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Exploring Bone Cell Research Using Bone-on-a-Chip Models and Microfluidics: A Literature Review

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Abstract

Introduction: Organ-on-a-chip models are becoming popular due to its success in modeling human tissues and organs, to mimic human physiology and understand how diseases or drugs affect organs. Traditional 2-dimensional *in vitro* models are limited in recreating complicated bone structure and examining cell-cell interactions. Alternatively, bone-on-a-chip models establish biomimetic conditions to accurately recapitulate the complexity of the bone. However, bone-on-a-chip models as 3D culture systems do not accurately replicate the bone microenvironment. Rather, microfluidic devices allow for fluid control on a microscale or nanoscale level and the incorporation of fluid shear stress normally experienced by bone cells. The goal of this review paper is to summarize advancements to bone-on-a-chip models.

Methods: Relevant articles were selected through a computerized search using GEOBASE and PubMED. Search terms included 'microfluidic devices AND bones', 'organ-on-a-chip models', 'bone-on-a-chip models', 'PDMS AND bone regeneration', 'PolyHIPE AND bone regeneration' and 'bone scaffolds'.

Results: Microfluidic chips are fabricated using soft lithography and poly-di-methyl siloxane (PDMS) which is a biocompatible, synthetic polymer that is used as a cell culture substrate but is too stiff to facilitate bone regeneration. Hydroxyapatite (HA), lined with PDMS, is commonly used, but the substrate degrades at a much slower rate. Moreover, β-tricalcium-phosphate (β-TCP) as a bone scaffold is both porous and degrades faster hence existing studies have used it to generate a dense extracellular matrix.

Discussion: The studies examined in this paper highlight contributions made to scaffolds and microfluidics using bone-on-a-chip models. Notably, scaffolds must be osteoconductive to allow bone cells to adhere, proliferate and form an extracellular matrix on its surface and pore. While PDMS is both osteoconductive and biocompatible, its rigidity poses a concern. Both β-TCP and HA have capabilities for cell-mediated resorption and are more favourable substrates. Additionally, by incorporating microfluidics with bone-on-a-chip models, cells experience greater fluid shear stress similar to that of loading within the bone.

Conclusion: In sum, advancements to bone-on-a-chip platforms are ongoing and the many published studies discussed in this paper aim to optimize both the design and materials used to create long lasting impacts on the rapidly growing field of cell and tissue engineering.

Keywords: organ-on-a-chip; bone-on-a-chip; microfluidics; scaffolds; osteoclasts; osteoblasts; osteocytes

Introduction

Organ-on-a-chip models mimic the structure, function, and physiology of human tissues by creating microenvironments to support the culture of human-derived cells [1]. Organ-on-a-chip devices allow researchers to study the structure and function of a specific organ [2]. There has been a lot of success with organ-on-a-chip models especially in bridging the gap between animal testing studies and human trials, yet advancements to bone-on-a-chip models have been much slower [1].

When considering the physiology of bone, bone is highly mineralized tissue that performs essential functions in the body such as tissue structural support and mobility [3,4]. As such, any imbalance in the structure of bone cells can lead to severe diseases like osteoporosis [3]. However, investigating bone related diseases and testing drugs for such diseases is restricted due to the employment of traditional models involving 2D *in vitro* models [3]. 2D cell culture systems are cost effective as they use cheap materials and simple technologies, but they cannot replicate the 3D bone microenvironment, creating a less complex system [4]. Bone-on-a-chip models are a better alternative as they offer more biomimetic conditions and replicate dynamic cell-cell and cell-matrix interactions [4].

The bone is a dynamic organ and one of the important functions of bone cells is to remove and replace damaged or

old bone [4,5]. Osteoblasts are bone forming cells located on the surface of the bone surface while osteoclasts remove the old, damaged bone [3-5]. Osteocytes are also important for bone remodelling as they regulate the activities of osteoblasts and osteoclasts and are located within the bone matrix [3,5]. Bone-on-a-chip devices establish a biomimetic environment that is engineered by culturing different types of cells in a microfluidic setup with all the necessary chemical and physical requirements to ensure cell viability [4,6]. As such, the device can be used to study intricate physiological processes such as bone remodelling.

One of the important factors to accurately recreate bone microenvironments and to study bone cells is to consider the chemical and physical gradients of bones [7]. The physical microenvironment is a vital element given that the fluid dynamics the cells are exposed to, and the type of substrate used to culture cells can drastically affect cell behaviour [6]. Notably, fluid flow within the bone is caused by loading due to physical activity [6]. With changes in loading, the impact of fluid shear stress on bone cells is associated with changes in remodeling and bone formation [6]. To incorporate said fluid flow, advancements in microengineering and tissue engineering have led to the development of organ-on-a-chip model using microfluidic devices [8].

Microfluidics is a technology that uses micro channels to employ small amounts of fluids and is used to assist the development of cell culturing conditions [4]. While the traditional organ-on-a-chip devices use biocompatible materials and one or two cell types in the microfluidic setup [4], microfluidic devices further recapitulate tissue and organ physiology by producing functionalities that cannot be studied using 2D or 3D culture systems [3]. Therefore, the examination of microfluidic bone-on-a-chip devices is vital, given that these devices can model the *in vivo* environment of these biological processes [4]. In this review, we describe how microfluidic devices are used to facilitate bone regeneration as well as how different substrates and scaffolds determine the environment the cells are cultured in.

Methods

Relevant literature published between 2010 and 2023 were selected through a computerized search through GEOBASE and PubMED. The search terms used included ‘microfluidic devices AND bones’, ‘organ-on-a-chip models’, ‘bone-on-a-chip models’, ‘PDMS AND bone regeneration’, ‘PolyHIPE AND bone regeneration’ and ‘bone scaffolds.’ Thirty papers were obtained, and the results were screened using the abstract to determine relevance to the research topic. Only peer-reviewed papers, both primary and review articles, published in English were considered.

Results

Scaffolds of Bone-On-A-Chip Models

To understand bone remodelling, which is the primary function of bone cells, 3-dimensional scaffolds are required to provide an environment that can facilitate bone regeneration and the type of biomaterial used determines the environment cells are being cultured in [9]. Namely, the chemical and physical properties of the substrate being used to fabricate the devices becomes important in facilitating the right microenvironment to culture bone cells [7]. Significant contributions have been made to determine the optimal bone scaffold that can facilitate bone tissue engineering [10]. One such scaffold is polydimethylsiloxane (PDMS). Microfluidic chips are fabricated using soft-lithography and PDMS, which is a biocompatible, synthetic polymer that is used as a cell culture substrate [7,11]. The physical and chemical patterns on PDMS help to study cell behaviour [7]. They are important for culturing cell behaviour because their mechanical properties help with cell-substrate interactions and fit fluidic valves that allow for a pump to regulate the delivery of fluids [7,11].

One such study that examines cell-substrate interactions is the research carried out by Tang et al. (2021). The investigators developed a microfluidic device that uses a hydroxyapatite (HA) substrate, sealed with a thin layer of PDMS. HA is much more stiff and rigid when compared to PDMS, and the features must be printed on the microchannels using stereolithography (SLA) as opposed to traditional photolithography processes [12]. The HA-PDMS microfluidic chip contains two layers with the microchannels embedded onto the ceramic substrates and the PDMS layer [12]. Three types of structures were produced for the ceramic substrate including the Y-type, the T-junction, and the Christmas tree shaped structure [12]. The PDMS layer was formed by mixing the base elastomer and the curing agent and heated in an oven. The PDMS sheet was cut to the shape of the ceramic substrate and the two layers were connected to enclose the microfluidic channels [12].

Tang et al. (2021) discovered that using the SLA method to print microchannels onto the HA substrate was successful and the investigators were able to make a chip that was 60 mm in size with the thickness of the substrate reaching 1253.6 ± 14.9 μm and the depth of grooves being 208.4 ± 3.6 μm. For the Christmas tree, there was only 0.8 mm for spacing between each branch with average width of the groove being 149.9 ± 12.5 μm [12]. The researchers used different spectroscopy methods to verify that the substrate consisted of high purity of HA. The microfluidic HA chip was compared with HA-PDMS microfluidic device. Despite the composition of HA being consistent with bone, the cells were not successfully cultured on a pure HA ceramic chip because it was too dense to allow for cell respiration to occur and the channel size was also limited due to uncured resin not being easily removed [12].

The HA-PDMS microfluidic device was found to be a better alternative even though the plasma oxidation treatment did not work and uncured PDMS prepolymer was applied to the PDMS sheet for it to bond with the substrate [12]. The microfluidic device was able to successfully concentrate the model drug doxorubicin hydrochloride (DOX) to the Christmas tree structure and was determined to have tremendous promise to successfully study bone related diseases [12].

Different types of scaffold material can specialize in different functions because of the specific properties the material offers. One such example is polymerised internal phase emulsions (PolyHIPEs) which are tissue engineered scaffolds that have porous matrices that are good for tissue regeneration [13]. Bahmaee et al. (2020) developed an osteogenesis-on-a-chip microfluidic device using 3-dimensional polymer scaffold. To develop a 3-dimensional bone tissue engineering scaffold, a microfluidic device with a microenvironment capable of culturing osteoblasts using a two-part device involving a bioreactor and reusable PolyHIPEs was created [14]. The main channel in the bioreactor is 2 mm in diameter while the sub-channels that are leading to the scaffold are 430 μm [14]. The scaffold had a repeating pattern with hexagonal pillars that were 280 μm in height which reduces variation in pressure and shear stress since the hexagonal pillars allow the channel width to be same [14]. The scaffold and the reactor were constructed using negative replica molding from polyethylene glycol diacrylate (PEG-DA) [14]. The PDMS was also made from the PEG-DA mold for the bioreactor and then the PDMS negative was used to model the PolyHIPE [14].

Scanning electron microscopy (SEM) was used to analyze pore size of the PolyHIPE scaffold which ranged from 5 to 30 μm, which was found to be suitable for cell attachment and proliferation [14]. Bone microfluidic chips were tested by culturing human embryonic stem cell-derived mesenchymal progenitor cells (hES-MPs) for 21 days in osteogenesis induction media (OIM). Four different flow rates and patterns were applied to find the optimal flow profile and it was determined that the highest flow rate for the static profile was 3.2 mL/min and had the highest metabolic activity [14]. Intermittent flow was also tested where the flow rate was 3.2 mL/min for 90 minutes followed by flow rate of 0.8 mL/min for 270 minutes in a repeating cycle for 21 days [14]. Continuous flow (3.2 mL/min) was compared with intermittent flow (0.8-3.2 mL/min) and it was discovered that intermittent flow had higher metabolic activity initially but the rate of metabolic activity decreased to the same rate as the intermittent flow [14]. However, intermittent flow demonstrated 2.3 times higher alkaline phosphate (ALP) activity, 1.8 times higher calcium deposition and 2.2 times more collagen synthesis when compared to continuous flow and it had potential in promoting osteogenic differentiation and matrix formation due to the shear stress the cells were exposed to [14]. Moreover, shear stress was not the only determinant in inducing osteogenic differentiation but also the chemical composition of the media the chips were placed in was also essential since the OIM contains dexamethasone which promotes osteogenic differentiation [14].

Alternatively, one of the materials suggested to make ceramic scaffolds is β-tricalcium-phosphate (β-TCP) due to their ability to fabricate porous scaffolds allowing for the development of a dense ECM that is required for bone remodelling [10]. Erbay et al. (2023) proposed a 3-dimensional bone co-culture where primary osteoblast and F4/F80^{+} osteoclast precursors were seeded in the TCP base scaffold and cultured in a microfluidic setup for up to 21 days. A polymer foam replication method was used to make the scaffold and the TCP powder was grinded down to control the geometry of the scaffold. X-ray diffraction (XRD) analysis was able to show that the scaffold was able to retain osteogenic properties and SEM was able to show that macropore sizes ranged from 500 to 50 μm, while micropore sizes ranged from 10 to 1 μm indicating that the scaffold is very porous [15]. Computational fluid dynamic simulations were able characterize the flow pattern in the bone-on-a-chip model which showed that the flow velocity was slower near the boundaries of the channels than in the corner [15]. Bone marrow mesenchymal stem cells (BMMSCs) and osteoclast precursors were cocultured [15]. After 21 days, SEM analysis was used to discover that a substantial amount of ECM was produced within the scaffold [15]. There was also a greater amount of cellular attachment and cell proliferation [15]. Tissue scaffolds were then placed in mice for 8 weeks which revealed the platform had high osteoinductivity [15]. Overall, Erbay et al. (2023) was successful in showing that β-TCP is a better alternative to PDMS and has potential in better understanding tissue microenvironment.

Microfluidics

The cell-loaded mineralized matrix of bone tissues is challenging to recapitulate *in vitro*. Since fluid dynamics plays an important role in creating physiological environments that cells face on the microscale, microfluidic devices can be used to fabricate complex bone tissues [16]. It does this by using channels to control fluids that can be as small as tens of micrometres or nanometers which is also useful for studying cell behaviour since it can perform experimental conditions that would not be possible on a macro level [4,7].

Galván-Chacón et al. (2022) successfully built a 3D bone-on-a-chip model that incorporated a microfluidic perfusion chamber to study bone regeneration and tissue development. This study combined microtechnology, biomaterials science and tissue engineering to create a physiological microenvironment that could culture cells to regenerate bone tissue [6]. Since trabecular bone has interconnected pores and previous studies have showed that trabeculae-like structure allows for cells that were cultured in it to modify their behavior to osteogenic differentiation,

it was scanned by a 3D-phase contrast nano-computed tomography (nanoCT) to be used as the design for the model [6]. Two-photon polymerization (2PP) laser lithography was used to fabricate a 3D structural model which enables for structures to be printed with sub-micrometer resolution [6]. A biomimetic coating method was used to cover the surface of 3D-model with a thin layer of bone mineral-like calcium phosphate (CaP) [6]. Energy-dispersive spectroscopy (EDS) and elemental mapping was able to show the surface had homogenous distribution of calcium and phosphorous on it [6]. The spectrum was also able to find the presence of carbon and oxygen [6].

The microfluidic device was engineered to incorporate several 3D bone models by having a chamber that had a size of 6.2 by 3.2 mm^2 [6]. For cell seeding and providing CaP solution to the cells, two lateral side channels were installed and connected to the main chamber by an array of pillars [6]. To test the sustainability of the bone-on-a-chip device, human mesenchymal stromal cells (hMCSs) were cultured for 21 days. On the first day the cells were seeded with any flow, but after 24 hours, the cells were perfused at a low flow rate of 100 nl min^{-1} [6]. The platform was able to produce bone-like ECM which was rich in collagen with limited amount of cell deaths [6]. The cells produced in the model with CaP coating showed a viability of 90% at day 7, but 60% on day 21 which was attributed to different CaP coating thickness [6]. The models of other studies were only able to culture cells with a viability of 60% on the 7^{th} day. It was concluded that the newly generated microfluidic model could be used to study bone remodelling and to support bone generative therapies [6].

Discussion

To recreate the chemical microenvironment, managing the cell culture medium and the space cells have between each other is vital as cells can easily respond to chemical gradients within a small space [7]. Since microfluidics involves the control of fluids, it can produce predetermined concentration profiles of gradients [6]. One of the chemical considerations for the bone microenvironment is the cell dense ECM which consists of osteoclasts, osteocytes, and osteoblasts [6]. Bones are indirectly affected by pressure on the interstitial fluid through the extracellular matrix [17]. These changes produce variations in shear stress that affect how osteoblasts and osteocytes respond to the stress [17]. Bone ECM is a composite material that has type I collagen as the main organic material which can be used to also fill in PDMS to reconstruct the physiology of the bone tissue [6]. As such, microfluidic devices can be utilized to understand the effects of shear stress on osteoblasts cultured in a collagen-rich microenvironment [4].

The ability for microfluidic platforms to mimic in vivo biological processes through the control of mechanic and chemical considerations the cells are cultured in allows it to study bone diseases and drug screening [4,18]. These platforms study osteoblasts and osteoclasts crosstalk in pathogenic diseases [4]. Microfluidic devices can co-culture human cells and immune cells in bone microenvironments and have high through-put measurements which improves predictive powers of clinical trials [4]. Although some platforms have derived bone cells from animals since they are hard to obtain from humans, a lot of bone-on-chips have been developed without using animals to study [3,4]. This can improve efficiency in drug development since animal models are limited in accurately predicting bone tissue response due to the difference in toxicity and physiology between humans and other species [3,4].

Determining the material for a scaffold is important in facilitating bone regeneration which is why there are many studies trying to find an ideal scaffold [19]. A scaffold needs to be osteoconductive so bone cells can adhere, proliferate, and form extracellular matrix on its surface and pores [10]. Both Tang et al. (2021) and Bahmaee et al. (2020) showed that PDMS is biocompatible and osteoconductive. However, an ideal scaffold also must match bone properties while also being porous for diffusion of oxygen and nutrients to occur to facilitate bone regeneration [10]. Since porosity reduce mechanical properties such as compressive strength and PDMS is a hard rigid material, it can be a barrier when making scaffolds for bone tissue regeneration [10,12]. Moreover, PDMS can also absorb organic solvents and biological materials which is not ideal for making bioreactors [14].

Erbay et al. (2023) proposed a β-tricalcium-phosphate (β-TCP) based bone scaffold that was porous and matched the mechanical properties of a cancellous bone. β-TCP scaffold is also known to be osteogenic and have capabilities for cell-mediated resorption [15]. Bioresorbability is another crucial factor in determining a good scaffold because to create space for new bone tissue, the host tissue should be able to degrade with time *in vivo* which explains how the β-TCP scaffold was able to produce a dense ECM network since degradation provides for Ca and P ions needed to make the network [4,10]. In comparison, since HA substrates have enhanced osteoinductivity and are very stable, the rate of degradation is slower [4]. Each platform has their own benefits, but improvements can serve as a better drug testing alternative compared to conventional models (Table 1) [10,12].

Table 1. Summary of the three different types of scaffolds and comparing them with traditional 2D and 3D platforms

In vitro platforms	Advantages	Disadvantages	References
2-D Platforms	- High through-put - Cheap and simple material	- Cannot replicate complex bone-level physiological environment	Mansoorifar et al. (2021) [4] Ma et al. (2021) [18]
3-D Platforms	- Provide 3-dimensional cell culture environment	- Cannot replicate the physiology - Cannot recapitulate pathology of a human body	Ma et al. (2021) [18]
HA-PDMS microfluidic chip	- High osteoinductivity - High through-put drug screening	- Slow rate of degradation	Tang et al. (2021) [12]
Osteogenesis-on-a-chip	- Suitable for long-term culture - Potential for improving investigation of bone therapeutics	- Absorb organic solvents - Low porosity	Bahmaee et al. (2020) [14]
β-TCP scaffold	- Good bioresorbability - Porous and osteogenic	- Characterization through optical and fluorescent imaging is limited	Erbay et al. (2023) [15]

Conclusions

Bone tissues have a complex structure which renders the study of bone regeneration to be a challenging task using conventional 2D cell culture systems. Therefore, improving bone-on-a-chip models is crucial to fully elucidate these physiological processes. Since microfluidic devices can control and monitor chemical and mechanical properties such as pressure control or providing nutrients to host cell, they can facilitate the microenvironment needed for regrowth [6]. Moreover, the type of scaffold used to place the chip in plays an important role in bone regeneration [10]. Although PDMS and HA substrates were able to show that bone-on-a-chip models can be used to study tissue microenvironment, PDMS is too stiff and rigid to facilitate bone regeneration while nanocrystalline HA sealed by PDMS is not able to degrade fast enough to provide the necessary nutrients to create a dense ECM [12,14]. β-TCP scaffolds are the best option as they have neither of the problems listed above, but more experiments need to be conducted for the optimum mimic of the bone niche [6]. In summary, successful technological advancements of bone-on-a-chip models and microfluidic devices lead to improvements in fields of personalized medicine, and the development of treatments for bone diseases.

List of Abbreviations

2D: 2-dimensional
2PP: 2-photon polymerization
3D: 3-dimensional
ALP: alkaline phosphate
β-TCP: β-tricalcium-phosphate
Ca: calcium
CaP: calcium phosphate
DOX: doxorubicin hydrochloride
ECM: extracellular matrix
EDS: energy-dispersive spectroscopy
HA: hydroxyapatite
hES-MPs: human embryonic stem cell-derived mesenchymal progenitor cells
hMCSs: human mesenchymal stromal cells
nanoCT: nano-computed tomography
OIM: osteogenesis induction media
P: phosphorous
PDMS: polydimethylsiloxane
PEG-DA: polyethylene glycol diacrylate
PolyHIPE: polymerised internal phase emulsions
SEM: scanning Electron Microscopy
SLA: stereolithography
XRD: X-ray diffraction

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

The study did not require ethics approval or participant consent as it is a literature review and did not involve the use of humans, animals, or tissues for its completion.

Authors' Contributions

ZZ: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, drafted the manuscript, and gave final approval of the version to be published.

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