paused for about half the time, which is not a useful generalization. Our definitions, like our tools, need sharpening if they are to sustain claims about unusual climate events. ■

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HUMAN DEVELOPMENT

Advances in mini-brain technology

Two studies integrate cutting-edge techniques to grow and analyse 3D cultured tissues that resemble human brain structures, enabling examination of how brain regions interact and neurons mature. SEE ARTICLES P.48 & P.54

J. GRAY CAMP & BARBARA TREUTLEIN

Over the past few years, the production of human-brain-like tissue from stem cells in 3D cultures[1,2] has allowed sophisticated analyses of how the brain develops, how its development has changed during evolution and how it is affected by disease[3–5]. But it has remained unclear precisely what cell types arise in these brain 'organoids', how much individual organoids vary, and whether mature neuronal networks can form and function in organoids. Using a combination of sophisticated techniques, two papers[6,7] in this issue describe key steps towards addressing these questions.

There are two general strategies for growing human brain organoids. In the first strategy, pluripotent stem cells (PSCs, which can give rise to any cell type in the body) are guided to form a layer of stem cells called a neuroepithelium that can make neurons. The neuroepithelium is left to develop alone, and this can result in the generation of multiple brain regions (Fig. 1a). This self-patterning strategy offers the potential to understand how brain regions self-organize and interact. However, there are often substantial differences between individual organoids, and between batches grown separately.

The alternative strategy is to use signalling molecules to control patterning of the neuroepithelium so that a defined region forms — the forebrain or hypothalamus, for instance (Fig. 1b). This technique might increase reproducibility, but researchers have yet to define all of the signals that create each subregion of the brain. Moreover, it is unclear whether certain regions can form in the absence of adjacent structures.

Quadrato *et al.*[6] (page 48) set out to examine the composition and functionality of maturing brain organoids in detail. The authors modified a self-patterning protocol[3] to reduce cell death, which can occur towards the centre of organoids owing to a lack of oxygen. Organoids grown using this modified method progressively matured for more than nine months, making it possible to study how neurons develop over a time equivalent to that of human gestation.

The researchers analysed the gene-expression profiles (the transcriptomes) of more than 80,000 cells from 3- or 6-month-old organoids — the most comprehensive single-cell analysis of organoid composition performed so far. These data revealed diverse cell populations from different brain regions. Focusing on retinal cell types, the investigators demonstrated that their organoids contained almost every cell type found in this tissue *in vivo*. They also found evidence that neurons mature over time, beginning to express genes that mediate synaptic connections with other neurons.

How mature do these neurons become? Electron microscopy on serial slices of tissue revealed that an 8-month-old organoid contained a density of synapses approximately

50 Years Ago

The evolutionary origin of mitochondria, chloroplasts and kinetoplasts has recently been the subject of some intriguing speculation; several workers have suggested that these organelles have had an exogenous origin, perhaps evolving from symbiotic bacteria. These ideas stem from genetic evidence for the existence of extrachromosomal genes and the discovery that mitochondria and chloroplasts contain DNA and ribosomes and are capable of synthesizing proteins *in vitro* … Although it is unlikely we shall ever be able to prove or disprove the hypothesis of the exogenous origin of these organelles, the fact that chloroplast and probably mitochondrial ribosomes differ from cytoplasmic ribosomes suggests that cells contain two independent protein synthesizing systems perhaps subject to different control mechanisms.
From *Nature* 6 May 1967

100 Years Ago

It is usually stated that the carat weight of jewellers and diamond merchants is derived from the hard seeds of the locust tree, *Ceratonia siliqua*, which were anciently used as weights. Having had occasion to obtain some of the beans, I weighed several of the seeds to see what sort of error would be incurred if they were used as weights … It would appear … that the carat weight could be recovered with some approach to accuracy by weighing a number of seeds of the locust bean. It is also evident that the use of such seeds as weights must have given opportunities for fraudulent dealing in the precious commodities gauged by means of them, since deviations of from 30 to 40 per cent. from the average may occur.
From *Nature* 3 May 1917