

Do we need an ethics of self-organizing tissue?

Some cells have a remarkable capacity to organize into tissue-like structures *in vitro*. As methods to enable self-organization improve, ethical aspects of some of these experiments will need to be considered.

In one of the faintly macabre short stories he wrote for adults, Roald Dahl, better known for his children's stories, told of an overbearing professor who lives on after death as a brain in a dish. The professor continues even in this diminished form to wish to control his long-suffering wife, until it dawns on her that he has lost the means for domination.

Compelling though Dahl's story may be as the starting point for various forms of speculation, it is in fact not yet possible to grow entire mature organs in dishes. Nevertheless, the research picture has changed considerably in the many decades since the story was published. In particular, we now know that differentiating adult and embryonic stem cells from mammals—including from humans—can organize *in vitro* into structures of surprising and tissue-like complexity, if given the right signals.

Stem cells from the intestine of both mice and humans, for example, can form organoids *in vitro* that contain all the complex cell types of the *in vivo* tissue. Embryonic stem cells embedded in a three-dimensional matrix can organize into primitive optic cups. Miniature stomachs, kidneys and livers (though all immature) have been generated *in vitro*. Mouse and human embryonic stem cells can even, under the right conditions, form layered structures that resemble the cerebral cortex. In a paper recently published in *Nature Methods*, for instance, researchers conclude that transcriptional profiles of *in vitro*-generated cortical spheroids match those of the *in vivo* brain at about 20 weeks after conception (Pasca *et al.*, 2015).

From an ethical perspective, there is little reason to consider human stem cell-derived tissue constructs as more problematic than human tissue explants—brain slices, for instance—maintained *in vitro*. But the situation is somewhat different for provocative new studies exploring the ability of pluripotent stem cells to organize into structures that have features of the early embryo, however poor the resemblance at present.

Two papers published in the past year—one focused on the mouse and the other on humans—report that embryonic stem cells differentiated under certain conditions can give rise to structures in which the three embryonic germ layers are reproducibly patterned (van den Brink *et al.*, 2014; Warmflash *et al.*, 2014). Furthermore, in the study on the human system, the biological pathways

involved are proposed to be similar to those functioning *in vivo*. Though more characterization is needed, patterned human cell colonies with embryo-like germ layers may therefore be potential models for research on early human development; such work is otherwise difficult or entirely unfeasible to carry out and could be hugely informative about human developmental disorders. Research both to understand patterned embryo-like structures and to improve them as models for human biology should therefore continue.

But should we be concerned from an ethical or regulatory perspective about growing embryo-like structures from pluripotent stem cells in a dish? Could such structures be seen, now or in the future, as violating current regulations on human embryo culture? Conversely, should such regulations be revisited when considering structures that are derived not from the union of gametes but rather from cells in a dish? Some of these questions are framed in a Commentary in this issue by a group of leading stem cell researchers (p917).

Furthermore, we must wrestle with how true to life an *in vitro* model of human development needs to be in order to be both scientifically valuable and ethically acceptable. From a pure research perspective, self-organizing stem cell-derived constructs should mimic *in vivo* human development as closely as possible. But the better and more developed the model, the more likely it is to pose an ethical and/or regulatory problem, or one of public perception. The theoretical extreme case—a human embryo perfectly engineered from pluripotent stem cells—makes this clear: it is a good research model, but generating or experimenting on such a structure could be argued to be unethical or even illegal, considering that many jurisdictions severely (and often justifiably) limit, and in some cases even prohibit, human embryo research. But the gray zone between an unpatterned clump of cells and this theoretical perfect embryo is more difficult to parse.

The currently reported structures, which do fall into such a gray zone, are very far from being embryos and thus do not pose an ethical or regulatory problem. But as methods development continues, it may well lead to more advanced *in vitro* development of embryo-like structures, which will require renewed attention from scientists, ethicists and regulators.