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Mathematical modelling of stretch-induced membrane traffic in bladder umbrella cells

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HIGHLIGHTS

- Multiscale model developed for vesicle traffic in response to mechanical stimuli.
- Explanation for counterintuitive non-monotonic behaviour observed in experiments.
- *In vivo* modelling uncovers potential root of bladder disorders in vesicle machinery.
- Clinical potential demonstrated with extensions to mechanical role in innervation.

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ABSTRACT

The bladder is a complex organ that is highly adaptive to its mechanical environment. The umbrella cells in the bladder uroepithelium are of particular interest: these cells actively change their surface area through exo- and endocytosis of cytoplasmic vesicles, and likely form a critical component in the mechanosensing process that communicates the sense of 'fullness' to the nervous system. In this paper we develop a first mechanical model for vesicle trafficking in umbrella cells in response to membrane tension during bladder filling. Recent experiments conducted on a disc of uroepithelial tissue motivate our model development. These experiments subject bladder tissue to fixed pressure differences and exhibit counterintuitive area changes. Through analysis of the mathematical model and comparison with experimental data in this setup, we gain an intuitive understanding of the biophysical processes involved and calibrate the vesicle trafficking rate parameters in our model. We then adapt the model to simulate *in vivo* bladder filling and investigate the potential effect of abnormalities in the vesicle trafficking machinery on bladder pathologies.

1. Introduction

Epithelial cells are continuously exposed to mechanical forces (e.g., stretch, compression, and shear stress), which affect all aspects of their biology. For example, inhaling air into the lungs stimulates surfactant release (Hildebran et al., 1981), shear stress and increased wall tension cause endothelial cells to release endothelin (Burnstock, 1999), and bladder filling stimulates the exocytosis of subapical Discoidal- and/or Fusiform-shaped Vesicles (DFVs) in umbrella cells, dramatically increasing their apical surface area (Apodaca, 2003; Truschel et al., 2002). Despite our understanding of the importance and physiological regulation of these events, we have limited insights into how mechanical forces affect these trafficking events. To gain insight into the complex interactions between epithelial cells and mechanical forces, in this paper we develop a mathematical model specifically aimed at understanding bladder epithelium.

The primary function of the mammalian bladder is the temporary storage of urine collected from the kidneys. The bladder must accommodate large changes in volume while maintaining strong impermeability. The bladder urothelium is comprised of three layers: basal cells (~10 μm in diameter) form a single layer, intermediate cells (10–25 μm in diameter) are from one to several cell layers thick, and the large (25–250 μm in diameter) polyhedral umbrella cells form a single layer on the lumen side of the bladder wall (see Fig. 1). While the basal and intermediate cells may slide past one another during bladder filling, the umbrella cells undergo key morphological changes (Lewis, 2000) and form the focus of this study.

The general understanding of the activities of the bladder urothelium during filling and voiding has changed significantly over recent decades. In early literature, the large changes in volume and

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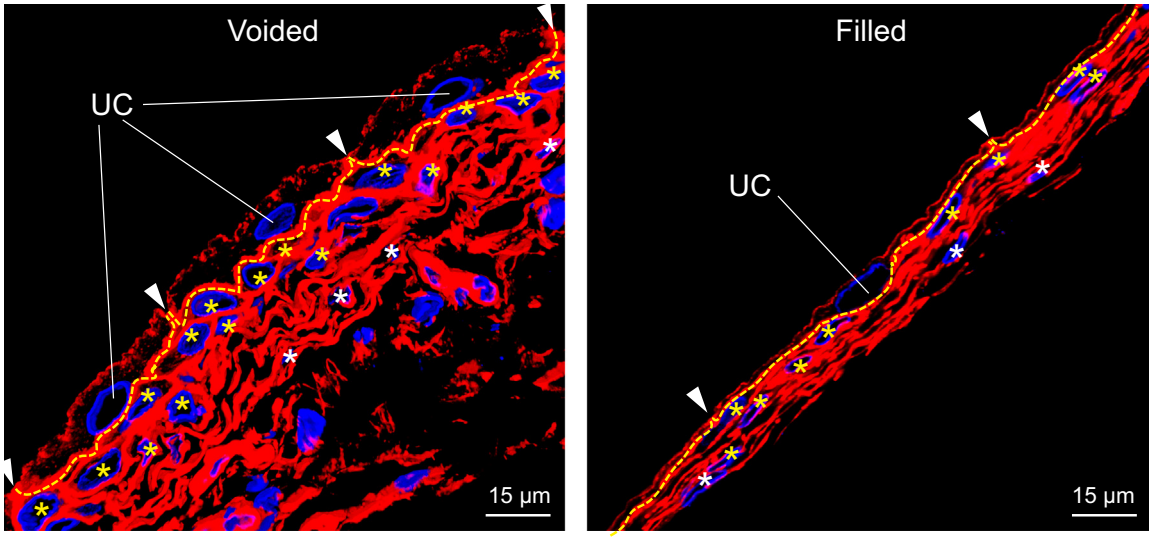

Fig. 1. Bladder urothelium in voided and filled bladder. The basolateral surface of the umbrella cells (UC) are marked by the yellow dashed line and the position of the tight junctions are indicated with arrowheads. Intermediate cells are marked with yellow asterisks, and basal cells with white asterisks. Reproduced with permission (Carattino et al., 2013). (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

pressure were thought to be accommodated solely by unfolding of the highly wrinkled apical membrane of umbrella cells (Lewis, 2000; Staehelin et al., 1972). There has since been mounting evidence that vesicle trafficking in the umbrella cells plays a key role as well. Several experimental studies found that exocytosis of cytoplasmic vesicles in the apical membrane occurs in response to mechanical stimuli (Lewis and de Moura, 1982; Wang et al., 2003). In exocytosis, vesicles fuse with the membrane wall, increasing the surface area and thus relieving mechanical stress and facilitating an increase in bladder volume. This understanding has since been revised, as it was found that both exocytosis and endocytosis in the apical membrane occur simultaneously (Truschel et al., 2002), with endocytosis[1] thought to be modulating the change in surface area.

Numerous in vitro experimental investigations have been performed to understand vesicle trafficking and mechanotransduction in umbrella cells (Wang et al., 2003; Truschel et al., 2002; Soldati and Schliwa, 2006; Lewis and de Moura, 1982; Lewis and De Moura, 1984; Apodaca, 2002). Of particular interest is the recent work of Yu et al. (2009), in which it was demonstrated that stretch, and not pressure, is the mechanical stimulus that induces exo- and endocytosis in umbrella cell tissues. Evidence was also found suggesting a feedback relationship in vesicle traffic between the basal and apical membranes of the umbrella cells and that tension in the basal membrane might trigger endocytosis in the apical side. This work also demonstrated an intriguing non-monotonic behaviour in the apical surface area during the so-called “early stage” of bladder filling: when subjected to a pressure difference across the epithelial tissue, the apical membrane showed a rapid increase in surface area on the time scale of the first minute, followed by a decrease in surface area over the next several minutes, and finally a slow increase in surface area over the course of an hour. While exo- and endocytosis are well confirmed on the apical membrane of umbrella cells and clearly triggered by mechanical events (Truschel et al., 2002), it is less clear whether similar vesicle traffic occurs on the basal membrane. Though mechanisms for vesicle insertion have been proposed for both membranes (Alroy and Weinstein, 1980), the basal membrane does not seem to undergo significant exo- and endocytosis, at least on long time-scale filling events (Truschel et al., 2002).

These experimental results highlight the importance of both mechanics and geometry in the urothelium. As the bladder fills, mechanical stimuli trigger unfolding and/or vesicle trafficking, each of which is effectively a change in geometry. This mechanically driven change can serve several important functions. An increase in apical surface area enables the bladder to accommodate an increasing volume; it also helps alleviate rising pressure, which may be needed for surface cells to maintain their barrier function. Moreover, the change in geometry feeds back to alter the stress levels in the bladder wall.

Along with volume accommodation and barrier function, of equal importance in a healthy bladder is communication with the brain. As with the morphological changes discussed above, the understanding of the urothelium's role in this process has changed over time. Initially thought of as a passive barrier, the urothelium is now seen as an active sensory organ (Birder et al., 2010). Urothelial cells sense and transduce information about physical stimuli (Korossis et al., 2006; Birder et al., 2009), make intimate connections with afferent nerves (Iggo, 1955; Birder et al., 2009), and can directly alter the activities of the underlying detrusor muscle (Birder et al., 2012). The bladder operates through a bi-directional signalling process, whereby the bladder wall must communicate the sense of “fullness” to the brain prior to the bladder reaching full volume, and the brain sends signals for contraction of the detrusor muscle during micturition. Malfunction in these signalling events may underlie various bladder disorders such as Detrusor Overactivity and Overactive Bladder (OAB) (Birder et al., 2012). The mechanisms through which the urothelium senses and transduces information about physical stimuli are not well understood. However, it is clear that mechanical stress in urothelial cells plays a vital role; for instance, urothelial cells contain various receptors that respond to mechanical changes by the release of transmitters (such as ATP) that influence afferent nerve activity (Birder et al., 2009, 2012).

It is evident that the mechanical environment within the urothelium is critical to the proper functioning of the bladder, and that a balance must exist between vesicle trafficking, geometry, stress levels, and signalling. There is a delicate nature to this balance: exocytosis increases the surface area of the apical membrane, thus decreasing the tension, while at the same time, the appropriate amount of tension at the right bladder volume is

[1] NB in this article endocytosis refers specifically to pinocytosis.