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Biological sensing of fluid flow - lessons from PIEZO1

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Abstract

The flow sensing endothelial cell lining of blood and lymphatic vessels is essential in vertebrates. While the mechanisms are still mysterious in many regards, several critical components became apparent through molecular biology studies. In this article, we focus on PIEZO1, which forms unusual force-sensing ion channels capable of rapid transduction of force into biological effect. We describe current knowledge and emerging challenges. We suggest the idea of using computation to construct the flow sensing mechanism of endothelium to advance understanding, develop testable hypotheses and potentially design novel therapeutic strategies and synthetic flow sensing devices.

Article

Vascular systems evolved for survival advantages such as gas and nutrient exchange across large anatomical structures [1]. They are diverse but in vertebrates they have in common an inner blood or lymph-facing endothelial cell monolayer that responds to fluid flow with profound implications for vascular development, size, structure, calibre, permeability, adaptability and response to injury [1-3]. PIEZO1 protein emerged as pivotal in this endothelial capability [4-8]. Three PIEZO1s assemble as a triplet (trimer) to form an unusual basket-like (dome) structure that embeds in and indents the outer cell membrane [9]. There are long, also unusual, tentacles (blades) that span out from the central core, sitting over which is a cap. Lateral tension in the membrane causes the basket to flatten and the tentacles to spread out [10-12]. The cap moves and there is opening of the core to allow ions from the extracellular and intracellular salt solutions to flood across the otherwise ion-impermeable barrier [10,13]. These special ion channels confer signalling on a rapid – electrical – timescale, triggering specific downstream events in proportion to tension [5,9]. Thus, in PIEZO1, the cells have an all-in-one force sensor and transducer at the nanometre scale [9]. The response time is milliseconds [14,15] yet there are implications over minutes, hours and years [5,7,15]. Through its identification, we have a window into a flow sensing mechanism that originated over 500 million years ago.

The mechanism as a whole comprises many components [3] but PIEZO1 stands out amongst them with its exquisite and robust sensing of force, apparent dedication to force sensing, very fast on-off response and ability to singularly reconstitute force sensing, at least when supported by a lipid bilayer [4,9,12,14]. With this advance, there have come challenging questions. How does a tension sensor enable the sensing of flow? Flow generates the frictional force of fluid shear stress [2] and activates PIEZO1 [4,6,8,15-19]. PIEZO1 is required for endothelial responses to fluid flow [4,20-22]. Does PIEZO1 sense shear stress as well as tension or is shear stress transduced into tension? Shear stress alters membrane lipid order and composition [23,24], so the lipid bilayer is a potential intermediate between flow and tension – but if so, how does it sense flow?

To understand such complexity, we may need to do more than identify the components. Understanding may come only once we can construct the components into a mechanism. After all, understanding of complex devices such as timepieces comes from building them, not

seeing them disassembled or watching them tick. Importantly, construction may be possible through computer algorithms. In biological sciences, computation is coming to the fore [25]. Already, molecular dynamics simulations of the PIEZO1 channel in an endothelial cell membrane have been computed with and without membrane tension [11,26]. It is then within our reach to increase the complexity, for example by incorporating fluid flow and additional molecular components such as proteins and glycans of the extracellular matrix, cytoskeleton of the intracellular matrix and downstream signalling pathways (Figure 1). Substantial computer power will be needed. There are many components, and endothelial cells contain hundreds if not thousands of copies of each one. There is the endothelial cell monolayer to consider along with its integration into blood vessels and the organism. We need to test the veracity of the simulations in laboratory experiments. The investment of effort and resources to achieve meaningful simulations will be big, but they could bring big rewards. We may come to understand this remarkable mechanism. We may learn how to engineer new flow sensing mechanisms. We may be able to use the information to design new medicines to reduce the disruptions of the mechanism that occur due to lifestyles and ageing, blighting the lives of millions of people worldwide through heart attacks, strokes and other vascular accidents.

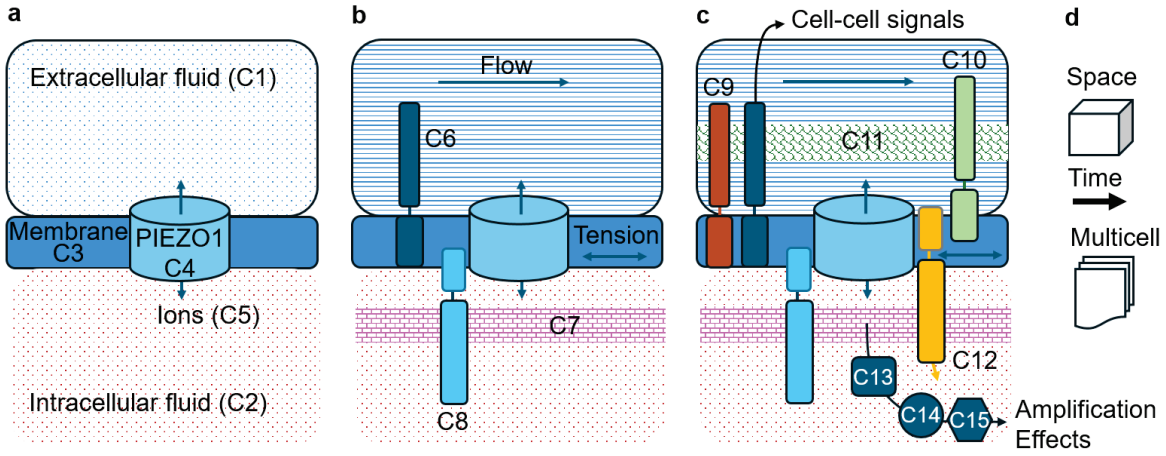

Figure 1 Illustration of 15 components (C1-C15) in the anticipated computer construction of the endothelial flow sensing mechanism. The selection of 15 is arbitrary but there are at least this many. PIEZO1 is the only named molecular component because it is the topic of this article. (**a**-**c**) Stepwise increases in the complexity of the flow sensing mechanism from **a** to **b** to **c**. Only parts of the cell membrane and extracellular (e.g., blood) and intracellular (e.g., cytoplasm) media are depicted. (**d**) Dimensions of the complexity in a living multicellular tissue.

Data Availability Statement

No novel data are included.

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