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ON THE IMPACTS OF FLOW ON THE MIGRATION AND GROWTH OF CANCER CELLS

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ABSTRACT

Our study aims to identify the role of fluid flow in the growth of human bone cancer cells during metastasis. In our experiments, the cancer cells are seeded on the surface of cylindrical scaffolds in a bioreactor. The flow is laminar flow, which mimics the physiological conditions of the human body. A full-scale 3D high-resolution computational mesh of scaffold was created based on the physical scaffold's Micro-CT scans using open-source imaging software Slicer3D and Meshmixer. To investigate the influences of the flow on the seeded cells, we performed Computational Fluid Dynamics (CFD) simulations with the immersed boundary method (Gilmanov, Le, Sotiropoulos, JCP 300, 1, 2015). The computational domain was generated using the commercial software Gridgen. Our results show that the fluid flow velocity is highly dependent on the shape and pore sizes. In addition, the magnitude of the velocity on the surface where the cells are seeded is in between [0-0.05] $\mu m/s$ *allowing the cells to grow without being detached from the surface of the scaffold. Our future work will focus on (i) investigating the role of the shear stress on the distribution and orientation of the cancer cells. (ii) Simulating multiple scaffolds within the bioreactor to further quantify the impact of the gap on the flow velocity and shear.*

Keywords: Bone, Cancer Cells, Scaffolds, CFD.

NOMENCLATURE

Micro-CT	Micro Computed Tomography
CFD	*Computational Fluid Dynamics*

1. INTRODUCTION

The mechanical behaviour of cancer cells has been studied extensively in the last decade, utilizing an integration between physics and mechanics with genomic approaches [1, 2]. However, in vitro tissue-engineering studies revealed that under the same flow conditions, different samples of seeded cancer cells on the surface of a bone mimicking scaffold were shown to grow and migrate differently [3].

In addition to the multiple molecular pathways driving metastasis, the mechanical forces are also responsible for tumour progression and response to classical therapies [4, 5, 6]. Various experimental studies were carried out focusing on the effects of mechanical stimuli on the growth of cancer cells [7]. The goal of these experiments was to find out how these signals can affect the behaviour of cancer cells [8,9,10]. For instance, high shear forces exerted on tumor cells can induce mechanical stress, leading to cell fragmentation and death [11], whereas intermediate shear forces have been shown to favour tumor intravascular arrest and extravasation [12]. Thus, an improved understanding of the fluid-derived mechanical cues experienced by cancer cells is crucial for fully elucidating the metastatic cascade for therapeutic intervention.

In this work, we generated a full-scale 3D high-resolution model of the physical scaffold based on micro-CT scans. We investigated the patterns of the flow within the scaffold to associate with the dynamics of the cancer cells resulting from the fluid flow velocity.

2. METHODOLOGY AND METHODS

Nano-clay based tissue-engineered scaffold can mimic the remodeling bone in which cancer cells possess the propensity to migrate and metastasis [13,14]. The bone scaffold model can thus be used as a testbed to evaluate behaviors of phenotypically different prostate cancer cells at the bone site [15]. Here, the scaffold specimen is scanned with Micro-CT under the resolution of 70 μm. The current scaffold model represents the final version we generated after several iterations we carried out in our previous works [16, 17, 18, 19]. In brief, the scanned images (DICOM files) were processed using the open-source imaging software Slicer3D to generate the 3D mesh of the scaffold. A series of thresholding trials were performed to find the optimum range, to capture the maximum possible interconnected pores resembling the physical scaffold. The mesh is then smoothed and resurfaced while preserving the overall porosity using the open-source software Meshmixer.

The scaffold porosity in particularly the pore size, can have a significant influence on fluid flow velocity and the shear stress. For instance, it was observed that higher average WSS occurred on the scaffold surface with small pore sizes [20]. In this work, the full-scale scaffold model was generated from a polymer nano-clay based scaffold that exhibit high porosity (86.1 %) with a pore size ranging from 10 - 30 μm to 100 - 300 μm, which are necessary for hard tissue growth.

The simulations were performed using Virtual Flow Simulator (VFS), which is an open-source CFD code based on the immersed curvilinear boundary method. VFS has been applied for many problems in biological applications including brain aneurysms [21,22], heart hemodynamics [23, 24, 25], and heart valves [26, 27]. The governing equations for the fluid are the three-dimensional, unsteady incompressible continuity and Navier-Stokes equations.

Fluid was assumed to be incompressible, considered as DMEM media with density and dynamic viscosity of 1000 kg/m^3 and 0.78 mPa s at 37 ◦C respectively [28]. The continuity and Navier-Stokes equations are solved using curvilinear-immersed boundary (CURVIB) method [29]. The discrete equations are integrated in time using a fractional step method. A Newton-Krylov solver is used to solve the momentum equations in the momentum step and a GMRES solver with multigrid pre-conditioner is employed for the Poisson equation.

At the inlet of the fluid domain, a uniform velocity of $U_0 = 16.57 \mu m/s$ is applied based on the flow rate ($Q = 0.2 mL/min$) and the diameter of the bioreactor chamber ($D = 16\, mm$).

The computational domain is discretized using a structured grid of size 401x401x491 (approximately 79 million grid points) with a rectangular geometry and average spacing of 20 μm, 20 μm and 8 μm defining the resolution of the domain in the directions x, y, and z respectively. This resolution is sufficient to resolve the pores.

3. RESULTS AND DISCUSSION

The CFD simulations were performed considering the entire scaffold geometry, characterized by its high irregular porosity distribution. The flow velocity contour at the surface of the scaffold is shown in figure 1. The results revealed a dispense velocity profile on both sides of the scaffold for all considered ranges. On the back where we're more interested (seeded cells), the range of the velocity is almost entirely in the interval [0-0.05] $\mu m/s$. This low velocity profile is due to the relaxation of the flow within the scaffold because of the dense porosity that break the magnitude of the flow. Under this low velocity range, the seeded cells can grow without being detached from the surface of the scaffold [3].

At the level of the pores (figure 2), the flow velocity is in the range of [0 - 0.5] $\mu m/s$. However, the profile is shown non uniform and changes according to the shape and size of the pores, which can affect directly the shear stress impacting the growth and orientation of the cancer cells [20, 30, 31].

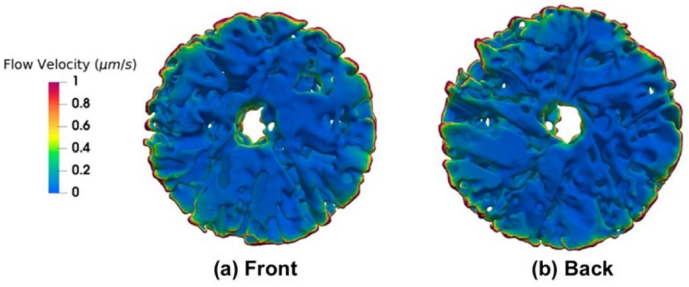

FIGURE 1: Computational Fluid Dynamics simulation between the full-scale 3D scaffold and the bio-reactor flow. The flow velocity contour is shown at the surface of both sides of the scaffold. The front surface is the side facing the flow and the back is the side where the cancer cells are seeded facing the outlet.

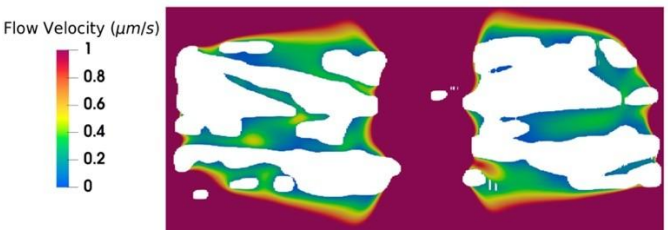

FIGURE 2: Flow velocity contour inside the scaffold pores, visualized from cross-sectional symmetry plan of the scaffold.

4. CONCLUSION

In the present study, we performed high-resolution CFD simulation on the full-scale scaffold model we generated based on the micro-CT scans. The results revealed insights on the impact of the porosity on the flow velocity and fluid shear stress, which is the parameter altering migration and growth of the cancer cells. Our future work will include multiple scaffolds within the perfusion bio-reactor to investigate the influence of the gap between the scaffolds on the flow velocity and fluid shear stress.

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