Engineering a lung-on-a-dish model to study lung fibrosis

Prof. Deepak Saini, MRDG / BSSE and Prof. Kaushik Chatterjee, Mat. Eng. / BSSE

Fibrosis of any tissue is characterized by elevated deposition of extracellular matrix (ECM), leading to a progressive increase in stiffness, thereby causing loss of tissue function resulting in morbidity and mortality. TGFβ, a well-known activator of ECM production and degradation, is seen as a key regulator of fibrosis induction (Meng et al, 2016). Additionally, profibrogenic cytokines like fibroblast growth factor (FGF), connective tissue growth factor (CTGF), endothelin-1, platelet-derived growth factor (PDGF), etc play important roles in fibrosis induction as well as progression in different organs (Abraham 2007). However, the progress in developing effective antifibrotic drugs is quite slow, due to the lack of suitable quantitative *in vitro* fibrosis models.

The 2-dimensional culture models for fibrosis utilize a monolayer of fibroblast cells which on treatment with TGFβ, differentiate into ECM producing myofibroblasts. However, when the features of 2D cultures are compared with *in vivo* systems, it was found that they do not faithfully manifest pathophysiological features of tissue fibrosis. The stiffness of the tissue culture dishes used to grow the 2-D cultures is much higher compared to the tissue stiffness *in vivo*. Moreover, the absence of 3D tissue microenvironment further makes the 2D culture system for fibrosis physiologically irrelevant. Though, as an obvious step, animal models would seem appropriate, however, they fail to mimic the features recorded in the human and they are also resolve fibrosis unlike in human (Minicis et al, 2007).

Recent advances in the generation of complex 3 D functional living tissues by layer-by-layer printing of biocompatible materials, cells, and supporting components along with the required growth factors can be utilized to study the aetiology of fibrosis, specifically lung fibrosis (Murphy et al 2014). The 3D bioprinted organs are: 1) able to mimic the tissue phenotype and functionality, 2) suitable for use in drug screening and, 3) tunable based on specific tissues as far as the mechanical properties and tissue microenvironment are concerned. Although issues like lack of temporal control over tissue development as seen during different stages of fibrosis may be there (Daniel et al 2020), yet 3D bioprinting represents a state-of-art platform for fibrosis disease modeling and drug testing. In addition, microfluidics can be integrated to recapitulate the transport of air and/or blood to mimic the transport phenomena of the lung tissues seen *in vivo*.

In this context the project aims to combine the emerging technologies of 3D bioprinting and microfluidics towards designing a 3D human lung fibrosis models to understand the molecular mechanisms leading to onset and progression of fibrosis as well as to screen relevant drugs for therapeutic intervention.

References

Abraham, D.J., Eckes, B., Rajkumar, V. et al (2007) New developments in fibroblast and myofibroblast biology: Implications for fibrosis and scleroderma. *Curr Rheumatol Rep*, **9:**136.

Daniel B. Hoffman DB, Sorensen JR, Call JA et al (2020) Temporal Changes in Pathologic Fibrosis Following Volumetric Muscle Loss Injury. The FASEB Journal, **34** (S1):1.

Meng XM, Nikolic-Paterson D & Lan H (2016) TGF-β: the master regulator of fibrosis. *Nat Rev Nephrol*, **12:** 325.

Minicis SD, Seki E, Uchinami H et al (2007) Gene Expression Profiles During Hepatic Stellate Cell Activation in Culture and In Vivo. *Gastroenterology*, **132** (5):1937.

Murphy, S., Atala, A. 3D bioprinting of tissues and organs. *Nat Biotechnol* **32,** 773–785 (2014).