DEVELOPMENT OF AN INTEGRATED TISSUE ENGINEERING BIOREACTOR SYSTEM FOR MICROVESSEL DEVELOPMENT IN A 3D ENVIRONMENT

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DEDICATION

First and Foremost, thankful to Allah The Almighty

To my beloved wife, Siti Marhaida binti Mustafa,
children Muhammad Zaid and Siti Sufiyyah, parents, family and friends,
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ABSTRACT

The development of functional and matured microvessels within constructed tissue is a great challenge in tissue engineering. It is crucial to allow better nutrient and oxygen supply as well as waste removal within the core of tissue construct. It is one of the main reasons why only few tissue substitutes are available for clinical replacement. Therefore, tissue engineering bioreactor could be as possible component to potentially improve the *in vitro* engineering of living tissues that can facilitate better mechanisms in governing physical, chemical and biological processes in a developed three-dimensional (3D) tissue culture environment. A pulsatile perfusion bioreactor was designed, built and validated to support *in vitro* cells growth and proliferation. This system enables the monitoring and controlling of the pressure, flow rate, temperature, dissolved oxygen (DO) concentration, pH, frequency and waveform of the pulsatile pressure, for the purpose of both physiological and non-physiological conditions simulation. All the parameters were controlled and adjusted to be stable similar to the *in vivo* condition (in the human body). This system was also designed to be an incubator independent, mobile, sterilizable (autoclavable) and compatible with a variety of cell or tissue scaffold configuration, geometry and size. Human Umbilical Vein Endothelial Cells (HUVECs) with a concentration of $1x10^5$ cells/ml were attached in 20 mm x 20 mm x 2 mm fibrin gel made in the Flow Culture Chamber (FCC) to be utilized as the 3D model system and connected either in the bioreactor, simple dynamic or static system (control). After 2 and 4 days analyses, the HUVECs cultured in the bioreactor system showed significantly higher proliferation and migration rate compared to the HUVECs cultured under the static and simple dynamic conditions. The development of cell-cell connection and the formation of microvessel under the bioreactor condition were also found to be faster than the performance under the simple dynamic and static conditions. The HUVECs were co-cultured with human fibroblast and vascular endothelial growth factor (VEGF) in another set of bioreactor experiment to improve the maturation and better formation of microvessel. The formation of microvessels and assessment of lumen formation were appraised using a fluorescent fibrin matrix, histology and confocal microscopy. The fluorescent and histology analyses confirmed the formation of matured microvessel-like structure. The utilization of fibroblasts and VEGF significantly improved the maturation of the microvessels compared to the samples without fibroblasts. In conclusion, the HUVECs were successfully cultured in the bioreactor, with a potential growth of microvessels in 3D tissue culture environment.

ABSTRAK

Perkembangan mikrovesel yang berfungsi dan matang dalam tisu yang dibentuk adalah satu cabaran besar dalam kejuruteraan tisu. Ianya adalah penting untuk memastikan pembekalan nutrien dan oksigen yang lebih baik serta penyingkiran bahan buangan dalam teras tisu yang terbentuk. Ini adalah salah satu sebab utama mengapa hanya beberapa pengganti tisu tersedia untuk penggantian klinikal. Oleh itu, bioreaktor kejuruteraan tisu boleh menjadi komponen yang mampu untuk meningkatkan potensi kejuruteraan *in vitro* tisu hidup yang dapat menghasilkan mekanisma yang lebih baik untuk mengawal proses fizikal, kimia dan biologi dalam persekitaran kultur tisu tiga dimensi (3D). Bioreaktor perfusi serba boleh direkabentuk, dibina dan disahkan untuk menyokong pertumbuhan dan perkembangan sel-sel *in vitro*. Sistem ini membolehkan pemantauan dan pengawalan tekanan, kadar aliran, suhu, kepekatan oksigen terlarut, pH, frekuensi dan bentuk gelombang tekanan, bagi tujuan simulasi keadaan fisiologi dan bukan fisiologi. Semua parameter dikawal dan diselaraskan supaya stabil seperti keadaan *in vivo* (dalam tubuh manusia). Sistem ini juga direka untuk menjadi inkubator bebas, mudah alih, boleh disteril dan serasi dengan pelbagai perancah sel atau tisu konfigurasi, geometri dan saiz. Sebanyak 1×10^5 sel-sel Endothelial Vena Umbilikal Manusia (HUVECs) dihidupkan dalam 20 mm x 20 mm x 2 mm gel fibrin di dalam Bilik Aliran Kultur (FCC), di mana ia digunakan sebagai sistem model 3D dan disambung sama ada dalam sistem bioreaktor, dinamik asas atau statik (sebagai kawalan). Selepas analisis 2 dan 4 hari, HUVECs yang dikulturkan di bawah sistem bioreaktor menunjukkan kadar pertumbuhan yang lebih tinggi berbanding HUVECs yang dikulturkan di bawah keadaan dinamik asas dan statik. Perkembangan pencantuman sel-sel dan pembentukan mikrovesel di bawah keadaan bioreaktor didapati juga lebih cepat berbanding keadaan dinamik asas dan statik. Dalam eksperimen bioreaktor berasingan, HUVECs dikultur dengan fibroblas manusia dan faktor pertumbuhan endotelial vaskular (VEGF) untuk meningkatkan pematangan dan pembentukan mikrovesel yang lebih baik. Pembentukan mikrovesel dan penilaian pembentukan lumen dinilai menggunakan matriks fibrin neon, histologi dan mikroskopi konfokal. Analisis pendafluor dan histologi mengesahkan pembentukan struktur seperti mikrovesel yang matang. Penggunaan fibroblas dan VEGF dengan ketara dapat meningkatkan kematangan mikrovesel berbanding sampel tanpa fibroblas. Kesimpulannya, HUVECs berjaya dikulturkan di dalam bioreaktor, dan berpotensi membentuk mikrovesel dalam persekitaran kultur tisu tiga dimensi (3D).

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LIST OF ABBREVIATIONS

ANOVA	-	Analysis of Variance
2D	-	Two Dimensional
3D	-	Three Dimensional
TE	-	Tissue Engineering
EC	-	Endothelial Cells
HUVECs	-	Human Umbilical Vein Endothelial Cells
ECM	-	Extracellular Matrix
M199	-	Culture Medium
FCC	-	Flow Culture Chamber
VEGF	-	Vascular Endothelial Growth Factor
bFGF	-	Basic Fibroblast Growth Factor
CO_2	-	Carbon Dioxide
O_2	-	Oxygen
DO	-	Dissolved Oxygen
PC	-	Polycarbonate
PBS	-	Phosphate Buffered Saline
HBSS	-	Hank's Balances Salt Solution
BSA	-	Bovine Serum Albumin
FBS	-	Fetal Bovine Serum
ECGS	-	Endothelial Cells Growth Supplement
CFSE	-	Carboxyfluorescein Succinimidyl Ester

µl	-	Microliter
ml	-	Milliliter
mg	-	Miligram
min	-	Minute
µm	-	Micrometer
g	-	Gram
m	-	Meter
mM	-	Milimeter
mg/g	-	Miligram per gram
cm	-	Centimeter
h	-	hour
rpm	-	Revolutions per minute
nm	-	Nanometer
RI	-	Refractive Index
%	-	Percentage
α	-	Alpha
β	-	Beta
℃	-	Degree Celsius

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Tissue engineering is defined by National Science Foundation in 1987 as interdisciplinary field that combines the life sciences and engineering principles. This combination was developed towards the biological substitutes that able to restore, maintain or improve tissue function (Sukmana, 2012). In addition, Atala (2004) reported that tissue engineering is the platform for repairing and restoration of various tissue and organ function (Atala, 2004). These actions were achieved through application of 3D scaffolds for cells and biomolecules delivery that limits the host rejection and side effects for the patients.

The process of developing and producing engineered tissue *in-vitro* addresses many challenges within the health science (Ikada, 2006). Soft tissues (skin, cartilage, bladder and vascular), hard tissues (bone, ligaments) as well as complex organs (heart, lung and kidney) have the potential to be reconstructed from a bulk of cells. The newly constructed tissues and organs will finally replace the damage or loss of the original tissues. Tissue engineering basically consists of five phases including cell harvesting, cell expansion, scaffold seeding, bioreactor culturing, and implantation. Each phase is still under further research and there are no definitively established protocols yet.

One of the main possible approach to regulate growth of cells and tissues is via three steps of creating, controlling and monitoring an *in-vivo* environment that represents the biochemical and mechanical signals. This approach can be attained using a bioreactor system. The bioreactor system applied in tissue engineering is differed to the industrial bioreactor that attempts to stimulate a physiological environment to promote cell or tissue growth through *in vitro* culture.

The aims of the bioreactor system is to create spatially uniform cell distributions on 3D scaffolds, to maintain a desired concentration of gases and nutrients in the culture medium, and to expose the developing tissue to appropriate physical stimuli which are important parameters to grow functional cells and tissues for transplantation (Junjie Zhao *et al.*, 2016).

Application of bioreactor is overwhelming in 3D tissue engineering substitutes since they allow the modulation of cell culture environments hydrodynamic. This condition plays important roles in growth, development, and function of tissues. The bioreactors function in several ways for tissue engineering purposes such as enabling *in vitro* condition that mimic the cells exist *in vivo*. This could give better understanding of normal cell and molecular physiology. Besides, cells harvested from bioreactor system offers benefits for clinical use such as in gene and cell therapies. This condition mimics a pathological state where the pathophysiology could be explored. The ability of bioreactor system as potential treatment for establishing new therapeutic targets offers more realistic setting than *in vitro* conventional culture which has simpler function (Selden and Fuller, 2018).

Utilizing bioreactors for tissue engineering is believed to be truly significant to the next generation. The bright future in this area would not only contributes beneficial alternatives for reconstruction and replacement of cells, but able to reduce burden of animals' usage in pharmacological testing. Therefore, this study was initiated to develop an integrated bioreactor system for simple and complex tissue engineering application. Sukmana (2012) mentioned that tissue engineering research relies on the increasing knowledge of angiogenesis and vasculogenesis mechanism occurs during capillary tube formation and blood vessel development. Thus, the application of bioreactor is essential to overcome the bottleneck of complex interplay between various factors that influencing tissue vascularization.

1.2 Problem Statement

The main purpose of tissue engineering is to produce functional tissues and artificial organ *in vitro.* Subsequently, the tissue would be utilized as transplants or implants in *in vivo* as well as clinical test systems. Indeed, current clinical strategies offers many benefits for replacement and repair of damaged organs or tissues by transplanting the *in vitro* constructed functional tissue. Although tissue engineering techniques have shown as a promising strategy, lack of clinical scale engineered tissue for *in vivo* implantation is the major problem. The size of engineered tissues is insufficient for clinical application due to lack of microvascular network as similar to the natural tissue. The lack of nutrient that diffuse from outside and forming of waste material inside the scaffold would limit the formation of mature and strong networking of microvascular.

On the other hand, there are some limitation with the *in-vitro* conventional cell culture techniques which were cultured of scaffolds and placed inside incubator (static and 2D condition). It produces a non-homogeneous growth of cells that limit the long-term growth of tissue and reduce the functionality of constructed tissue. One of possibility to overcome this problem is through placing the cultured cells scaffold in a bioreactor system that enables the culture media (fluid) passing through the scaffold. Currently, the available bioreactors have limitations in terms of supporting large-scale and long-term cells/tissue culture. A main challenge is to design a tissue culture bioreactor system that efficiently supports tissue-based construction. Thus, in this study a continuous pulsatile flow bioreactor system was designed and developed to meet the pre-requisite features in order to build and produce mature and functional engineered tissue or artificial organ.

Using this complete automated bioreactor system, the effect of mechanical stimulation on cellular guidance and microvessels development could be further investigated in order to find the optimum parameters. The effect of co-culture system and angiogenic growth factor in dynamic conditions was also crucial to be investigated to improve the maturation and functionality of constructed microvessels.

1.3 Research Objectives

The objectives of this study are as follows:

1. To design and develop a 3D dynamic bioreactor system for cell culture and growth of tissue.
2. To determine the effect of 3D dynamic bioreactor system on cell response and behavior.
3. To determine the effect of 3D dynamic bioreactor system on microvessel development.
4. To analyze the potential of 3D dynamic co-culture system and angiogenic growth factor on cellular function and microvessel formation.

1.4 Scopes of Research

Experimental works of this study was started with the development of two types of dynamic culture system which were simple dynamic culture and pulsatile perfusion bioreactor (integrated) system. The simple dynamic system was used to obtain the appropriate dynamic flow parameter like flow rate and shear stress for HUVECs growth and microvessel formation. The integrated bioreactor was designed and fabricated with heat and gas exchanger units in order to maintain and control temperature (37℃), pH (7.4) and dissolved oxygen (DO) concentration (13 mg/L). All the components/parts of bioreactor were biocompatible, reusable, autoclavable and easy to handle.

The cell proliferation, migration, cell-cell connections and lumen formation (tube-like structures) were compared between static (control), simple dynamic culture and integrated bioreactor system for 2- and 4-days culture duration. The cell growth and microvessel formation were improved by co-culturing of HUVECs with fibroblast and supplemented with vascular endothelial growth factor (VEGF). The immunofluorenscene and histological staining were used to analyse the formation of lumen (tube-like structure) inside the microvessel development.

1.5 Hypothesis of Research

The effect of dynamic and 3D conditions over microvessel development was investigated in this study using the integrated bioreactor system. Previous study stated that the dynamic parameters (flow rate, shear stress, pressure) would affect the behaviour and morphology of endothelial cell. On the other hand, dynamic shear stress also possibly enhances the formation of microvessel. Meanwhile, the perfusion dynamic culture and pulsatile condition would affect the cellular response of microvessel development in the bioreactor system. It is crucial to ensure that the application of bioreactor system would fulfil the requirements of the constructed tissue. Other factors like co-culture and angiogenic growth factor have the potential to improve the cells and tissues growth.

1.6 Significance of Research

This investigation offers several contributions mainly in tissue engineering field and as a wide range of biomedical applications. The application of bioreactors for the next generation of functional tissue replacements are truly needed and being as a matter of interest by scientist. Cultivation of cells in the bioreactor is important as the culture parameters such as temperature, pH, pressure, oxygen concentration, waste removal, pulsation and nutrient transfer can be adjusted to have to the optimum condition. At the same time, bioreactor could be as a beneficial platform to find the optimal biological, chemical and mechanical stimuli, that able to support cell vascularization. Bioreactors can also enable control over the mechanical stimulation for cellular guidance inside the scaffold in order to improve tissue vascularization. The endothelial cells are lining the inner surface of blood vessels of the entire capillary and circulatory system, they experience fluid shear stress and dynamic flow conditions to allow mechanical stimulation upon utilization of grown tissue construct.

The optimization of parameters like flow rate, pressure and pulsation were believed to be able to achieve dynamic culture condition. The *in vivo* mimic conditions are important to produce better cellular organization and mechanical properties as

compared to the constructs culture in static condition. The structural organization of smooth muscle cells was improved through the usage of pulsatile flow. The optimal condition achieved was important for the vascularization process. Overall, bioreactor operations offer a rational basis for the structural and functional design of engineered tissues for the use as model systems, to reduce time of innovation, discovery, and production in biological and clinical research. The use of bioreactors should accelerate the development, evaluation, and delivery of engineered tissue products to patients.

1.7 Thesis Structure and Organization

This thesis is divided into five chapters. Chapter 1 covers the overview of the research background, problem statement, objective with its related scopes and significance of the study.

Chapter 2 describes and introduces tissue engineering as beneficial tools in biomedical application. The bioreactor design requirement and its classification in tissue engineering field are critically reviewed. The chapter also highlights the application of three-dimensional (3D) culture system as a dynamic condition for microvessels development and a new integrated bioreactor system.

Chapter 3 presents the materials and methodologies to design the three-dimensional (3D) culture system for the umbilical cord cells, starting with cells and fibrin gels preparations and proceed until bioreactor performance testing for a good system development.

Chapter 4 denotes the comprehensive results and discussion on the performance of three-dimensional (3D) culture as an integrated bioreactor system on cellular function and microvessels development.

Chapter 5 summarizes and concludes the research findings and suggests relevant recommendations for future works.

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