Cerebral Organoids will Play an Essential Role in Understanding the Development of the Brain

Serebral Organoidler Beyin Gelişimini Anlamada Önemli Bir Rol Oynayabilir

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"Scientists have grown miniature human brains in test tubes"

News from The Guardian

Stem cell studies are being currently widely used in neuroscience particularly for degenerative, developmental, and neoplastic disorders in addition to trauma. Laboratory studies of recurrent glioblastoma multiforme (GBM) stem cell vaccinations have already been completed and a Phase I safety study in human volunteers with recurrent GBM is in progress (1). Findings derived from animal studies with stem cells in degenerative brain disease and traumatic brain injury models are also promising (4, 5).

All this research has been conducted with cultured stem cell derivatives that yield mostly a monolayer of neuronal cells. Although these final cells can definitely connect to each other or targeted neuronal tissue *in vitro* or *in vivo* and also generate a functional component, they do not evolve into a three-dimensional formation, a system that is necessary for organ development.

On the other hand, previous studies have shown that vertebrate cells have huge self-organizing capacity (3). Even after complete disconnection, cells can reassemble and rebuild the original architecture of an organ. More recently, this exceptional feature was used to reestablish organ parts or even complete organs from tissue or embryonic stem cells. Such stem cell-derived three-dimensional cultures are called organoids (3). Because organoids can be grown from human stem cells and from patient-derived induced pluripotent stem (iPS) cells, they have the potential to model human development and disease. Furthermore, they have potential for drug testing and even future organ replacement strategies (3).

Studying the development of the brain and also developmental brain diseases in *in vitro* models are challenging due to the complexity of the human brain. To solve this problem, Lancaster et al. have established a human pluripotent stem cell-derived 3D organoid culture system, termed cerebral organoid, which develops various distinct brain regions including a cerebral cortex containing progenitor neuronal cell groups (Figure 1) (2). The researchers identified features of human cortical development, namely characteristic progenitor zone organization with abundant outer radial glial stem cells (Figure 2). Additionally, they attempted by using RNA interference (RNAi) and patient-specific induced

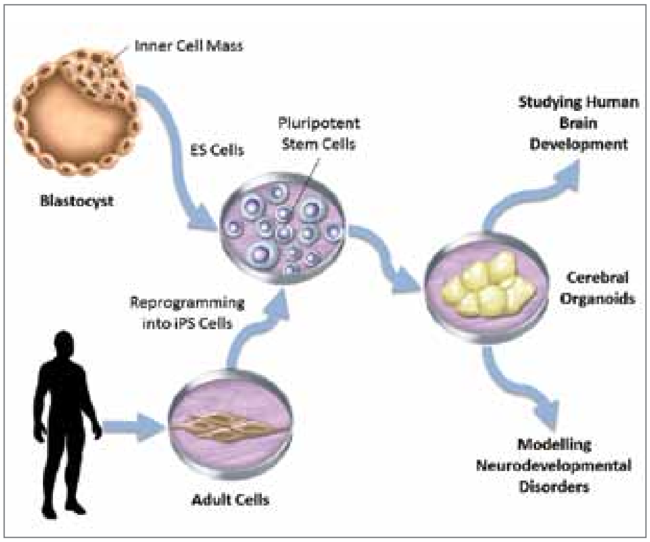

Figure 1: Organoid generation from human induced pluripotent stem cells (iPS). These cells can be derived from the inner cell mass either as embryonic stem (ES) cells or induced pluripotent stem cells through the reprogramming of adult cell types (Based on Brüstle O. Developmental neuroscience: Miniature human brains. Nature 501: 319-20, 2013).

pluripotent cells to model microcephaly, a disorder that has been difficult to recapitulate in mice. Their data demonstrate that 3D organoids can mimic the development and disease of even this most complex human tissue (2).

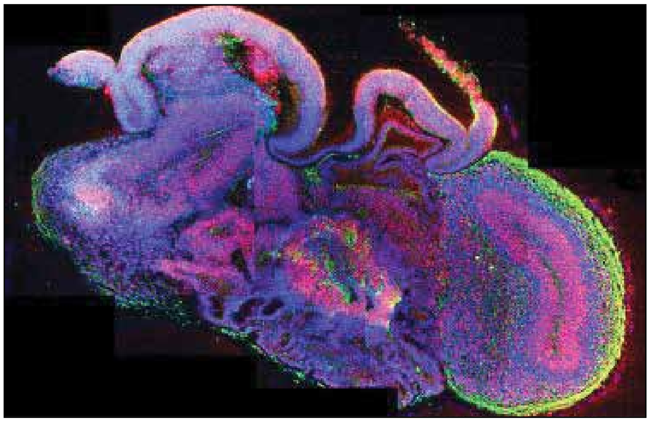

Figure 2: Photomicrograph shows a cross-section of an entire cerebral organoid with different brain regions. Cells are blue, neural stem cells are red and neurons are green. Photo: EPA / Institute of Molecular Biotechnology / MA Lancaster. (Accessed at http://www.taipeitimes.com/News/world/archives/2013/08/30/2003570958)

REFERENCES

1. Ji J, Judkowski VA, Liu G, Wang H, Bunying A, Li Z, Xu M, Bender J, Pinilla C, Yu JS: Identification of novel human leukocyte antigen-a*0201-restricted, Cytotoxic T lymphocyte epitopes on CD133 for cancer stem cell immunotherapy. Stem Cells Trans Med 3: 356-364, 2014
2. Lancaster MA, Renner M, Martin CA, Wenzel D, Bicknell LS, Hurles ME, Homfray T, Penninger JM, Jackson AP, Knoblich JA: Cerebral organoids model human brain development and microcephaly. Nature 501: 373-379, 2013
3. Lancaster MA, Knoblich JA: Organogenesis in a dish: Modeling development and disease using organoid technologies. Science 345:124-125, 2014
4. Tajiri N, Duncan K, Antoine A, Pabon M, Acosta SA, de la Pena I, Hernadez-Ontiveros DG, Shinozuka K, Ishikawa H, Kaneko Y, Yankee E, McGrogan M, Case C, Borlongan CV: Stem cell-paved biobridge facilitates neural repair in traumatic brain injury. Front Syst Neurosci 8: 116, 2014
5. Tatarishvili J, Oki K, Monni E, Koch P, Memanishvili T, Buga AM, Verma V, Popa-Wagner A, Brüstle O, Lindvall O, Kokaia Z: Human induced pluripotent stem cells improve recovery in stroke-injured aged rats. Restor Neurol Neurosci 32: 547-558, 2014