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Underhill working to decipher microenvironments of liver

07/28/2016 - 10:13am

Since joining the University of Illinois faculty in 2012, Bioengineering Assistant Professor Greg Underhill has been conducting research on the stem cells that develop into the liver, a notoriously difficult organ to study.

“It’s a very large organ that has a complex set of functions,” said Underhill, whose research currently focuses on mouse stem cells. “In fact, it’s suggested it has over 500 functions. Also, the overall mass and cell density of the liver make it very challenging for tissue engineering applications.”

Underhill is concentrating on the mechanisms that regulate the development of particular stem cell types. He wants to understand how the tissue surrounding the stem cells — the microenvironment — can influence the stem cell development. The microenvironment includes such things as other cells, matrix proteins (such as collagen), and other factors found in body tissue. Studying the microenvironment can be difficult because of the many influences that can impact stem cell development. Also, liver cells are unstable outside the body, so they are difficult to culture with standard techniques.

One innovation that Underhill and his team are using is a cell microarray. The team created a process that enables them to place up 4,000 “islands” on a slide, each representing a different environmental condition that may be present in a developing liver. Then they place specific cells onto each of these islands. Using computer imaging, the researchers analyze these islands and determine how the differing conditions affect cell development. As Underhill explains, these types of studies are called “high-throughput” because so many different conditions and potential influencers can be studied in parallel.

Underhill’s approach to studying the development of liver stem cells has resulted in a number of recent research articles published in Acta Biomaterialia, Biomaterials, and Scientific Reports. These articles describe in detail how the microarrays provide new insights into what takes place during the development of liver stem cells and how they have pointed to specific conditions that can influence this development.

Kerim Kaylan is an M.D./Ph.D. student in Bioengineering working with Underhill and a lead author on two of the articles. He sees the work they are doing as a way of combining several research interests.

“We work in this liminal space,” Kaylan said, “where we do material science, we care about the biological outcomes and understanding that we gain from our work, and we care about the systems and engineering approaches that enable us to answer impactful questions about development.”

As they increase the understanding of how the liver cells develop, there is great potential for improving human health. A number of diseases can be attributed to problems stemming from the developmental stages of the liver, for example, a congenital condition in which too few bile ducts are formed. This causes a buildup of bile in the liver, which can become toxic. Understanding why and how liver cells develop normally into a variety of cells — including cells that become bile ducts — could lead to insights on treatment.

“That’s one of our main focus areas: trying to understand these developmental disorders in the liver,” Underhill said. “It’s primarily a lack of proper stem cell differentiation, where the cells don’t properly form into these ducts. Often in disease, the microenvironment is altered — or a combination of the microenvironment and the genes that the cells express. Our goal is to deconstruct these disease processes.”

Another potential beneficial area for this research is in the development of tissue-

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engineered therapies. “If a patient is lacking these structures in the liver, can you deliver these cells to the person, or even an artificial liver to that person?” Underhill said. “If we can better understand how these cells behave, we can better engineer liver systems.”

In addition to his lab’s focus on the liver, Underhill has been working with the Mayo Clinic, developing his microarrays for use in studying lung cancer. “In this work, we are exploring the hypothesis that the environment of the lung cancer cell would change how the cell responds to drugs,” he said.

Driven by the potential for improving human health, Underhill plans to continue exploring these avenues, even with the challenges of studying such a complex element as liver stem cells.

“[These tissues] require unique technologies and analyses to tease apart that complexity,” Underhill said. “By using high-throughput systems and controlled environments, we can reveal previously unknown mechanisms of disease, opening the door for new treatment strategies.”

Acta Biomaterialia article:
http://www.sciencedirect.com/science/article/pii/S1742706116300575

Biomaterials article:
http://www.sciencedirect.com/science/article/pii/S0142961216301831

Scientific Reports article:
http://www.nature.com/articles/srep23490

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