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Two-dimensional numerical study of flow dynamics of a nucleated cell tethered under shear flow

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HIGHLIGHTS

- We developed a model to study the dynamics of a nucleated cell tethered under flow.
- Properties of nucleus significantly affect the flow dynamics of tethered cells.
- Presence of nucleus leads to leukocyte tether dynamics different from platelets.
- Varied internal viscosity leads to the variation in tether dynamics of leukocytes.

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ABSTRACT

When blood components (*e.g.*, leukocytes and platelets) adhere to a surface (*e.g.*, blood vessel wall), shear flow causes the elongation of the non-adherent part of the cell membrane forming a long thin cylinder shape (*i.e.*, cell tether). The formation of cell tether is important for regulation of cell adhesion strength and stabilization of cell rolling, and may significantly affect the flow dynamics inside the vessel, as well as the motion of other cells and bioactive molecules. Although significant efforts have been made to reveal mechanisms underlying cell tether formation, the role of nucleus, nucleus/cell volume ratio, nucleus/plasma viscosity ratio and cytoplasm/plasma viscosity ratio remains unknown. As such, we developed a two-dimensional mathematical model, in which leukocytes are regarded as compound viscoelastic capsules with a nucleus. We investigated the effects of several factors on flow dynamic characteristics of tethered cells, including the cell length, the inclination angle, the drag and lift forces acting on the cell. The presence of a nucleus (with nucleus/cell volume ratio of 0.44) led to a decrease of 33.8% in the cell length and an increase of 152%, 113% and 43.6% in the inclination angle, the drag force and lift force respectively compared to those of a cell without nucleus. For a cell with nucleus/cell volume ratio of 0.2, a 10-fold increase in cytoplasm/plasma viscosity ratio resulted in a decrease of 19.3% in the cell length and an increase of 93.9%, 155% and 131% in the inclination angle, the drag force and lift force respectively. These results indicate that nucleus and cytoplasm play a significant role in flow dynamics of nucleated cells tethered under shear flow. The developed mathematical model could be used to further understand the mechanisms of cell-adhesion related bioprocesses and to optimize the conditions for cell manipulation in microfluidics.

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1. Introduction

When blood components adhere to a surface (*e.g.*, the wall of a blood vessel) and are subject to a flow at the same time, cell tethers (*i.e.*, long thin membrane cylinders extruded from adhered cells) may form due to the cooperation of hydrodynamic forces and adhesion forces. This phenomenon has been observed in *in vitro* experiments for different blood components. For example, leukocyte tethers with an average length of 5.9 μm (approximately radius of a leukocyte) were observed under physiological flow conditions (Schmidtke and Diamond, 2000), whereas platelet tethers with lengths of 3.2 – 16.6 μm (about 2 – 10 cell radii) were observed at a shear rate ranging from 150 to 10,000 s^{-1} (Dopheide et al., 2002). Cell tethers play an important role in cell adhesion related bioprocesses (*e.g.*, lymphocyte homing) and applications (*e.g.*, cell capture/release in microfluidic devices) (Tasoglu et al., 2013; Gurkan et al., 2012; Rizvi et al., 2013). For instance, dynamic alterations of cell tethers were revealed to stabilize leukocyte rolling (Ramachandran et al., 2004), which widely happens during lymphocyte homing. Cell tethers can also regulate cell adhesion strength, which may lead to flow-enhanced cell adhesion (Yago et al., 2007) and thus may affect the cell capture efficiency of microfluidic devices. Furthermore, numerous cell sorting applications (*e.g.*, sperm sorting) are strongly dependent on cell-microchannel wall interactions and potentially post-effects of adhered cells on flow dynamics inside channels (Tasoglu et al., 2013). However, the flow dynamics of tethered cells under shear flow are not yet completely clear, which has limited the understanding of cell adhesion related bioprocesses and applications.

Significant efforts have been contributed to understanding of tether formation and the flow dynamics of tethered cells under shear flow. A rigid microsphere model was firstly developed to study the formation of cell tethers under shear flow (King et al., 2005; Yu and Shao, 2007). A viscoelastic drop model (Khismatullin and Truskey, 2005) and an elastic capsule model (Berry et al., 2011) were further presented to incorporate dynamical cell deformation into tethered cell dynamics. However, some experimental observations were not discussed in these studies, *e.g.*, different cell tether lengths of leukocyte tethers and platelet tethers (Schmidtke and Diamond, 2000; Dopheide et al., 2002), large variations in leukocyte tether length ranging 1 – 25 μm (about 0.1 – 4-fold leukocyte radii) (Schmidtke and Diamond, 2000). The differences in size and morphology of leukocytes (spherical shape with a diameter of 10 – 20 μm) and platelets (discoidal shape with a diameter of 2 – 3 μm) were found to affect the adhesion dynamics (Berry et al., 2011). Another apparent difference between leukocyte and platelet is that a leukocyte has a nucleus but a platelet does not. In addition, mechanical properties of intracellular fluids, which were revealed to affect tether dynamics by *in vitro* experiments (Heinrich et al., 2005; Girdhar and Shao, 2007; Jauffred et al., 2007; Schmitz et al., 2008; Pospieszalska and Ley, 2009), may significantly vary even for the same types of cell, see Table 1. However, effects of these factors on the flow dynamics of tethered cells under shear flow are missing. Therefore, to develop a better understanding of tethered cell dynamics, further comprehensive investigations are required.

In this study, we developed a two-dimensional mathematical model to study the effects of several factors on the flow dynamics of tethered cells under shear flow. Among these factors are presence and absence of a nucleus, nucleus/cell volume ratio, nucleus/plasma viscosity ratio and cytoplasm/plasma viscosity ratio. Here, we developed a viscoelastic compound capsule model incorporating a nucleus, and evaluated hydrodynamic forces acting on the tethered cell. The results showed that the presence of a nucleus, nuclear and cytoplasmic properties significantly affected the flow dynamics of tethered cells under shear flow. These findings could explain experimental observations such as large variations in cell tether length and distinct characteristics of cell tethers between leukocytes and platelets. Our study provides new insights into tethered cell dynamics under shear flow, and the model presented here could be used to study functions of cell tethers in cell adhesion related bioprocesses, *e.g.*, regulating cell adhesion strength or stabilizing cell rolling.

2. Computational method

In Fig. 1, an initially spherical blood cell with radius R is tethered by a microvillus on cell membrane to the bottom plate. Computational domain extends approximately 12 drop radii in the x direction and 6 drop radii in the y direction. The cell is subject to a shear flow with an initial fluid velocity governed by a parabolic profile $\boldsymbol{u}^0=[ky(1-y/H), 0]$, which is a representative of the flow in a parallel-plate flow chamber. Here k is the bulk shear rate defined as $k=4u_{max}/H$, where u_{max} is the centerline velocity in the absence of cells. The blood cell (*e.g.*, leukocyte) with a nucleus is modeled as a compound viscoelastic capsule, which is a viscoelastic fluid including cytoplasm (density ρ_1 and viscosity μ_1) and nucleus (density ρ_2 and viscosity μ_2) surrounded by an elastic membrane (i.e., plasma membrane with shear modulus E_s). The cell without a nucleus (*e.g.*, platelet) is modeled as an elastic capsule, which is composed of a viscoelastic fluid with density ρ_1 and viscosity μ_1 surrounded by an elastic membrane with elastic modulus E_s. The

Table 1
Parameter values used in our computational model.

Parameter	Definition	Values	Reference
R (μm)	Cell radius	5	Bai et al. (2013), Luo et al. (2011b) and Geissmann et al. (2003)
L (μm)	Channel length	60	Bai et al. (2013) and Luo et al. (2011a, b)
H (μm)	Channel height	30	Stone and Kim (2001), Popel and Johnson (2005), Squires and Quake (2005), N'Dri et al. (2003) and Pappu et al. (2008)
k (s^{-1})	Shear rate	200–8000	Schmidtke and Diamond (2000), Dopheide et al. (2002) and Ramachandran et al. (2004)
ρ_0 (kg/m^3)	Density of plasma	1000	N'Dri et al. (2003), Khismatullin and Truskey (2004) and Berry et al. (2011)
μ_0 (mPa s)	Viscosity of plasma	1.0	N'Dri et al. (2003), Khismatullin and Truskey (2004) and Berry et al. (2011)
ρ_1 (kg/m^3)	Density of cytoplasm	1000	Bai et al. (2013) and Luo et al. (2011a, b)
$\lambda_{\mu 1}$	Cytoplasm/plasma viscosity ratio	500 – 5000	Schmid-Schonbein et al. (1980) and Khismatullin and Truskey (2004)
λ_1 (s)	Cytoplasmic relaxation time	0.176	Khismatullin and Truskey (2004)
α	Nuleus/cell volume ratio	0.2 – 0.44	Schmid-Schonbein et al. (1980), N'Dri et al. (2003) and Khismatullin and Truskey (2004)
ρ_2 (kg/m^3)	Nucleus density	1000	Khismatullin and Truskey (2004) and Bai et al. (2013)
$\lambda_{\mu 2}$	Nucleus/plasma viscosity ratio	5000 – 10,000	Schmid-Schonbein et al. (1980) and Khismatullin and Truskey (2004)
λ_2 (s)	Nuclear relaxation time	0.2	Khismatullin and Truskey (2004)
E_s (μN/m)	Elastic modulus of cell membrane	5 – 2500	Jadhav et al. (2005), Tasoglu et al. (2011, 2012) and Pappu et al. (2008)
k_b (μN/m)	Spring constant of adhesion bond	10,000	Khismatullin and Truskey (2004, 2005) and Luo et al. (2013)