3cr1*<sup>KO</sup> mice had an increased density of hippocampal spines, small protrusions from a neuron's dendrite that receives synaptic input from presynaptic axons. This observation is consistent with a role for microglia in “pruning” of unneeded spines in normal mice during brain development. Indeed, the researchers observed postsynaptic-density (PSD) immunoreactivity within microglia cytoplasm, suggesting that microglia engulf and remove spines during this period of synaptic remodeling. In addition, electrophysiological and behavioral experiments demonstrated a delay in the maturation of hippocampal synapses in the KO mice. For example, elec-

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**Synapse pruning by microglia.** During normal brain development, neurons undergo remodeling in which some pre- and postsynaptic elements are maintained (blue), while others are eliminated (red). **(A)** In one model of pruning, synaptic elements to be eliminated release fractalkine, which activates microglia

via the *Cx3cr1* fractalkine receptor (left). Microglia prune elements (center) and then return to a resting state near maintained elements (right). **(B)** In an alternative model, fractalkine signaling globally activates microglia, but a more local, undetermined signal regulates pruning.

trophysiological recordings in hippocampal CA1 neurons revealed altered frequencies of signals known as spontaneous and miniature excitatory postsynaptic current (sEPSCs and mEPSCs), increased connectivity, and a reduction in synapse efficacy known as enhanced long-term depression (LTD). The authors also showed that the KO mice had seizure patterns that suggested a delay in brain circuit maturation. Over time, however, the differences between the KO and control mice disappeared; adult control and *Cx3cr1*-deficient mice were indistinguishable by anatomical, electrophysiological, and behavioral measures.

Together, these findings establish that microglial cells are key mediators of synapse development. They also raise questions. First, how do microglia contribute to synaptic maturation and plasticity in the postnatal brain? A critical component of nervous system development is the pruning of extra synapses. Paolicelli *et al.* propose that engulfment of postsynaptic elements by microglia is necessary for proper synaptic maturation and connectivity in the hippocampus. Their study, however, could not distinguish between the failure of synapses to mature and actual synapse elimination. As a result, it will be important to determine whether the synaptic deficits and transient increase in spines observed in *Cx3cr1*<sup>KO</sup> mice result from microglial regulation of synaptic plasticity (e.g., LTD) (9, 10) and/or synapse elimination (9, 10). In addition, it remains unclear whether microglia are actively interacting with and engulfing presynaptic termini, which are also in excess

in the developing brain. Imaging studies of interactions between microglia and synaptic elements will help resolve these questions.

Second, what is the precise mechanism by which a microglial cell identifies and interacts with a synapse destined for elimination? In *Cx3cr1*<sup>KO</sup> mice, Paolicelli *et al.* observed a transient reduction in microglial numbers that correlates with alterations of synapse elimination, suggesting that CX3CR1 may affect synapse maturation in part by governing the density and localization of microglia at synaptically enriched sites (see the figure) (8). CX3CR1 could also affect synaptic elimination by its regulation of microglial activation and phagocytic capacity, a function that has been demonstrated in CNS disease models (11–14). In addition, immune-related molecules, such as proteins involved in the innate immune system's complement pathway, are found near developing synapses and could serve as “tags” for synapses to be eliminated. Studies have shown that mice unable to produce two complement pathway proteins—C1q and C3—exhibit sustained defects in synaptic pruning and connectivity (15, 16). This raises the intriguing possibility that the fractalkine and complement pathways cooperatively regulate microglia-mediated synaptic pruning during development.

Finally, does abnormal microglial function contribute to sustained synaptic dysfunction and/or altered brain wiring? Paolicelli *et al.* found that the effects on microglia and synaptic dysfunction in the hippocampus of *Cx3cr1*<sup>KO</sup> mice were transient. How-

ever, defects in microglial function at synapses may have a global and long-lasting impact on brain wiring and behavior. If so, this possibility has substantial implications for diseases associated with synapse loss and aberrant connectivity, including autism and psychiatric disorders such as schizophrenia (17–20).

Paolicelli *et al.* have helped take a step toward identifying the molecular and cellular processes involved in such diseases by revealing a mechanism by which microglia control brain wiring and synaptic plasticity.

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