Experimental Models for approaching the "functional biological unity": a focus on explants of the adult brain neurogenic zone and a promising extension of this technique for investigating the biological effect of any candidate therapeutic agent

Frédéric Mercier, Deep Matrix Microsystems, Manoir de Keryvoas, Kerlouan

Morphogenesis, physiological regulations in adulthood, regeneration after injury, wound healing, structural and functional adaptations to a new environment, progress of disease, all involve regulations at a multicellular, tissular or organ level, if not the level of the entire organism. Enormous progresses have been performed by physiologists through the 20th century via *in vivo* experiments, or experiments in perfused organs, which resulted in efficient therapies to fight numerous diseases. Experimentations *in vivo* appear the most significative in terms of biological relevance and testing molecules. However, several difficulties quickly raise for reasons as diverse as ethics, costs, and complexity of the experimental design. A major problem of the *in vivo* approach is to understand the dynamic aspect of a construction, regenerative process, or disease progression. It requires numerous organisms as source of experimentations, control organisms, and limited biological aspects can be investigated. Despite substantial progress, imaging on live is limited on large animals, resulting from low tissue penetration, or resolution problems (microscopy level). Cell culture is easy to manipulate for testing molecules, but the significance of results is questionable. Cell co-cultures (multiple cell types), spheroids and organoids necessitate by principle artificial procedures, and as such raise questions of relevance, compared to investigations on a whole organism. On the other side (technically descending from *in vivo*), xenografting marked cells from an animal to recipient animals or using the technique of explants (whole pieces of a tissue in culture without vascular perfusion) are worth of consideration regarding biological relevance. We generated brain explants from adult mice to investigate the function of the generative zones of the adult brain. The explants are whole surgical pieces that contain the natural stem cells, all their surrounding cells, the extracellular matrix environment, including fractones, macrophages and cells of the vascular wall (endothelial cells, pericytes, fibroblasts). The explants are functional units that produce their own growth factors, cytokines and necessitate only basic culture media without any additives. The explants grow through months and numerous biological phenomena, such as cell proliferation, differentiation, migration, and apoptosis, wound healing, regeneration, inflammation can be investigated on these explants by fluorescence on-live microscopy. Neangiogenesis occurs naturally on neurogenic explants, ash an attempt to regenerate the lost vascular network. The explants can be xenografted by fluorescent-marked cells or pieces of tissues from different species, the explant being not subject to graft rejection. We propose to extend the model of explants to investigate cancer, neurodegenerative diseases, wound healing, and tissue regeneration. We will offer possibility for testing the biological activity of any kind of compound or extract on our explants. This will provide alternatives to the current biological models and their biases of significance.