Advanced Nanofibrous Scaffolds to Influence Endothelial Cell Activity

Valorisation

In this chapter, an attempt is made to discuss the clinical and commercial value of our findings and how they can be translated into the clinic in the field of tissue engineering and regenerative medicine. The final goal of our scientific output is to transfer the research findings into practice, via which they can contribute to clinical and commercial application. The application to generate value in this process is called “valorisation”. The development of tissue engineering scaffolds are likely to bring clinical and commercial benefits to the society. Our study on fabrication of self-assembled honeycomb scaffolds to induce angiogenesis in Chapter 4 showed high potential for valorisation.

Clinical and commercial relevance

The biomedical research has risen rapidly because people could benefit from it. The life expectancy of young generation is increasing and the chronic disability of old people is decreasing, these trends is mainly due to the fast development of biomedical technologies [1]. Our society emphasizes the importance of biomedical development and has spent lots of money in biomedical research. For example, the estimated yearly cost of pharmaceutical, biotechnology, and medical companies on biomedical research is more than $60 billion worldwide [2]. Despite some biomedical products have shown initial successes in translating from the lab to the clinic, the ability to regenerate complex tissue/organ is still one of the great challenges for clinical use [3]. In tissue engineering, cells from patients are seeded into an appropriate 3D scaffold to generate the tissue construct. However, the lack of adequate and fast vascularization often lead to cell death after seeding [4]. The formation of new tissue constructs needs blood vessels to continuously supply oxygen and nutrition [5]. Insufficient blood supply limits the size of tissue-engineered constructs and results in failure of translation [6]. In order to solve this problem, we developed a self-assembled honeycomb scaffold that could afford biophysical cues to induce initial blood vessel formation.

Honeycomb nanofibrous scaffolds created by the self-assembly of electrospun fibers could mimic the capillary network of endothelial cells (Figure 1). Some studies reported that the honeycomb-like network of endothelial cells is a very important morphogenetic feature that could simulate tube formation during angiogenesis [7, 8]. The wall of honeycomb scaffolds contains connected fiber clusters and beads, therefore allowing cells to adhere on the wall and possibly guide cell migration. In chapter 4, we showed that the fabricated honeycomb scaffolds significantly promoted HUVECs proliferation and influenced the distribution of cells. Especially, honeycomb electrospun scaffolds could regulate HUVECs morphogenesis into capillary-like structures with a central lumen.

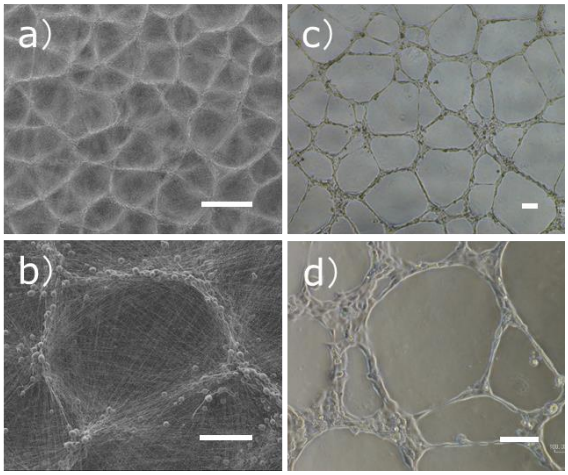

Figure 1. SEM images of honeycomb (a) PCL electrospun nanofibers. Images (c and d) showed the tube formation of HUVECs cultured on Matrigel-coated wellplate after 16 h. Scale bars are 500μm (a) and 100μm (b, c and d).

Target group

Our findings on the development of honeycomb nanofibrous scaffolds for vascular tissue engineering can benefit other researchers. For example, many studies reported how geometrical cues affect endothelial cell tube formation by using micropatterned stripes. To the best of our knowledge, no study was performed so far on the influence of honeycomb patterns on tube formation.

Here, we focused on the effect of honeycomb patterns on vessel formation. Investigating the effect of honeycomb pattern on angiogenesis will pave the way towards the fabrication of advanced angiogenic scaffolds that hold to be more promising for clinical applications. Beyond the preliminary studies that we have here reported, the efficacy and safety of honeycomb scaffolds have to be tested by further *in vitro* and *in vivo* assays, before finally being translated in patients [9]. After getting approval for clinical trials, the final products could attract the attention of investors, making it possible to enter into the market.

Innovation and implementation

Chapter 4 investigated the positive role of honeycomb patterns in promoting angiogenesis. The novelty of this study is 1) using a self-assembled electrospinning approach to fabricate a honeycomb pattern, and 2) guiding endothelial cells morphogenesis into capillary network through the honeycomb scaffolds, finally promoting tube formation. This honeycomb scaffold in principle could be used for some applications where prevascularization is highly needed to rapidly generate vascular network before implantation. Serval studies have reported the addition of endothelial cells sheets for vascularized bone regeneration [10, 11]. During prevascularization, human mesenchymal stromal cells (hMSCs) are seeded on honeycomb scaffolds and human umbilical vein endothelial cells (HUVECs) are seeded on the top of hMSCs in order to generate vascularized tissue constructs. The geometric cues of honeycomb scaffolds could accelerate the initial vascular network formation. This could shorten the time during which tissue construct suffers from hypoxia and lack of nutrition.

The honeycomb scaffolds are made from poly(caprolactone), which has been approved by Food and Drug Administration (FDA) and already used in patients as drug delivery devices and sutures. Furthermore, to fabricate thermal-triggered cells sheets, honeycomb patterns could be produced from electrospinning of thermosresponsive polymers (e.g. pNIPAAm). After using

such honeycomb thermal scaffolds, cultured endothelial layers or mixtures of endothelial cells with other cell types could be easily harvested by changing temperature. This improvement could be more promising for tissue implantation.

Our findings has only been proved by *in vitro* studies, so that the application of honeycomb scaffolds *in vivo* should be further investigated. The next step is to perform animal tests to confirm the efficacy and safety of honeycomb scaffolds on angiogenesis. If our results were confirmed in larger animal tests, these honeycomb scaffolds would then be eligible for further clinical experimentation, after having passed regulatory and medical ethical approval. Clinical testing without significant side effects or safety issues would provide these scaffolds a chance to secure further investment for introduction into the market. Another potential value of our findings is that researchers may also consider the role of geometric cues when designing biomaterials for vascular regeneration. Especially, highly vascularized tissues may require the fast formation of blood vessels to support regeneration.

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