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EDITORIAL

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, 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, 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.* 2018; Zhao *et al.* 2018) (Fig. 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 nine repetitive units of four TMs assembled into a highly curved peripheral blade-like structure which is critical for mechano-sensing and transduction (Zhao *et al.* 2018; Fig. 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 the 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 the *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 3 August 2017. The series focuses on three key topics from the symposium: Piezo1 channel structure (Wang & Xiao, 2018), Piezo1 in vascular physiology (Beech, 2018) 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, 2018). 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, 2018). The disease article reviews *PIEZO1* mutations which cause disease, 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 be 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 focused 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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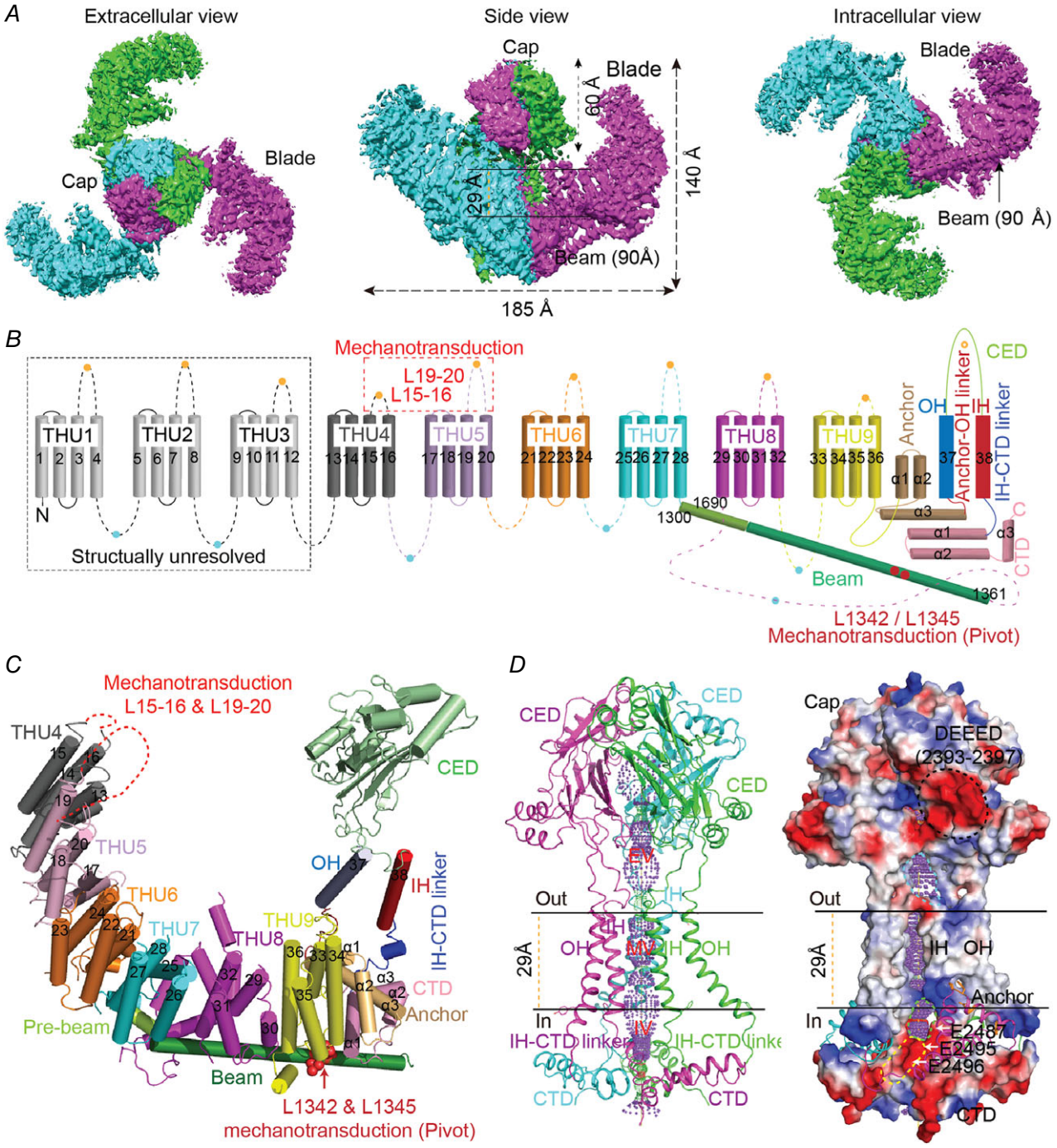

Figure 1. Structure and topology of the mechanosensitive Piezo1 channel
A, the three-bladed, propeller-like cryo-EM structure of the Piezo1 ion channel. *B*, nine repetitive transmembrane helical units (THUs) and the 38-TM topology model. *C*, a cartoon model showing one subunit with featured structural domains labelled. *D*, the ion-conducting pore module shown as a 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*. Figure reproduced with permission from Zhao *et al.* (2018).

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Additional information

Competing interests

None of the authors has any conflicts of interests.

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