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EDITORIAL HIGHLIGHT

Neural progenitor cells and blood–brain barrier modeling

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Read the full article '*Blood-brain barrier modeling with co-cultured neural progenitor cell-derived astrocytes and neurons*' on page 507.

Two major problems in blood–brain barrier (BBB) research are that *in vitro* models do not fully recapitulate the *in vivo* BBB and difficulties in obtaining the appropriate human tissue necessary for *in vitro* modeling. The paper in this issue by Lippmann *et al.* (2011) from the group of Eric Shusta, is an important step towards resolving both these issues.

The BBB is formed by the cerebral endothelial cells and their linking tight junctions. However, BBB function is impacted by other cells of the neurovascular unit: astrocytes, pericytes and neurons (Abbott *et al.* 2006). The BBB is a physical barrier (as reflected by a very low passive permeability to hydrophilic molecules and very high transendothelial electrical resistance; TEER), a transport barrier (which may prevent or facilitate the entry of compounds to brain) and a metabolic barrier (with the cells of the BBB degrading specific blood-borne compounds) (Abbott *et al.* 2006). With current *in vitro* mono-culture endothelial models, these barrier properties are markedly altered, for example, TEERs are much lower than *in vivo*. There is some improvement in BBB properties when brain endothelial cells are co-cultured with astrocytes (Abbott *et al.* 2006). Instead of using primary astrocytes, Lippmann *et al.* (2011) have differentiated rat and human neural progenitor cells (NPCs) into astrocytes and neurons and mimicked the effects of primary astrocytes on the in vitro BBB TEER and P-glycoprotein transport activity. P-glycoprotein is an efflux transporter that impacts the influx of many drugs from blood to brain (Miller 2010). The mixed neural cells derived from NPCs actually improved the expression of some BBB genes more than primary astrocytes.

One reason the Lippmann *et al.* (2011) study is important are the difficulties in obtaining quality human astrocytes and neurons for *in vitro* BBB modeling. Human NPCs are capable of self-renewal and may be kept in culture for long periods of time. They may, therefore, provide a more ready source of human astrocytes and neurons. Such studies on human cells are important as there may be differences between the human and animals at the BBB, for example, the affinity of P-glycoprotein for some compounds differs between human and mouse (Baltes *et al.* 2007).

One concern over the use of human NPCs is the human embryonic source. It is possible that induced pluripotent stem (iPS) cells derived from adult somatic cells might provide an alternative source of neural cells. iPS cells have been used to generate neural stem cells which have in turn been used to generate astrocytes and neurons (Onorati *et al.* 2010).

Another reason why the Lippmann *et al.* (2011) study may be important is that it may be possible to use human NPCs or iPS cells to derive another important cell of the neurovascular unit, the pericyte. Exciting recent findings indicate that pericytes are important determinants of BBB function (Armulik *et al.* 2010; Daneman *et al.* 2010). The role of pericytes within the neurovascular unit has been much less studied than astrocytes (Dore-Duffy and Cleary 2011) and the mechanisms by which they affect BBB function require further study *in vivo* and *in vitro*. A ready source of human pericytes would greatly facilitate the *in vitro* studies. Current studies are hampered by the fact that pericytes are a fairly rare cell type in the brain and that their phenotype alters in culture. It is to be hoped that co-culture of brain endothelial with different combinations of pericytes, astrocytes and neurons may aid in producing better *in vitro* BBB models.

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Abbreviations used: BBB, blood–brain barrier; iPS, induced pluripotent stem; NPCs, neural progenitor cells; TEER, transendothelial electrical resistance.

In vitro models of the BBB are becoming increasingly complex to examine the interactions of the different cell types of the neurovascular unit. The use of NPCs to derive such cell types is an important methodological step that will help in the elucidation of such interactions.

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