Human Brain Organoids

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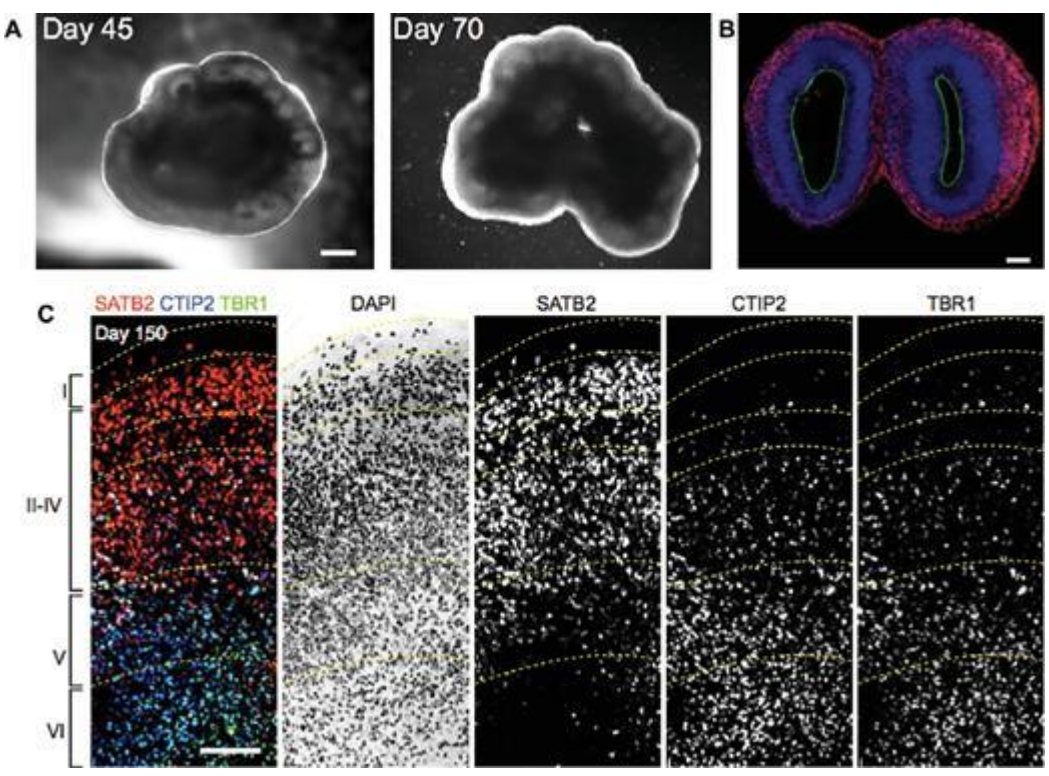
Organoids – in Vitro collections of organ-specific cells derived from stem cells that self-organize in a 3D manner similar to in Vivo development.

- technology exploits the self-organizing properties of pluripotent stem cells and recapitulates ***brain development with a high degree of spatial and temporal fidelity*** (i.e. surprising degree of similarity to the human brain).
- valuable for studying cortical neurogenesis and a variety of congenital human brain disorders.
  - most notably, brain organoids played a key role in elucidating the pathogenesis of Zika virus associated microcephaly.

Two categories of brain organoids

1. **Whole-brain organoids ("mini-brains")** (Lancaster et al 2013) - exhibit a variety of cerebral structures, ranging from cortical to choroid plexus to cerebellar tissues.
2. **Region-specific organoids** (Qian et al, 2016) - model specific brain structures, including the cortex, midbrain, hippocampus, hypothalamus, cerebellum, anterior pituitary, retina.



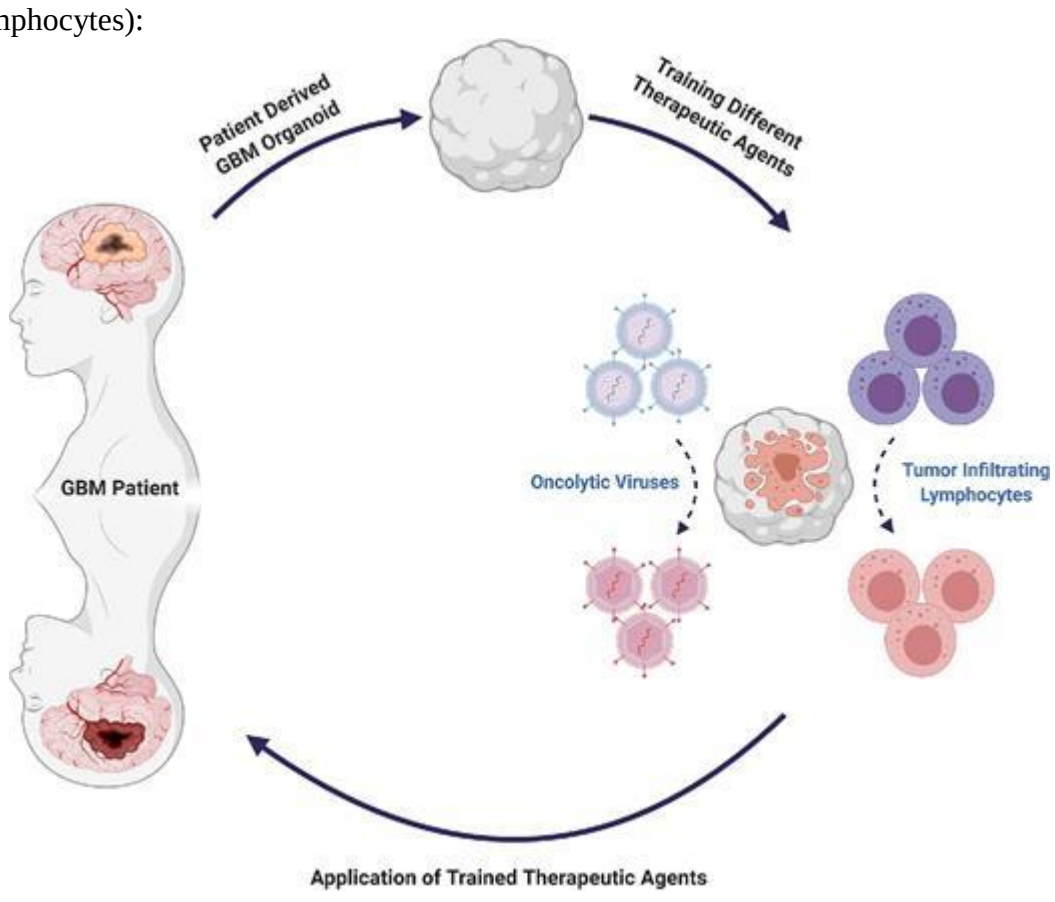
- Mansour et al, 2018 transplanted human brain organoids into the adult mouse brain - grafts were vascularized and continued to survive/mature in Vivo; electrophysiological studies showed intragraft neuronal activity and suggested graft-to-host functional integration

Limits

- diffusion constrains organoid growth to a maximum of 3-4 mm, after which necrosis within the organoid core prevents further growth.
- brain organoids do not possess gyrencephalic folds.
- brain organoids lack *microglia*, and other immune cells, as current protocols direct cellular differentiation along exclusively ectodermal pathways.
- brain organoids lack *endothelial cells* (recently, embryonic stem cells have been engineered to ectopically express human ETS variant 2 (ETV2) = lack of *complex vascularity*.
- maturation beyond the *end of the second trimester brain* has not yet been achieved.
- spontaneous action potentials have been reported but organoids lack complexity of their neural activity - no direct evidence of communication across multiple network nodes.

CLINICAL APPLICATIONS

1) patient-specific glioma organoids → high-throughput screening of patient-specific therapeutics / biofactory to test and train therapeutic agents (e.g. oncolytic viruses, tumor infiltrating lymphocytes):



   - within a single glioma organoid, a broad variety of cell types were identified, mirroring the parent tumor.
   - glioma organoids derived from different geographic regions of the same tumor exhibited a great deal of interorganoid variability (a single organoid line is not sufficient to understand the global biology of GBM).

2) high-throughput drug testing, development, and validation (s. **patient-less coclinical trial** = **hyper-personalized medicine**).

3) in the future:
   - organoid-derived axon tracts could act as "jumper cables" to rewire areas of the brain that had lost connectivity (TBI, stroke, iatrogenic);
   - organoids could be inserted as supplementary cortical columns to increase computational capacity after brain injury.

BIBLIOGRAPHY

Rachel Blue et al. A Primer on Human Brain Organoids for the Neurosurgeon. Neurosurgery 87:620–629, 2020