Organs-On-Chips

By Chelsea Brown

Think about the complexities of your body. You are made up of many different bits and pieces. Now think of how complex you are inside your body. You have a brain, lungs, a stomach, intestines, a heart, blood vessels, muscles, tendons, bones, etc. Now think about what these are made up of: tissues, cells, molecules, atoms. The Russian nesting dolls that are the complexity of your physiology seem almost endless. The analogy doesn't quite work though; nesting dolls are all separate, distinct—one fits into another which fits into another. We do have distinct organ systems in our bodies, but everything works together. Each process intertwines so many different systems that it is almost impossible to detangle them. Now imagine something isn't working properly. How do we get to the bottom of it? We could strap you down to a table, poke, and prod at you and run all kinds of experiments, but that seems a little evil. All to say that there is a need for scientists to create models that can recapitulate the complexities of our bodies to study mechanisms of disease and drug potential. Models are tricky, though—they must be complex enough to accurately model what we see in the human body, but they must also be simple enough to extract relevant information (1).

Perhaps you've heard of animal testing. Although the use of animals as test subjects has some questionable ethics, animals are widely used as model systems for human diseases and for testing therapeutics (2). Aside from ethical issues, one big drawback of using animals is that they are not always good at emulating the problem that needs to be solved—for example, they may present human diseases differently and they sometimes have altered responses to therapeutics when compared to humans. There's also the issue that animal models are very complex and can be hard to get discrete information from (2).

Another method of disease modeling is two-dimensional (2D) cell culture (2). For this approach, scientists grow cells as a single layer in a dish. Scientists can watch how the cells grow and move, as well as how different drugs affect their behavior (3). There is strong control over experimental parameters in 2D cell culture studies, making it easy for scientists to measure cause and effect. The big drawback with 2D cell culture is that the cells do not emulate complex systems like we see in the body (4).

An important breakthrough in the field of 2D cell culture is the ability of scientists to take a sample of cells from a patient and then use those cells to form any cell type in the body. Scientists can take fully developed cells (like a cell from skin or fat

tissue) and “reprogram them.” To do this, the scientists would first reprogram the cells to revert back to an early embryonic-like, unspecified cell called an induced pluripotent stem cell or iPSC. These iPSCs are then reprogrammed into the cell type that needs to be monitored. What’s innovative here is that the cells come from the patient—so if the patient has a disease, the cells would model the disease on their own. For example, if the patient has a lung disease, we can take their skin cells, convert the skin cells into iPSCs, then reprogram the iPSCs into lung cells. Scientists could then test the resulting lung cells to understand how their function was impaired by the disease or test potential therapeutics to see how this patient might respond. Although this is a great system for looking at simple problems, because iPSCs are typically grown in 2D cell culture formats, they can also lack the complexity that is often needed to study disease pathology.

A step above general 2D cell culture and iPSCs is three-dimensional (3D) organoid generation. This approach builds on the ideas of the prior methods, but instead of focusing on building a monolayer of cells, scientists generate 3D structures. These structures consist of many specified cell types and exhibit some of the same functions performed by the original organ (1). These features make organoids a handy tool for studying development and disease of specific organs. Organoids are technically challenging to generate, though, and often lack some important cell types and function.

All of these cell-based methods are relatively easy to study, but they don’t get us out of the Russian nesting doll dilemma—with each method, discrete cells are examined, thereby preventing us from understanding how the cells might function within an actual organ, with all of its many cell and tissue types. So, there is a need for a model that highlights the interactions between different cells and tissues. This is where organs-on-chips emerged (1-4).

Organs-on-chips can be compared to when goldilocks found the porridge that was just right. This modeling system can provide just enough complexity to resemble the interactions that actually occur in our bodies, but is still easily manipulated and assessed (1-4). The chips themselves are made up of chambers connected by microchannels (Figure 1). The chambers themselves are less than 3/100ths of an inch and is where cells are seeded and grown. Cells of different types are grown in the chambers and their interactions are highlighted in the connecting network of channels (3). It's this aspect that gets us out of the nesting doll dilemma. Aside from how they connect, these chambers are innovative because they can be supplied with fluids at varying velocities and physically stretched. These features create a much more accurate environment when compared to what cells experience in the body. Therefore, the behavior we can observe will better emulate what happens naturally. The chips are also equipped with sensors and microscopes so measurements can be taken noninvasively

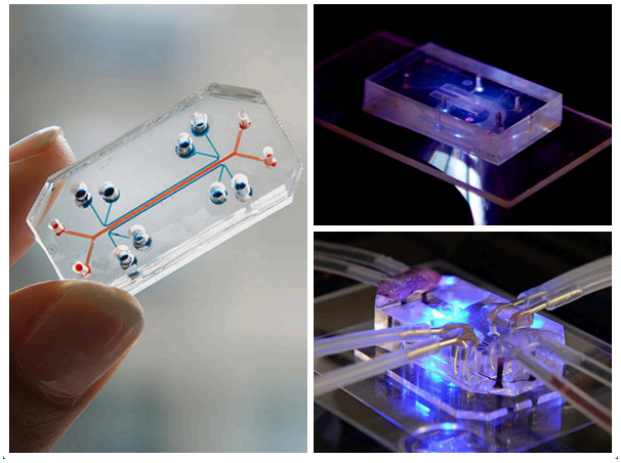

Figure 1: Organs-on-chips

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(3). Coupling these chips with iPSCs will provide a system capable of modeling very complex, patient-specific diseases, and testing drug efficacy (3).

Although this technology has been developed, organs-on-chips are not yet widely commercialized or used in the field. The design will need to be streamlined so that they are fast and easy to use. There will also need to be experiments that demonstrate the chip's advantages over more commonly used techniques (3). After more widespread commercial manufacturing, organs-on-chips may become a common tool in patient-specific care that will hopefully advance the study of disease, organ systems, and drug efficacy (1-4).

References

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