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Recent microfluidic devices for studying gamete and embryo biomechanics

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ABSTRACT

The technical challenges of biomechanic research such as single cell analysis at a high monetary cost, labor, and time for just a small number of measurements is a good match to the strengths of microfluidic devices. New scientific discoveries in the fertilization and embryo development process, of which biomechanics is a major subset of interest, is crucial to fuel the continual improvement of clinical practice in assisted reproduction. The following review will highlight some recent microfluidic devices tailored for gamete and embryo biomechanics where biomimicry arises as a major theme of microfluidic device design and function, and the application of fundamental biomechanic principles are used to improve outcomes of cryopreservation.

1. Introduction

Biomechanical studies of gametes and embryos are critical to understanding the process before fertilization where the gametes need to physically find each other, the fertilization process, and how physical stimuli affect embryo development. Recently there have been large leaps of knowledge added to mechanics by which sperm exhibit rheotaxis phenomena (Miki and Clapham, 2013). On the other hand, the material property of the zona pellucida of the oocyte and its seemingly instantaneous change during zona hardening is of high biomechanical interest (Braden et al., 1954). It is also thought that mechanics play a role in development, where applied mechanical forces provides a feedback to embryo development by mimicking the fallopian tube's physical stimulation of the embryo as it peristaltically pumps the embryo into the uterus (Eytan et al., 2001; Kim et al., 2009).

Classical methods of biomechanical studies involve the use of micromechanical testing, optical tweezers, micropipette aspiration or atomic force microscopy (Thoumine et al., 1999; Hochmuth, 2000; Guck et al., 2001; Lulevich et al., 2006). Such techniques are normally of high cost and labor for single cell analysis. Biomechanics in general is therefore well suited for the incorporation of microfluidic tools to decrease cost, introduce high-throughput screening to reduce labor while simultaneously increasing the accuracy of measurement. Recent applications of microfluidics in biomechanical studies of gametes and embryos have revealed structural mechanisms of sperm that allows swimming with relative ease against direction of fluid flow and discoveries of never-before seen rheotaxis behavior that increases the sperm's chances of encountering an oocyte in its journey through the female reproductive tract (Su et al., 2012; Kantsler et al., 2014). In oocytes, microfluidic tools suggest that the zona pellucida is even stiffer than what was measured previously: further providing evidence that there is more to penetrating the glycoprotein membrane than physical force (Murayama et al., 2004). Microfluidics has shown that mechanical stimuli enhances embryo development and has provided evidence to advance current embryo culture techniques beyond the static petri dish (Kim et al., 2009). Lastly, microfluidic tools have also been applied to reduce osmotic and mechanical stress on oocytes and embryos during cryopreservation with vitrification: a now widespread component of infertility treatment and fertility preservation (Lai et al., 2015).

2. Sperm biomechanic studies under microfluidic shear

The studying of sperm mechanical behavior is key to understanding underlying mechanisms of male-derived infertility as the inability to physically reach the egg is one key element of failure to conceive. The journey spermatozoa undergo between ejaculation and fertilization spans a distance on the order of 10 cm: a perilous journey through diverse microenvironments in the cervix, uterus and oviduct where the sperm must contend with high viscosity and shear flows.

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Such a long journey requires strong navigational mechanisms to direct the sperm to the oocyte. Such mechanisms for navigation include chemotaxis (Inamdar et al., 2007; Kaupp et al., 2008), thermotaxis (Bahat et al., 2003), and rheotaxis (Miki and Clapham, 2013). While chemotaxis is a strong navigational mechanism for the sperm to reach the oocyte, it is likely only for short-distances as long-distance convection within the female reproductive tract is disrupted by muscle contractions (Eisenbach, 1999). Thermotaxis is also thought to be based on ovulation-dependent temperature gradients between only the isthmus and ampulla (Bahat et al., 2003), leaving rheotaxis as the universal mechanism for sperm navigation that is effective throughout all parts of the female reproductive tract.

2.1. Sperm motion mechanics

Sperm motility is critical to successful fertilization in normal reproduction. The mechanism for male infertility can often be attributed to the inability for the sperm to reach the egg. Using resistive force theory (RFT) and modeling the sperm with a rigid spherical head attached to a thin elastic flagellum swimming in shear flow (Marcos et al., 2014) it was discovered that the sperm number (Sp; Eq. (1)) of the flagellum is key to influencing the swimming sperm's tolerance to fluid shear rate. It is worthy to note that Sp in this biomechanical study is not the number of sperm or sperm concentration as is often used but rather a physical dimensionless parameter characterizing the period of traveling wave of the sperm flagellum to its bending relaxation time (Lauga and Powers, 2009). Sperm flagellum with low Sp behaves like rigid rods which are almost completely free from the influence of shear flow regardless of shear direction (towards or against swimming direction) and shear rate. However, if the sperm has a higher Sp, its flagellum behaves more flexibly and the shear flow starts to affect the sperm's swimming velocity where the sperm swims faster in the forward direction at high shear conditions regardless of shear direction. At conditions with very high Sp, there is an even more favorable response to forward sperm progression when the shear flow is against that of the swimming direction due to the advantageous shape change of the beating flagellum against shear flow.

$$\mathrm{Sp} = L\left(\frac{\omega k_{\mathrm{N}}}{EI}\right)^{1/4} \tag{1}$$

where L is the tail length, ω is the beating frequency, k_{N} is the resistive coefficient in the perpendicular axis which positively correlates with viscosity, and EI is the bending stiffness where E is the elastic modulus and I is the area moment of inertia. Based on the definition of Sp, it will increase as the beating frequency increases, rigidity decreases, or viscosity increases although it is noteworthy that the increased viscosity would also decrease beating frequency and thus by extension decrease Sp as well. The RFT model designed for enhancing motile sperm purification by microfluidics is a thorough and fascinating biomechanic basis for the sperm's ability and favoritism to swimming against fluid flow direction commonly known as rheotaxis.

2.2. Sperm rheotaxis

The biophysical microenvironment of the mammalian sperm dictates its movement inside the female reproductive system. A combination of cell secretions, ciliary beating, and muscle contractions within the female reproductive tract produce a fluid flowing opposite of the swimming direction of sperm. Microgrooves on the periphery walls of the female reproductive tract provide a safe-haven as the high surface boundary decreases fluid velocity. Sperm trajectory studies demonstrate that there is a clear directional bias towards the sidewalls

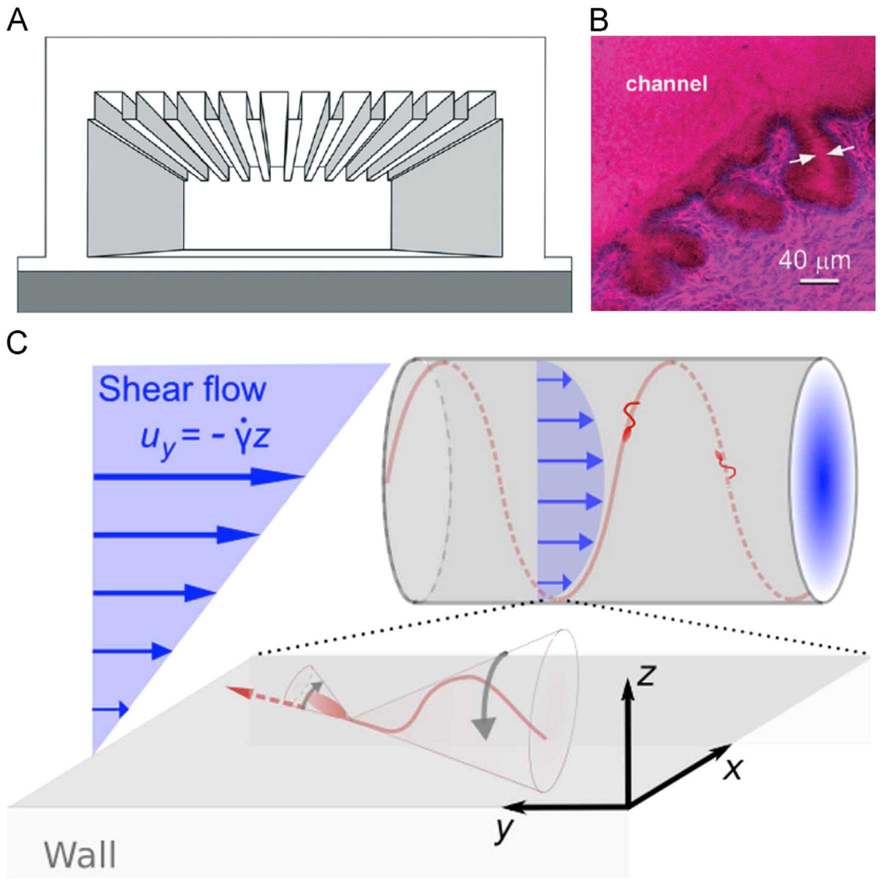

Fig. 1. (A) Microfluidic devices designed to mimic the microgrooves of (B) the female reproductive tract. Newly discovered spiral trajectory of sperm by microfluidic devices. Reproduced with permission from (A) (Tung et al., 2014) and (B) (Kantsler et al., 2014) respectively.

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