Response analysis of primary cilia of the cell to the oscillatory fluid flow by using fluid-structure interaction method

Bahram Ahmadian[1], Bahman Vahidi[2)]

[1] Department of New Sciences and Technologies, University of Tehran, Tehran, Iran
[2] Department of New Sciences and Technologies, University of Tehran, Tehran, Iran

ABSTRACT

Primary Cilia is appendage that extrudes from cell surface into the extracellular matrix. These organelles play a sensor role for mechanical stimulation in the cell and due to stretch ion channels in its base, play critical role in induce osteogenic differentiation of stem cells. Primary cilia deflected under fluid flow passing through the surface of the cell, which deflection causes tensile ion channels to be opened. In this study, cilia is assumed as linear elastic. The innovative aspect of this research is exerting of oscillatory fluid flow to the primary cilia and evaluating the response of cilia to the fluid flow. The results show that under conditions of exerting the oscillatory fluid flow, maximum strain occur in the base of the cilia which experienced by tensile ion channels, is 0.5 and in the condition of steady flow is 0.3, Accordingly, mechanical stimuli are sensed by the tensile ionic channels during oscillatory flow higher than steady flow. osteogenic differentiation of stem cells, in addition, the result showed that by using the oscillatory fluid flow the mechanical stimulation better senses by cilia and It is anticipated that exerting oscillatory fluid flow facilitate osteogenic differentiation of stem cell.

KEYWORDS

Oscillatory fluid flow, Primary cilia, Mechanotransduction, Cell mechanics, Fluid-structure interaction

[1] Corresponding author: Email: bahman.vahidi@ut.ac.ir

Introduction

Cilia is appendage that extrude from the cell surface to the extracellular region [1]. This organelle is present in all mammalian cells and is divided into two categories of motile and primary cilia in the body [2, 3], motile cilia are known as the cause of movement in some cells, including respiratory cells. While the primary cilia act as sensors of fluid flow, pressure and vibration in the body [1, 3].

In the models performed [2, 4, 5] to study the response of the primary cilia to the fluid flow, a steady flow has been used, while laboratory observations show that the primary cilia have critical role in differentiating of mesenchymal stem cells to bone cells in response to oscillatory fluid flow [6]. Because TRPV4-type of tensile activated ion channels, which play the role of receiving mechanical stimulation and osteogenic induction, are located at the base of the cilia [7].

In the previous studies [2, 4, 5], steady fluid flow is used to evaluated the response of cilia to the fluid flow, but in this study, three dimensional model of cilia is generated and the response of it to the oscillatory fluid flow is evaluated. In this modeling, to justify different movements of the cilia a two-dimensional elastic layer is used at the base of the cilia.

1. Materials and Methods

In this study, a rectangular cube with a height of 7 μm, a length of 9 μm and a width of 6 μm was used to model the fluid domain. A cylinder with a diameter of 200 nm and a height of 4 μm is used for modeling of cilia and on top of this cylinder a hemisphere with a radius of 0.1 μm was modeled as the head of the cilia. the cilia connect to the surface of the fluid domain by a fillet with a radius of 0.1 μm and two-dimensional elastic layer was used to connect the base of the cilia to the surface of the channel. (Fig.1)

The equations used for the incompressible oscillatory fluid flow is solved time-dependently. The governing equations include the momentum conservation equation (Navier-Stokes) and the continuity equation, which are given in Equations 1 and 2, respectively [2]:

$$u_{Fluid} = \rho\nabla \tag{1}$$

$$\rho\frac{\partial u_{Fluid}}{\partial t} + \rho\left(u_{Fluid}.\nabla\right)u_{Fluid} = \nabla.\left[-pI + \mu\left(\nabla u_{Fluid} + \nabla u_{Fluid}{}^{T}\right)\right] \tag{2}$$

which ρ is the fluid density, u_{Fluid} is the fluid velocity vector, t is the time, p is the pressure, I is the unit tensor and μ the fluid viscosity.

2.1 Solid Domain

In this research, a linear elastic model has been used for the solid domain [11]. Accordingly, the equations of isotropic linear elastic material was used as follows [10]:

$$\frac{\partial^2 x_{Solid}}{\partial t^2} - \nabla.\sigma = \left(I + \nabla u_{Solid}\right)\upsilon\rho \tag{3}$$

Where υ is the Poisson's ratio and x_{Solid} is the displacement of the solid domain. The basic boundary conditions of the cilia, which use the elastic layer constraint, are as follows [10]:

$$n = -k\left(x_{Solid} - x_0\right)\sigma \tag{4}$$

Whereas k is the spring constant.

In finite element numerical simulations, a computational grid must be used to solve the problem. In this research, COMSOL software version 5.3 was used in which the computational network was created by the software itself. The proposed model has narrow areas in some parts and deformation and stress distribution in those areas are of great research importance. For this reason, manual computational grid is used and small elements are applied in narrow areas to increase computational accuracy.

2. Results and Discussion

As shown in Fig. 2, most of the stress changes occur at the base of the cilia, and most of the cilia under the fluid flow experience small von Miss stress. Observations have shown that TRPV4-type of activate ion channels are located at the base of the cilia [12]. Accordingly, to investigate the strain distribution at the base of the cilia at a time interval of t = 0.25 s, where the highest amount of displacement occurred at the tip of the cilia, strain distribution at different heights in the base of the cilia has been investigated (Fig.2).

Experimental studies [12] have shown that TRPV4-type ion channels, which play an important role in the osteogenic induction process of stem cells, are located in the areas where the most strain occurs. As shown in Fig.2. most strain occurs in the ciliary base membrane. Therefore, it can be concluded that TRPV4 tensile activated ion channels are located in the ciliary membrane, which is in consistent with the experimental observations of Praetorius et al. [13].

Comparing the strain distribution at the base of the cilia under the influence of oscillatory and steady fluid flow showed that magnitude of strain created at the base of the cilia under oscillatory flow is higher than the steady fluid flow condition. By increasing the strain around the membrane of cilia, mechanical stimulation is sensed better by cilia [10]. Accordingly, it is predicted that the use of oscillatory fluid flow is more efficient than steady fluid flow in activating these channels and inducing osteogenic differentiation.

In the research of Rydholm et al. [4], a viscoelastic layer was used on the ciliary membrane and the cilia were attached to the surface of the channel by cantilever constraint. comparing result of this study with the model of Rydholm et al. [4], showed that von Mess stress in both models are in the range of kPa and the difference between the results is due to differences in the geometry of the two models.

3. Conclusions

In this study, the cilia were examined under oscillatory fluid flow. The innovative aspect of this study is the evaluation response of cilia to the oscillatory fluid flow, which has been neglected in previous studies. In this research, the method of fluid-structure interaction has been used to investigate the response of the cilia to the fluid flow. The results show that the starch active ion channels when expose to oscillatory fluid experience more strain than the steady-state flow pattern. Accordingly, mechanical stimulation by starch active ion channels is sensed better and the osteogenic induction process is facilitated.

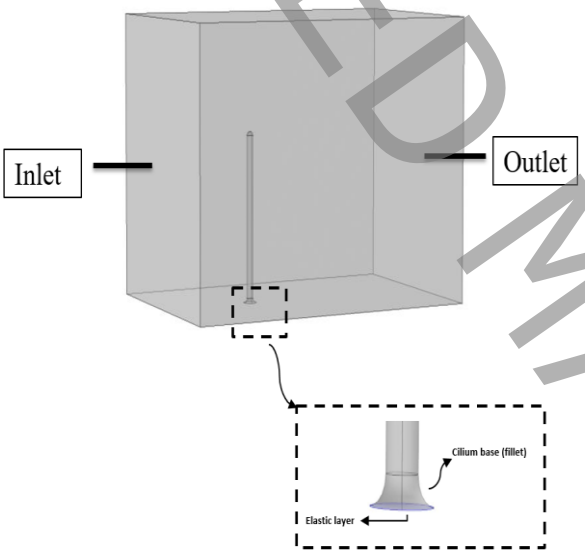

Fig. 1 Complete view of the model

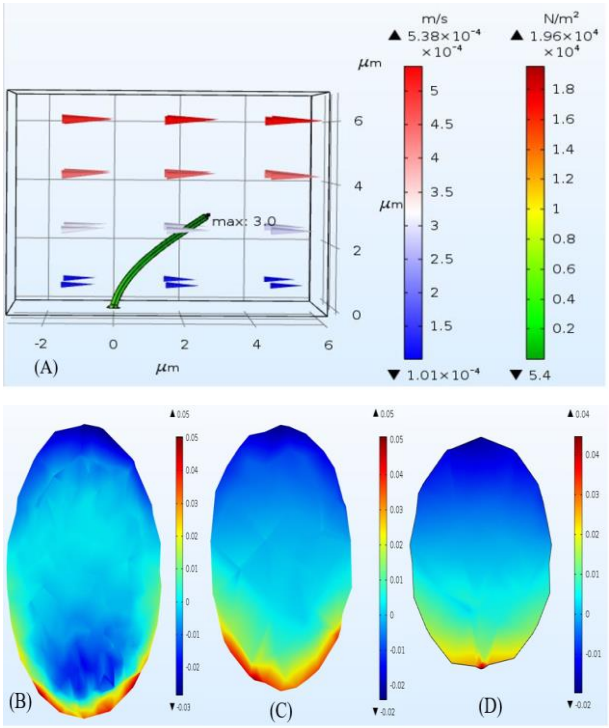

Fig. 2 (A). response of cilia to the fluid flow. Strain distribution at cilia base under oscillatory flow in height of b) 0.03 µm, c) 0.05 µm and d) 0.07µm

4. References

[1] M. Adams, The primary cilium: An orphan organelle finds a home, Nature Education, 3(9) (2010) 54.

[2] A. Abbasszadeh Rad, B. Vahidi, A finite elements study on the role of primary cilia in sensing mechanical stimuli to cells by calculating their response to the fluid flow, Journal of Computational Applied Mechanics, 47(1) (2016) 35-44.

[3] V. Singla, J.F. Reiter, The primary cilium as the cell's antenna: signaling at a sensory organelle, science, 313(5787) (2006) 629-633.

[4] S. Rydholm, G. Zwartz, J.M. Kowalewski, P. Kamali-Zare, T. Frisk, H. Brismar, Mechanical properties of primary cilia regulate the response to fluid flow, American Journal of Physiology-Renal Physiology, 298(5) (2010) F1096-F1102.

[5] P.S. Mathieu, J.C. Bodle, E.G. Loboa, Primary cilium mechanotransduction of tensile strain in 3D culture: Finite element analyses of strain amplification caused by tensile strain applied to a primary cilium embedded in a collagen matrix, Journal of biomechanics, 47(9) (2014) 2211-2217.

[6] 6 P. Tummala, E.J. Arnsdorf, C.R. Jacobs, The role of primary cilia in mesenchymal stem cell differentiation: a pivotal switch in guiding lineage commitment, Cellular and molecular bioengineering, 3(3) (2010) 207-212.

[7] D.A. Hoey, S. Tormey, S. Ramcharan, F.J. O'Brien, C.R. Jacobs, Primary cilia-mediated mechanotransduction in human mesenchymal stem cells, Stem cells, 30(11) (2012) 2561-2570.

[8] P. Pisani, M.D. Renna, F. Conversano, E. Casciaro, M. Di Paola, E. Quarta, M. Muratore, S. Casciaro, Major osteoporotic fragility fractures: Risk factor updates and societal impact, World journal of orthopedics, 7(3) (2016) 171.

[9] L.C. Espinha, D.A. Hoey, P.R. Fernandes, H.C. Rodrigues, C.R. Jacobs, Oscillatory fluid flow influences primary cilia and microtubule mechanics, Cytoskeleton, 71(7) (2014) 435-445.

[10] A.H. Abbasszadeh Rad, B. Vahidi, The Effect of the Kind of Attachment of Primary Cilium to Cell in Its Response to the Fluid Flow: A 3D Computational Simulation, Journal of Solid and Fluid Mechanics, 8(1) (2018) 203-213.

[11] M.E. Downs, A.M. Nguyen, F.A. Herzog, D.A. Hoey, C.R. Jacobs, An experimental and computational analysis of primary

cilia deflection under fluid flow, Computer methods in biomechanics and biomedical engineering, 17(1) (2014) 2-10.
[12] M.A. Corrigan, G.P. Johnson, E. Stavenschi, M. Riffault, M.-N. Labour, D.A. Hoey, TRPV4-mediates oscillatory fluid shear mechanotransduction in mesenchymal stem cells in part via the primary cilium, Scientific reports, 8(1) (2018) 3824.
[13] H. Praetorius, K.R. Spring, Bending the MDCK cell primary cilium increases intracellular calcium, The Journal of membrane biology, 184(1) (2001) 71-79.