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Theoretical Evaluation of "Skin for Scaffolds" in Tissue Engineering

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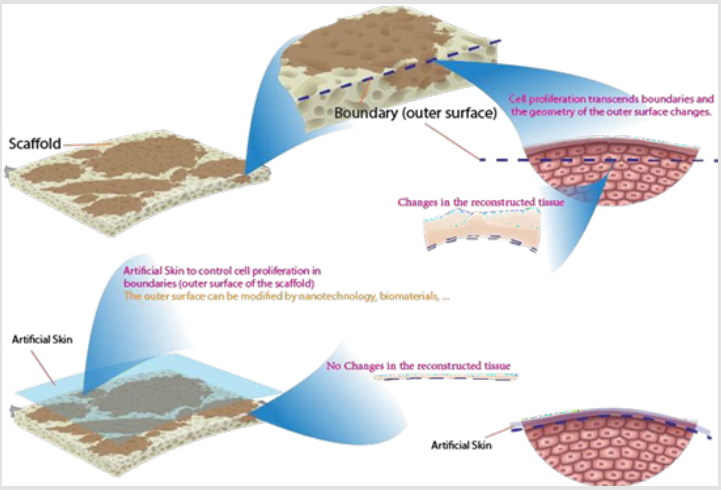
ABSTRACT

The main idea of using 3D bioprinting in tissue engineering (TE) is to fabricate scaffolds similar to the real organ/tissue in the viewpoint of morphology and size. It is not desired if the final size and morphology of the final reconstructed tissue (FRT) be different in comparison with the primarily designed scaffold. Previous studies showed that cells grow and fill up the whole scaffold. Then, cells continue proliferation and invade the boundaries of the scaffold. At this time, a tissue with a new morphology is reconstructed. We thus hypothesize that an artificial skin for scaffolds, can notably help to reach a high control over the size and morphology of FRT.

Keywords: Scaffold; Tissue Reconstruction; Cell; Proliferation; Morphology; Regeneration

Graphical Abstract



Graphical Abstract.

Introduction

In the TE paradigm, engineering and life sciences tools are combined to develop bioartificial substitutes for organs and tissues, which can, in turn, be applied in regenerative medicine, pharmaceutical, diagnostic, and basic research (Ikada [1]). The complex three-dimensional microenvironment, known as a scaffold, plays a vital role to reach FRT with appropriate functions (Mabrouk, et al. [2]). Cells can attach to the scaffold matrix and start proliferation and migration as well as the extracellular matrix (Padhi, et al. [3]). The main idea of scaffold fabrication has been designing a scaffold similar to the injured tissue/organ in size and shape. The design of 3D engineered tissue models is currently in its development stage, showing high potential in overcoming the limitations of already available models to reach a targeted FRT (Mabrouk, et al. [2,4]). According to our literature review, many researchers developed 3D-printed scaffolds in which the FRT was different in size and morphology compared to the primary scaffold, which means 3D bioprinting technology does not guarantee accurate tissue reconstruction (Jia, et al. [5]). However, many issues are discussed in literature while still opened, concerning the identification of the optimal scaffold-forming materials, cell source, and fabrication technology, and the best cell culture conditions (biochemical and physical cues) to finely replicate the native tissue and the surrounding environment.

Theory

We hypothesize that scaffolds need an outer layer to control cells proliferation and migration in the boundaries of scaffolds to keep the original geometry of the FRT. This outer layer can be considered as a skin that owns specific features including lack of cell adhesion, appropriate porosity, biodegradability, biocompatibility with a low rate of degradation in comparison with the inner part.

Discussion

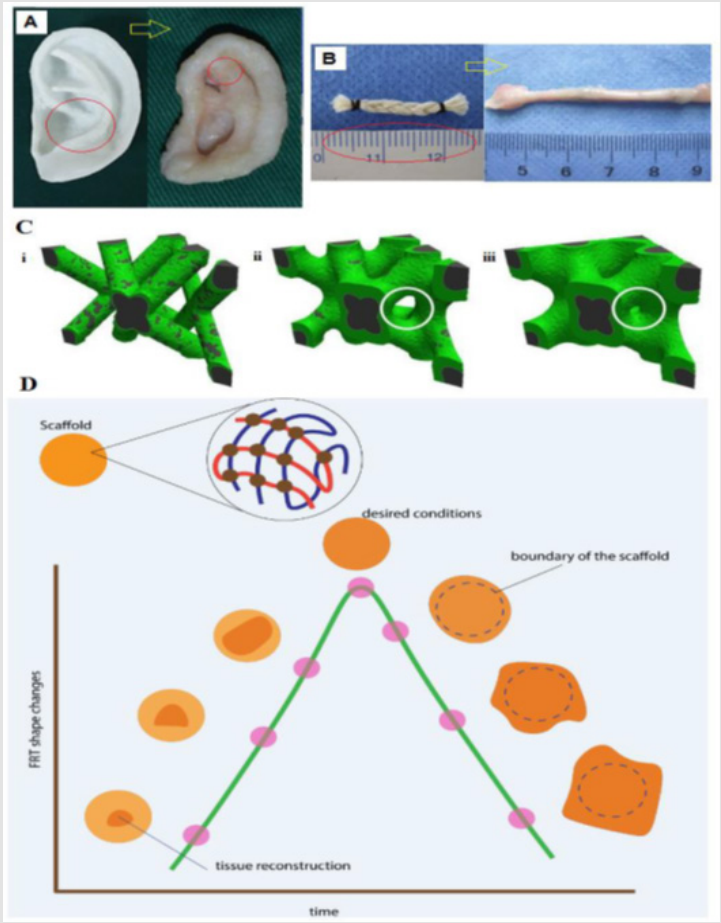


Figure 1:

(A) The reconstructed ear differs from the original scaffold (Jia, et al. [5]).

(B) The reconstructed tendon is longer than the original scaffold (Fang, Chen et al. [17]).

(C) Cells start proliferation and create layers one by one.

(D) The morphology of the FRT will change over time.

TE applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ (Langer, et al. [6]). We do believe that TE has a long way ahead to make tissue. However, numerous studies have been carried out to create tissues like bone, cartilage, skin, vessel, and so on with appropriate functions (Ott, et al. [7-14]). One of the main strategies in TE focuses on the fabrication of scaffolds similar to the real organ or tissue (Langer, et al. [15]). 3D bioprinting is the most effective technique to fabricate scaffolds in desired geometry (Wang, et al. [16]). It is predicted that 3D bioprinting has removed many obstacles in TE and helped in morphogenesis, but there are still challenges that appear after scaffold fabrication and tissue reconstruction. Focusing on the morphogenesis of FRTs in the literature and comparing them with their original scaffolds in the viewpoint of geometry, size, and morphology, it can be concluded that they are different. Notably, the FRTs were larger than their primary scaffold. For instance, in research done by Litao Jia et al. (Jia, Zhang et al. [5]), the reconstructed ear did not have the size as same as the original scaffold especially the inner zones (Figure 1A). In another study by Fang Qian and his colleagues (Fang, et al. [17]), the tissue-engineered tendon was longer than the initial scaffold (5 cm vs. 2 cm) (Figure 1B). More studies are confirming this issue in TE (Cervantes, [18]).

Based on the previous studies, tissues reconstruction can happen due to cell proliferation and creating monolayers one after one (Lewis [19,11]). To validate our hypothesis, we use the activator-inhibitor model of Gierer and Meinhardt presented as (Eq. 1&2) (Gierer, et al. [20]). The chemical and mechanical effects are neglected. u(x,t)(mol/m^3) is the concentration of activator and υ(x,t) (mol/m^3) is the concentration of inhibitor at position x and time t. u and υ are always > 0 because cells are alive during the reconstruction process. Here Du, Dv, ρ_u , ρ_v , ρ, μ_u and μ_v are known as positive constants which characterize the rates of diffusion, production, and decay of the two species. The first terms on the Eqs. 1&2 account for diffusion; the second and third terms account for production {the activator enhances its production (forming an autocatalytic positive feedback loop) and that of the inhibitor, while the inhibitor represses production of the activator} and the fourth terms account for the decay of both species with constant half-lives. These terms cannot be limited to zero, otherwise, reconstruction in scaffolds fails.

$$\frac{\partial u}{\partial t} = D_u \nabla^2 u + \rho_u + \frac{\rho_u}{(1+ku^2)\upsilon} - \mu_u u \quad (1)$$

$$\frac{\partial \upsilon}{\partial t} = D_\upsilon \nabla^2 \upsilon + \rho_\upsilon + \rho_u^2 - \mu_\upsilon \upsilon \quad (2)$$

Our hypothesis says that during 3D cell culture, u and υ are more than zero all over the scaffold including the boundaries. As it can be seen in (Figures 1C & 1D), the outer layer starts creating monolayers which finally alters the morphogenesis and desired size and shape. It is necessary to control this phenomenon in boundaries (outer layer). Hence, our hypothesis proposes that each scaffold can be divided into two parts: core (main body) and skin (outer layer). Considering this hypothesis, Eq.1 & 2 need to be modified as below:

To aim this, it is consumed that:

i. a scaffold is made of n layers: i=1,2, …, n

ii. The outer layer is known as skin and is considered as an individual layer.

$$\frac{\partial u}{\partial t} = \sum_{i=1}^{n} \{D_u \nabla^2 u + \rho_u + \frac{\rho_u}{(1+Ku^2)\nu} - \mu_u u\}_i + \{D_u \nabla^2 u + \rho_u + \frac{\rho_u}{(1+Ku^2)\nu} - \mu_u u\}_{skin} \quad (3)$$

$$\frac{\partial \nu}{\partial t} = \sum_{i=1}^{n} \{D_\nu \nabla^2 \nu + \rho_u + \rho_u^2 - \mu_\nu \nu\}_i + \{D_\nu \nabla^2 \nu + \rho_\nu + \rho_u^2 - \mu_\nu \nu\}_{skin} \quad (4)$$

In which, the first term accounts for core, and the second term accounts for the skin. Based on our hypothesis, the second term is considered as the main reason for the phenomenon in (Figure 1D). Thereby, it is necessary to limit this term to zero. To aim this,

1. The diffusion of the cells into the outer layer must be prevented (D → 0).

2. No cell attachment must happen.

To validate our hypothesis, we focused on Fisher's equation, which has been presented to study the spread of a favored gene through a population (Murray [21]). However, it has been shown that this model can be a good candidate to study the expansion of an *in vitro* monolayer cell colony. Proliferation and cellular migration are considered in this equation. If n(x,t) represents the cell number density (the number of cells/m^2 for monolayer culture) at position x and time t, Fisher's equation is shown as below:

$$\frac{\partial n}{\partial t} = rn(N-n) + D\nabla^2 n \quad (5)$$

In which, rn(N-n) shows the cellular proliferation (linear growth rate: rn) and $D\nabla^2 n$ describe random cell movement with motility coefficient D (similar to a diffusion coefficient). This equation considers the rate of change of cell number density in space and time. However, this equation claims that as the cell number density reaches the maximum at the confluence (N), the proliferation rate tends to zero attributed to the inhibition of cell division due to the cellular crowding phenomenon (Sengers, Dawson et al. 2010). Considering this claim and comparing it with (Figures 1A & 1B), it can be hypothesized that cellular crowding won't happen in scaffold-based cell culture, thereby, Eq.5 needs to be modified for scaffolds. To focus on our hypothesis, based on Figure 2 (a spherical scaffold is imagined just to explain details), a scaffold is supposed to be made of m monolayers, then:

$$\frac{\partial n}{\partial t} = \sum_{i=1}^{m} (rn(N-n) + D\nabla^2 n)_i + \sum_{j=m+1}^{s} (rn(N-n) + D\nabla^2 n)_j \quad (6)$$

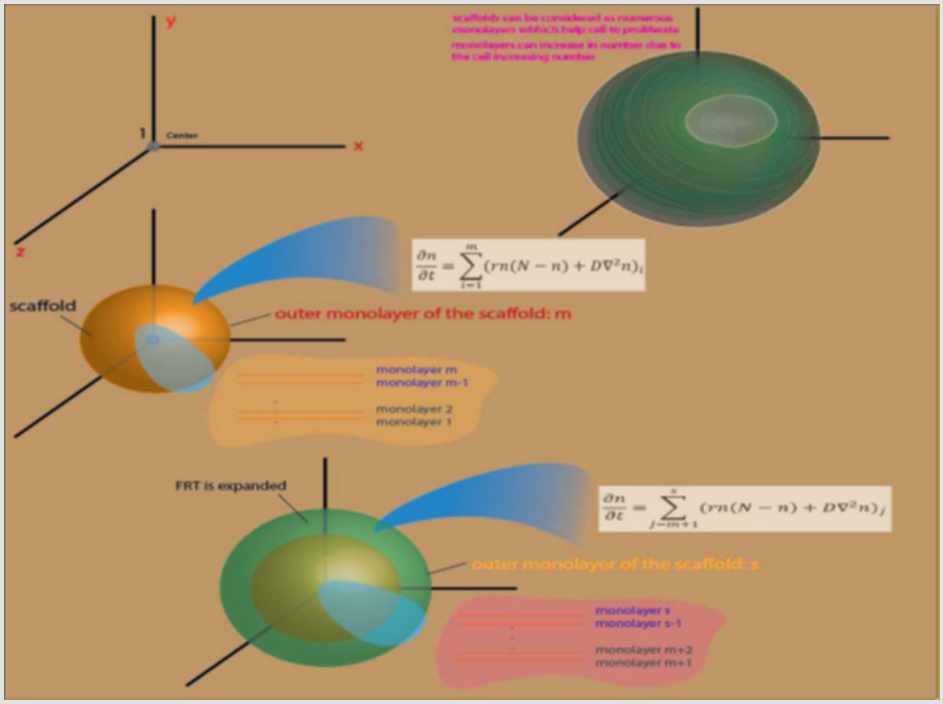


Figure 2: Schematic illustration of increasing monolayers created by cells and causing undesired FRT.

In which the first term describes cell proliferation over through the original scaffold and the second term describes the proliferation of the cells which cause new monolayers (s). if j tends to s (s ϵ N), then undesired FRT will be obtained (Figure 1D). Eq.6 shows that cell proliferation is not limited to the designed scaffold and there is the possibility of changes in size. Therefore, it is necessary to limit the second term to zero which means controlling the number of monolayers is created by cells that consequently helps to keep the FRT equal to the original scaffold. Eq.6 can be summarized as below:

$$\frac{\partial n}{\partial t} = \sum_{i=1}^{s} (rn(N-n) + D\nabla^2 n)_i \quad (7)$$

Based on Eq.7, if s=m, then it can be claimed that cells will reconstruct the desired FRT and no changes in shape and size happen. To sum up, to have s=m, employing a thin layer as coating with no cell attachment ability can be useful to prevent cell proliferation and create a new monolayer. Besides, modifying the outer surface of the scaffold can also be useful in controlling the FRT morphology. In this regard, Eq.7 can be written for the main scaffold and the considered skin as below:

$$\frac{\partial n}{\partial t} = \sum_{i=1}^{m} (rn(N-n) + D\nabla^2 n)_i + (rn(N-n) + D\nabla^2 n)_{skin} \quad (8)$$

By controlling the cell growth and proliferation in the skin layer, Eq.8 can be summarized as below:

$$\frac{\partial n}{\partial t} = \sum_{i=1}^{m} (rn(N-n) + D\nabla^2 n)_i \quad (9)$$

Conclusion

Based on our hypothesis, cells use their extracellular matrix to experience more growth and monolayers. This issue happens on the outer layer of the scaffold and there is a likelihood of changes in the size and shape of FRT. The outer layer can be considered artificial skin. By modifying this skin, the activity of the cells can be controlled and consequently, the final morphology and size of FRT will not differ from the primary scaffold.

Conflicts of Interest Statement

The authors announce that they do not have any conflict of interest.

Author Contributions

All authors contributed to the study conception and design. The main hypothesis proposed by Javad Esmaeili and developed by Dr. Aboulfazl Barati.

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