A tree of the human brain

Genomes of single neurons trace the developmental and mutational history of the brain

By Sten Linnarsson

Every cell of your body was generated by cell division, forming a lineage tree that goes back to the fertilized egg. Mutations are introduced by errors in DNA replication at every cell division, as well as by mutational processes that operate continuously, such as exposure to ultraviolet light. As a consequence, every cell may have its own unique genome, with potentially distinct gains and losses of function. Furthermore, these mutations create a record of the developmental ancestry of each cell, which can be used to reconstruct their lineage tree. Now, on page 94 of this issue, Lodato et al. use single-cell whole-genome sequencing to show these processes at work in the human brain (1). This is important because many unresolved questions in human biology and medicine are in fact questions about the human cell lineage tree in development and disease (2). Charles Darwin famously drew the first phylogenetic tree in 1837. This was only a month after he had started his first notebook on evolution, but the idea had already gelled in his mind that all species are linked like the branches on a tree. A few years later, around the time he was completing On the Origin of Species, a similarly remarkable insight was forming among a small group of scientists in Germany. Theodor Schwann and Matthias Schleiden had realized that both plants and animals are made of nothing but cells, but it was Robert Remak who showed that new cells arise through binary fission. These insights lead to the conclusion that every individual is also a tree—a cell lineage tree.

More than 150 years later, in 2005, Frumkin et al. showed that somatic mutations occur at cell division, in sufficient numbers that they can in principle be used to reconstruct complete human cell lineages (3). More recently, single-cell whole-genome sequencing was used to reveal patterns of clonal evolution in breast cancer (4). Last year, Behjati et al. used organoid culture to amplify the genomes of individual mouse cells for whole-genome sequencing (5). They found that lineages could be reconstructed back to the early embryo, revealing that the earliest cells contribute to all tissues, but in highly skewed proportions.

Lodato et al. now extend the study of naturally occurring somatic mutations to the human brain. Sequencing 36 single neurons from human prefrontal cortex, they found more than a thousand mutations per millimeters of prefrontal cortex, showing that lineages must have become physically mixed in the early embryo (see the figure). Indeed, any given neuron in the prefrontal cortex was more closely related to a cardiomyocyte than to 75% of its neighboring neurons.

These findings were enabled by recent advances in sequencing technology, single-cell sample preparation, and computational analysis. In the coming years, we can expect additional lineage trees of individual humans to deepen our understanding of embryogenesis as well as of how somatic mutations may contribute to brain disease.

In this way, the first small tree that Lodato et al. have drawn is a glimpse of the scientific and medical rewards that lie ahead as we begin exploring the human cell lineage tree in full. ■

REFERENCES