Article:
Beech, DJ and Xiao, B (2018) Piezo channel mechanisms in health and disease. The Journal of Physiology, 596 (6). pp. 965-967. ISSN 0022-3751

https://doi.org/10.1113/jp274395

Piezo channel mechanisms in health and disease

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Introduction

Piezo proteins are large membrane proteins which assemble to form mechanically-activated Ca^{2+} permeable non-selective cationic channels (Coste et al., 2010; Coste et al., 2012; Murthy et al., 2017; Wu et al., 2017). They serve to regulate membrane potential and Ca^{2+} signalling coupled to downstream effectors such as calpain in cells of mammals and other classes (Coste et al., 2010; Coste et al., 2012; Li et al., 2014; Murthy et al., 2017; Rode et al., 2017; Wu et al., 2017). They are a distinct type of ion channel subunit which assembles as trimers with a central ion-conducting pore covered by a single cap and three complex arms reaching out into and curving the membrane (Ge et al., 2015; Guo & MacKinnon, 2017; Saotome et al., 2017; Zhao et al., 2018) (Figure 1). The last two C-terminal transmembrane segments (TMs) form the functional pore module (Zhao et al., 2016) while the rest of the protein comprises 9 repetitive units of 4 TMs assembled into a highly curved peripheral blade-like structure which is critical for mechano-sensing and transduction (Zhao et al., 2018) (Figure 1). The channels are inherent sensors of membrane tension and increases in this tension seem to be the primary physiological activator (Lewis & Grandl, 2015; Cox et al., 2016; Syeda et al., 2016). Activation or sensitisation to membrane tension occurs in response to a synthetic small molecule called Yoda1, which is a useful pharmacological tool (Syeda et al., 2015).

The Piezo proteins are widely expressed and a range of functions is emerging. Piezo1, for example, regulates epithelial cell crowding and division (Gudipaty et al., 2017), is critical for endothelial shear stress-sensing and vascular development (Li et al., 2014), regulates blood pressure and exercise performance (Rode et al., 2017) and determines neural stem cell lineage (Pathak et al., 2014). Mutations in the human PIEZO1 gene cause anaemia (dehydrated stomatocytosis) consistent with importance of Piezo1 channels in erythrocyte function

(Zarychanski et al., 2012) and generalised lymphatic dysplasia consistent with functional importance in lymphatic endothelial cells (Fotiou et al., 2015). Piezo2 is important in touch sensation (Woo et al., 2014; Chesler et al., 2016) and airway stretch sensation mediated by sensory neurones (Nonomura et al., 2017). Mutations in PIEZO2 gene cause distal arthrogryposis and other diseases (Coste et al., 2013; Alper, 2017).

Focus of the review series

Here we present a review series associated with our "Piezo channel mechanisms and disease" symposium at the International Union of Physiological Sciences (IUPS) congress in Rio de Janeiro on 3rd August 2017. The series focusses on three key topics from the symposium: Piezo1 channel structure (Wang & Xiao, 2017), Piezo1 in vascular physiology (Beech, 2017) and Piezo1 in genetic disease (Martin-Almedina et al., 2018). The structure article reviews the breakthrough in determining the tri-blade propeller-like arrangement of Piezo1 channels and discusses the hypothesis that the channels comprise discrete mechano-transduction and ion-conducting modules which coordinate to fulfil the overall purpose of the channels (Wang & Xiao, 2017). The physiology article reviews current knowledge of the role of Piezo1 channels in the endothelium, discussing the hypothesis that the channels are key sensors of the frictional force of blood flow, leading them to be essential in vascular development and necessary for redistribution of blood flow in exercise and optimal physical performance (Beech, 2017). The disease article reviews PIEZO1 mutations which cause disease in patients, discussing the relationship between stomatocytosis and lymphatic dysplasia and the challenges of understanding the disease consequences of loss-of-function and gain-of-function mutations (Martin-Almedina et al., 2018).

Conclusion and perspective

Piezo channels are relatively newly discovered – perhaps one of the last major ion channel families which had to be identified. What has been particularly striking has been the unanimous agreement from independent investigators across the world that these channels are indeed bona fide sensors of membrane tension in mammalian and other cell types and that their primary biological purpose is likely to be as sensors of mechanical force and transducers of this force into biological effect. Because of the importance of mechanical

force sensation in biology, the implications are substantial. The symposium reviews provide important insight into this new field but should naturally been seen alongside the wider field and literature. As we are at the beginning of the Piezo era of biological discovery we can expect and hope for many more original research articles on this topic as well as more symposia – small and large – and review articles as this field achieves its true potential and perhaps position alongside other great fields such as those focussed on other membrane proteins such as the ionotropic glutamate receptors and tyrosine kinase receptors. We encourage you to read and enjoy the review articles and join the Piezo field.

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Acknowledgements

We thank the Physiological Society and IUPS for the opportunity and conference framework and the Journal of Physiology for sponsoring the symposium. Our research is supported by research grants from the Wellcome Trust (110044/Z/15/Z), British Heart Foundation (RG/17/11/33042) and Medical Research Council (MR/L019051/1) (DJB) and the National Key R&D Program of China (2016YFA0500402, 2015CB910102) and the National Natural Science Foundation of China (31630090) (BX).

Competing interests

None of the authors has any conflicts of interests.

Figure Legend

Figure 1. Structure and topology of the mechanosensitive Piezo1 channel

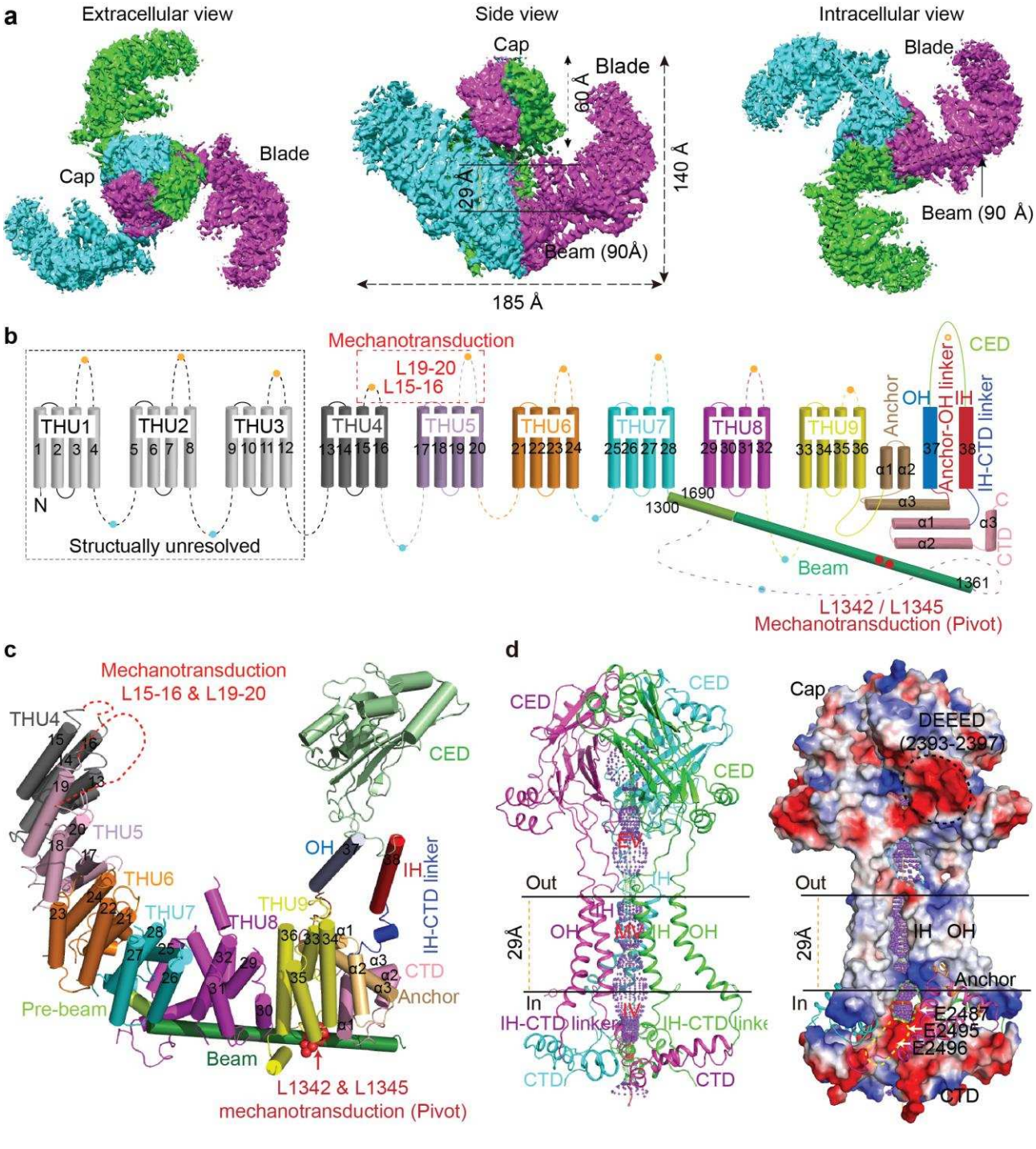
a. The three-bladed, propeller-like cryo-EM structure of the Piezo1 ion channel.

b. 9 Repetitive transmembrane helical units (THUs) and the 38-TM topology model.

c. A cartoon model showing one subunit with featured structural domains labelled.

d. The ion-conducting pore module shown in ribbon diagram (left) and surface electrostatic potential (right). The functionally identified regions and residues critical for mechanical activation of Piezo1 are indicated in **b** and **c**.

From (Zhao et al., 2018)


a
Extracellular view
Cap
Blade
Side view
Cap
Blade
60 Å
140 Å
29 Å
Beam (90Å)
185 Å
Intracellular view
Blade
Beam (90 Å)
b
Mechanotransduction
L19-20
L15-16
THU1
THU2
THU3
THU4
THU5
THU6
THU7
THU8
THU9
Anchor
OH
IH
CED
Anchor-OH linker
IH-CTD linker
N
Structually unresolved
1690
1300
Beam
1361
CTD
C
L1342 / L1345
Mechanotransduction (Pivot)
c
Mechanotransduction
L15-16 & L19-20
THU4
CED
THU5
OH
IH
IH-CTD linker
THU6
THU7
THU8
THU9
CTD
Anchor
Pre-beam
Beam
L1342 & L1345
mechanotransduction (Pivot)
d
CED
CED
CED
Out
IH
OH
29Å
In
IH-CTD linker
CTD
Cap
DEEED
(2393-2397)
Out
29Å
IH
OH
Anchor
In
E2487
E2495
E2496
CTD