Pitfalls of in vitro systems: why we still need animal experiments?

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In recent years much progress has been made in the field of in vitro system development. Most intensively cell culture systems with liver, kidney and neuronal systems have been studied (Barral et al., 2013; Eckerle et al., 2013; Godoy et al., 2013; Hammad, 2013; Janssen et al., 2013; Grinberg et al., 2014; Lundquist et al., 2014; Gómez-Lechón et al., 2014). The goal of these test systems is to have an easy to handle and to manipulate model organs, to be able to predict, e.g. toxicity in vivo (Mielke et al., 2011; Schug et al., 2013; Nigsch et al., 2011; Taguchi et al., 2014). However, two problems have to be overcome to reach this goal. A first, cultivated cell does not necessarily reflect all functions of a cell may have in real organ environment. For example, when hepatocytes are isolated from livers and brought into culture they lose their zonation. Zonation is a kind of ‘job-sharing’ in the liver where e.g., only hepatocytes in the pericentral region express cytochrome P450 enzymes while only periportal hepatocytes express some phase II metabolizing enzymes. When brought into culture, even in complex 3D systems, zonation is usually lost (Godoy et al., 2013; Sato et al., 2014).

While the problem of loss of function or ‘dedifferentiation’ is meanwhile fully acknowledged in the field of alternative methods research (Godoy et al., 2010; Zellmer et al., 2010; Fraczek et al., 2013), there is relatively little awareness that cells may also gain functions in vitro that would not be present in an organ. For example, cultivated hepatocytes have been shown to up-regulate anti-apoptotic or proliferation associated genes (Grinberg et al., 2014). Moreover, proteins expressed only at the apical pole of the hepatocyte in vivo have shown a wider distribution also to the basolateral cell membrane in vitro.

Both types of alterations in vitro, loss of function as well as gain of function, mean that we have to make sure whether a studied mechanism in cultivated cells really corresponds quantitatively and ideally also quantitatively to the in vivo situation. Currently, there is no alternative to this systematic in vitro –in vivo comparison, if one wishes to guarantee the relevance of the in vitro data.
REFERENCES


