# Drosophila senses

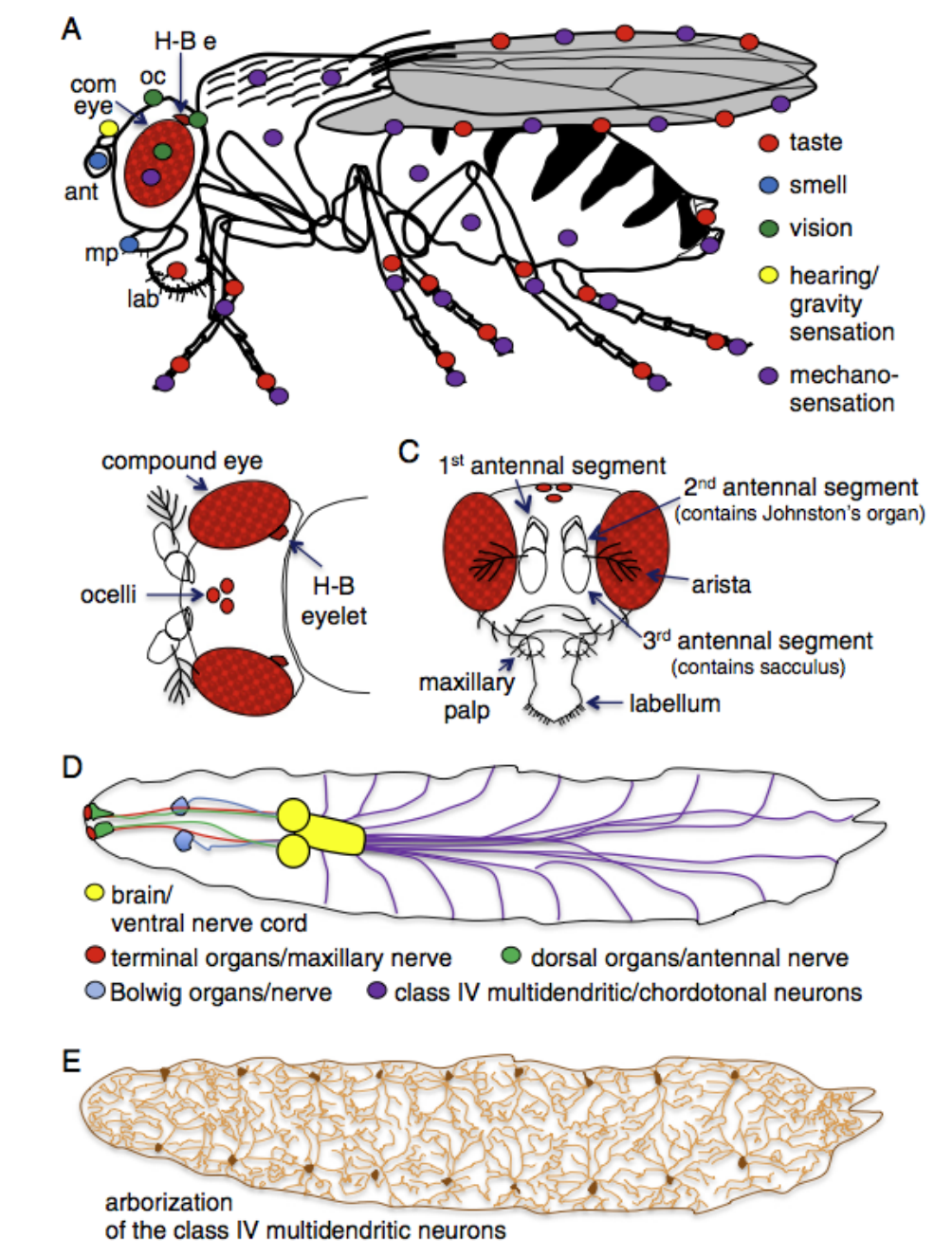


**Table 1**
Properties of *Drosophila* Transient Receptor Potential (TRP) channels.

TRP channels with known sensory roles

| Sub family | Channel | Abbrev. | Selectivity $P_{Ca}/P_{Na}$ | Physiological modes of activation | Sensory functions |
|---|---|---|---|---|---|
| TRPC | Transient Receptor Potential | TRP | 25–40 | $G_q$/PLC signaling, PUFA, $H^+$, $PIP_2$ depletion | • Phototransduction |
| | TRP-Like | TRPL | Nonselec. cation | $G_q$/PLC signaling, PUFA, H+, $PIP_2$ depletion | • Phototransduction<br>• Cold sensation |
| | TRPγ | TRPγ | Nonselec. cation | $G_q$/PLC signaling, PUFA | – |
| TRPA | TRPA1 | TRPA1 | – | Heat (>26 °C) reactive electrophiles (AITC, NMM, CA)<br>Temp (18-24 °C, Rh1/PLC signaling)<br>arist. acid ($G_q$/PLC sig.),<br>citronellal ($G_q$/PLC sig.),<br>light | • Warm temperature sensation<br>• Avoidance of noxious heat<br>• Comfortable temperature sensation<br>• Avoidance of aversive non-volatile irritants<br>• Avoidance of aversive tastants<br>• Avoidance of aversive odorants<br>• Avoidance of bright light<br>• Avoidance of mechanical stimulation |
| | Painless | Pain | 40 | Heat (~39–42 °C) | • Avoidance of noxious heat<br>• Avoidance of mechanical stimulation<br>Avoidance of dry environments<br>• Gravity sensation |
| | Pyrexia | Pyx | 0.7 | Heat (~40 °C) | • Noxious heat resistance<br>• Gravity sensation |
| | Waterwitch | Wtrw | - | - | • Humid air detection |
| TRPN | No Mechano-receptor Potential C | NOMPC | – | Mechanical stimulation | • Light touch<br>• Locomotion<br>• Hearing |
| TRPV | Inactive | Iav | 2.8 | Hypo-osmotic solution | • Locomotion<br>• Hearing<br>• Gravity sensation<br>• Cold sensation |
| | Nanchung | Nan | – | Hypo-osmotic solution | • Locomotion<br>• Hearing<br>• Gravity sensation<br>• Dry air detection |

TRP channels without known sensory roles

| Sub family | Channel | Abbrev. | Selectivity $P_{Ca}/P_{Na}$ | Physiological modes of activation | Functions |
|---|---|---|---|---|---|
| TRPM | TRPM | TRPM | – | – | • $Mg^{2+}$ and $Zn^{2+}$ homeostasis |
| TRPP | Almost there | Amo | – | – | • Sperm storage |
| TRPML | TRP Mucolipin | TRPML | – | – | • Locomotion<br>• Autophagy<br>• Clearance of apoptotic cells |

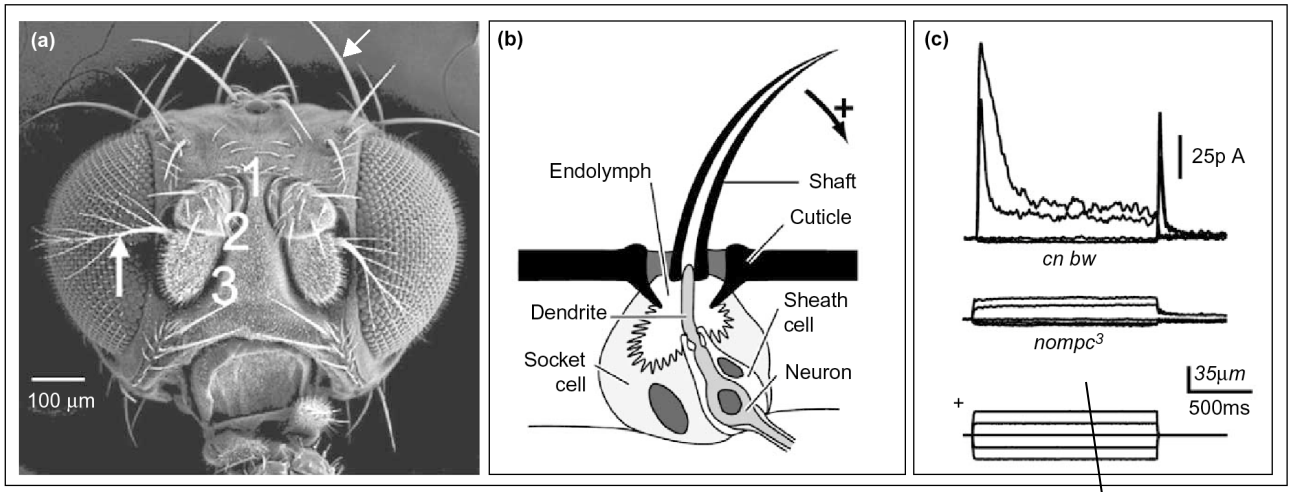
Abbreviations: AITC, allyl isothiocyanate; arist. acid, aristolochic acid; NMM, *N*-methyl maleimide; CA, cinnamaldehyde; PLC, phospholipase C; PUFA, polyunsaturated fatty acid; Rh1, Rhodopsin 1.

**TRP channels in mechanosensation**
Shuh-Yow Lin and David P Corey

# Mechanosensors

TRPN (Nompc), TRPA (painless) and TRPV (Nan/Iav)

Antennae (Johnston organ) & sensory bristles




Structure of the hearing and touch organs of *Drosophila*. **(a)** Antennae and sensory bristles on the head. The antenna comprises three segments (numbered) and the arista (arrow). Sound moving the arista causes flexion at the 2–3 joint. Mechanosensitive bristles (arrowhead) occur all over the body surface. (Reproduced with permission from Nature Publishing Group (http://www.nature.com/) and Kim *et al*. 2003 [17].) **(b)** Schematic of a sensory bristle. Receptor current can be recorded through the endolymph in a cut bristle shaft. **(c)** Receptor current evoked by mechanical deflection (bottom) of a bristle in a wild type (top) or nompC mutant (middle) fly. (Parts b and c reproduced with permission from Walker *et al*. [19] copyright 2000 AAAS.)

TRPV (Nan/Iav): hearing
Mutations lead to mating deficiency
(activated by hyposmolarity in vitro )

TRPN
(worms, fish, no mammals)

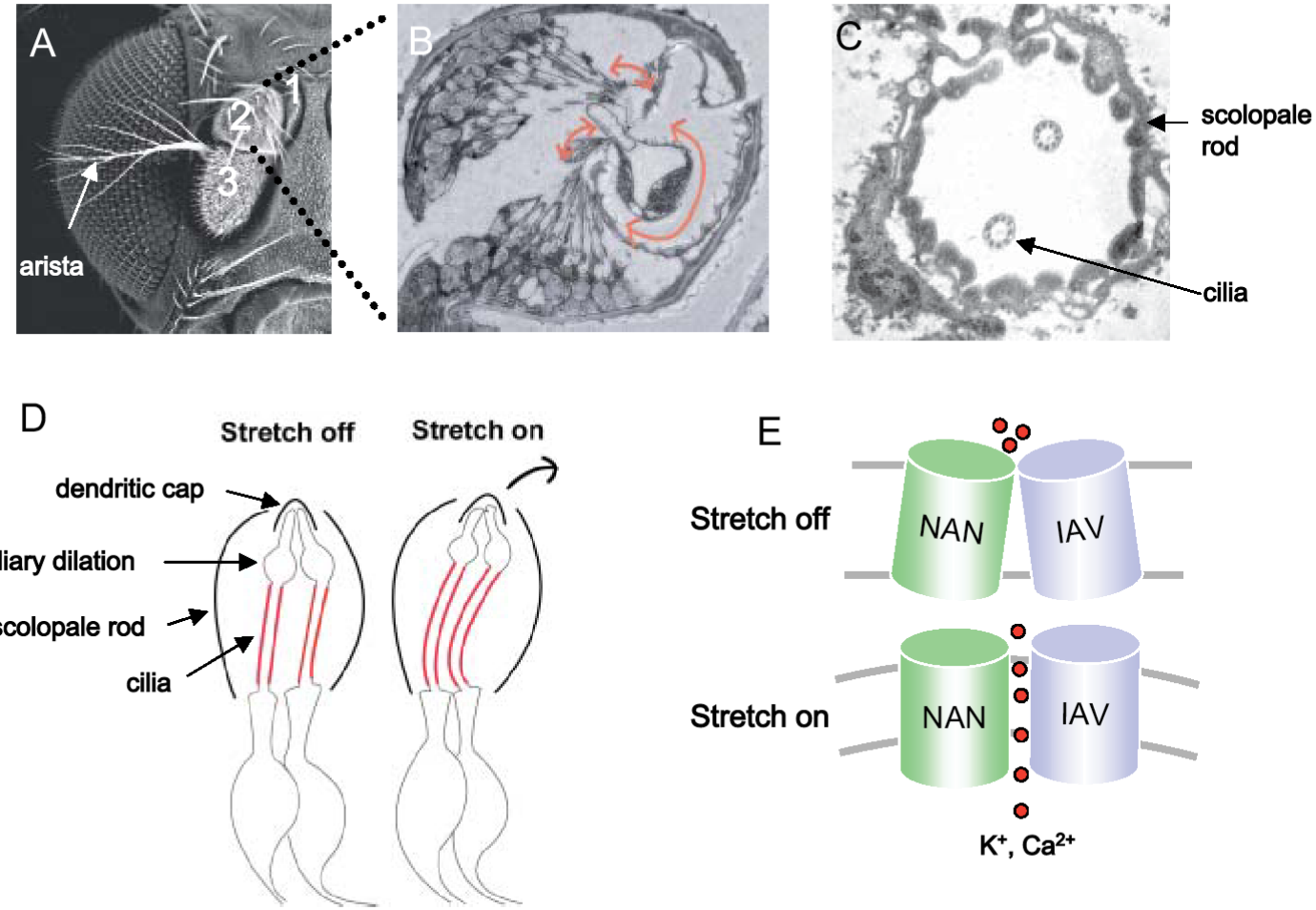



Figure 3. A hypothetical model of the NAN-IAV channel gating. (A) Scanning electron microscopy of a *Drosophila* eye, next to it the *Drosophila* antenna. (B) Higher magnification transmission electron microscopy of ultra-thin sections of antenna; depicted is the Johnston's organ. Arrows indicate the vibration of cuticles caused by sound. (C) Higher magnification transmission electron microscopy shows a transverse section of scolopidia. (D) Schematic drawing of scolopidia. NAN-IAV heteromeric channels are located in the proximal region of the cilia (depicted In red) [62]. Stretch causes bending of cilia at the proximal region [156]. (E) Stretch opens the NAN-IAV heteromeric channel.

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DOI 10.1007/s00018-005-5181-5

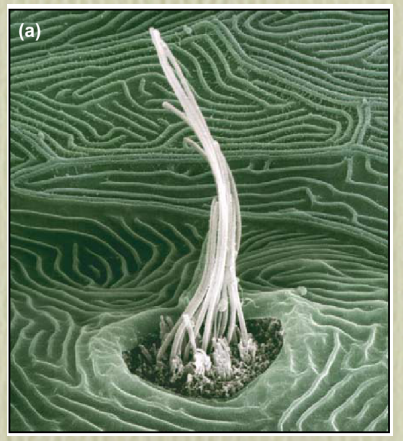

Cellular and Molecular Life Sciences

Review

**Functionality of the TRPV subfamily of TRP ion channels: add mechano-TRP and osmo-TRP to the lexicon!**

W. Liedtke[a] and C. Kim[b,*]

# Lateral line hair cells




neuromast

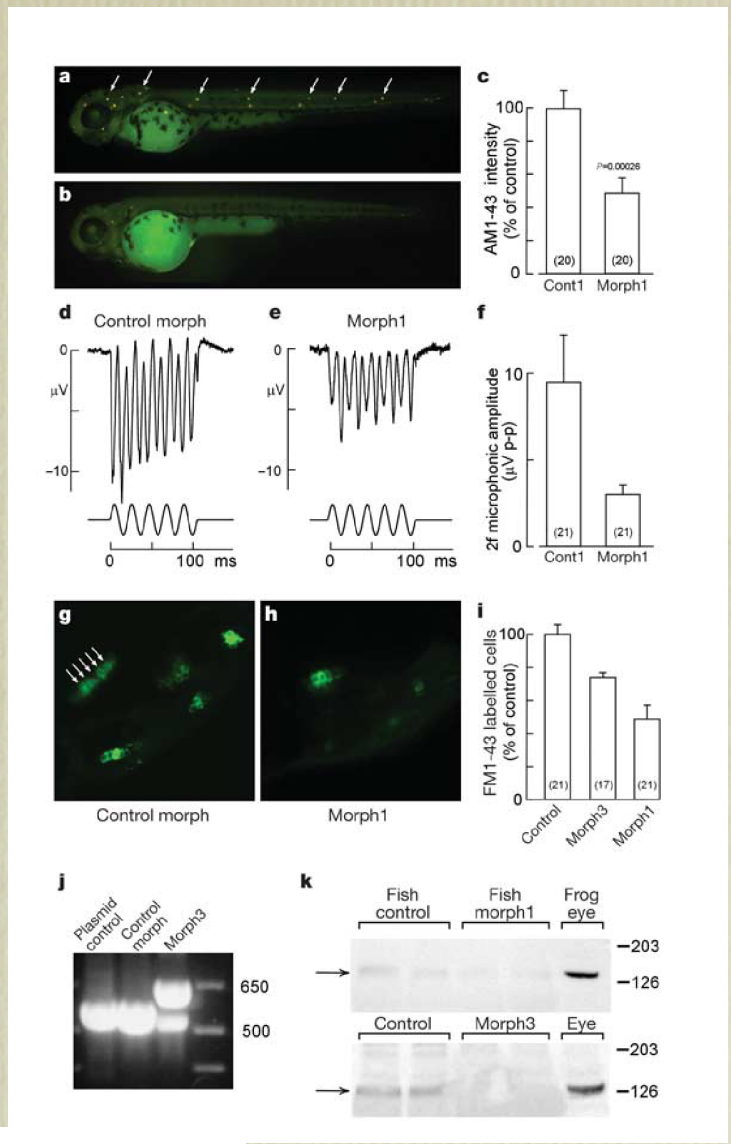



**Figure 4** Inhibition of transduction in zebrafish by morpholinos. **a**, AM1-43 in lateral line hair cells (arrows); 60 h.p.f. embryo injected with control morpholino. **b**, Labelling of a 60 h.p.f. embryo injected with morph1. **c**, Total AM1-43 intensity in fish neuromasts. Data are mean ± s.e.m., $N = 20$, $P < 0.0003$. **d**, Microphonic potential in the otocyst of a control-injected fish. **e**, Fish injected with morph1. **f**, Summary of microphonic potentials; peak-to-peak (p-p) amplitude at twice the stimulus frequency (2f). Data are mean ± s.e.m., $N = 21$, $P < 0.03$. **g**, FM1-43 in zebrafish inner ear hair cells (arrows) after dye injection into the otocyst. Projection of ~40 optical sections through a control-morpholino-injected zebrafish at 55 h.p.f. **h**, Otocyst of a morph1-injected zebrafish. **i**, Summary of FM1-43-labelled hair cells. Data are mean ± s.e.m. **j**, RT–PCR of control plasmid and morpholino-injected embryos (60 h.p.f.). **k**, Immunoblot of whole 60 h.p.f. embryos injected with control morpholino, morph1 or morph3; bullfrog eye is positive control. Numbers along the right are bases in **j** and kDa in **k**.

# Sensing sound: molecules that orchestrate mechanotransduction by hair cells

Piotr Kazmierczak and Ulrich Müller

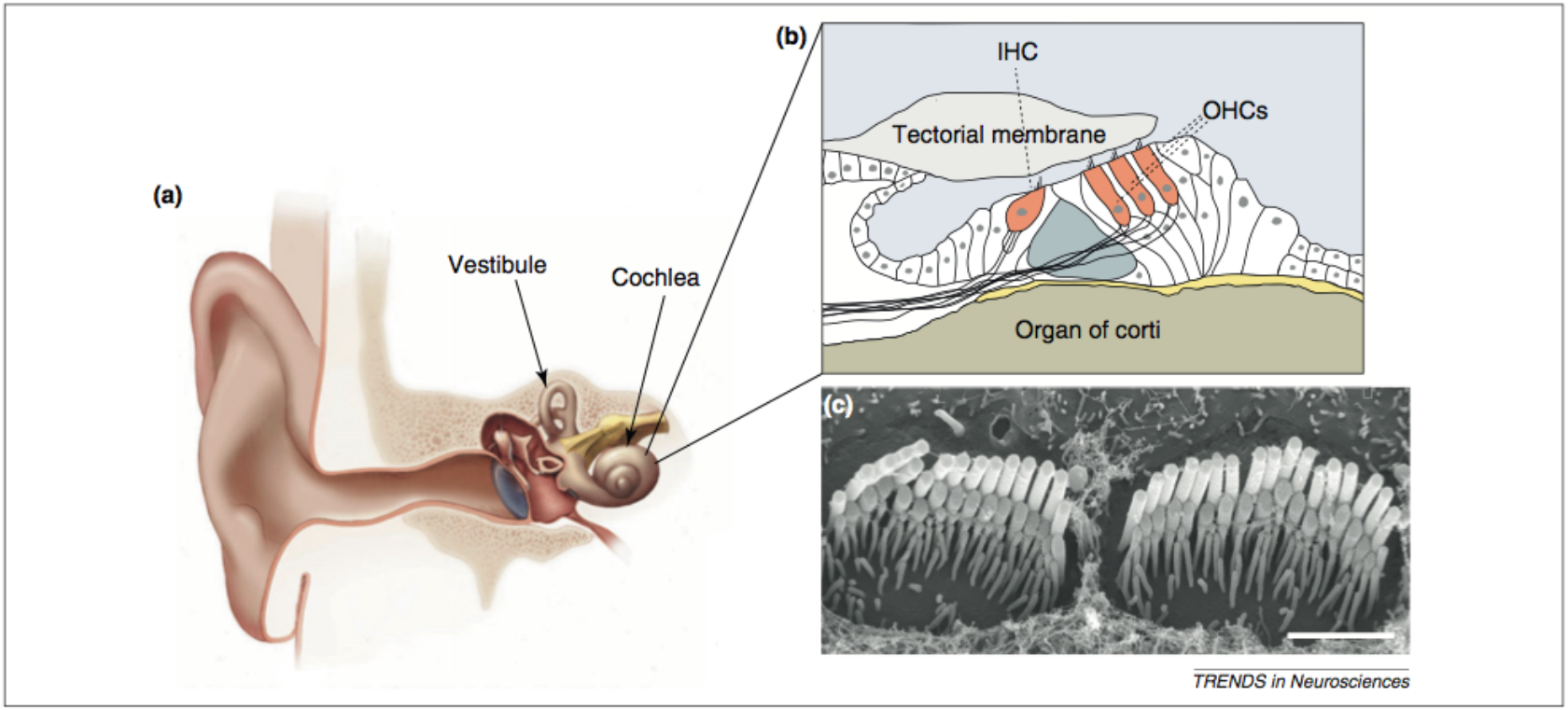
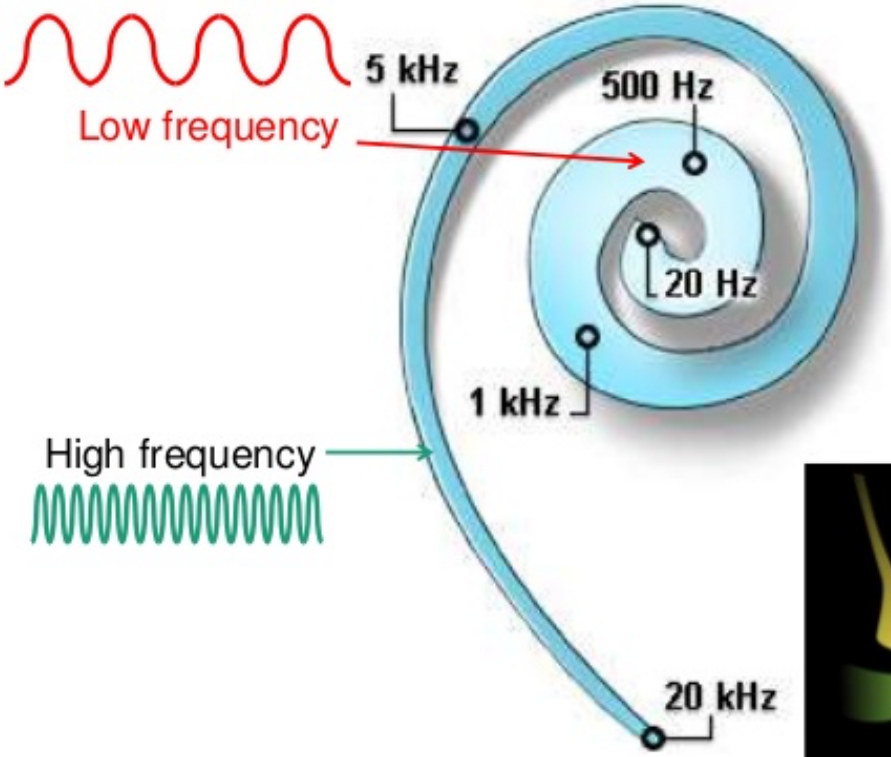
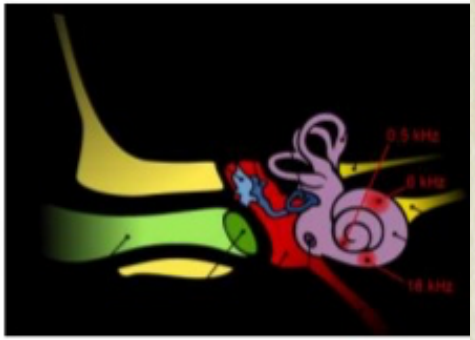



**Figure 1.** The mammalian auditory sense organ and its hair cells. **(a)** Diagram of the inner ear. The snail-shaped cochlea (end-organ for the perception of sound) and parts of the vestibule (end-organ for the perception of head movement) are indicated (panel modified from [4]). **(b)** Diagram of the organ of Corti. One inner hair cell (IHC) and three outer hair cells (OHCs) are indicated. **(c)** Scanning electron micrograph of the cochlear sensory epithelium of the mouse after removal of the tectorial membrane (kindly provided by Dr Nicolas Grillet, The Scripps Research Institute). The image shows the stereociliary bundles of two IHCs. Note the staircase arrangement of the rows of stereocilia. Scale bar, 2 μm.

# Tones and the Cochlea: Tonotopic!



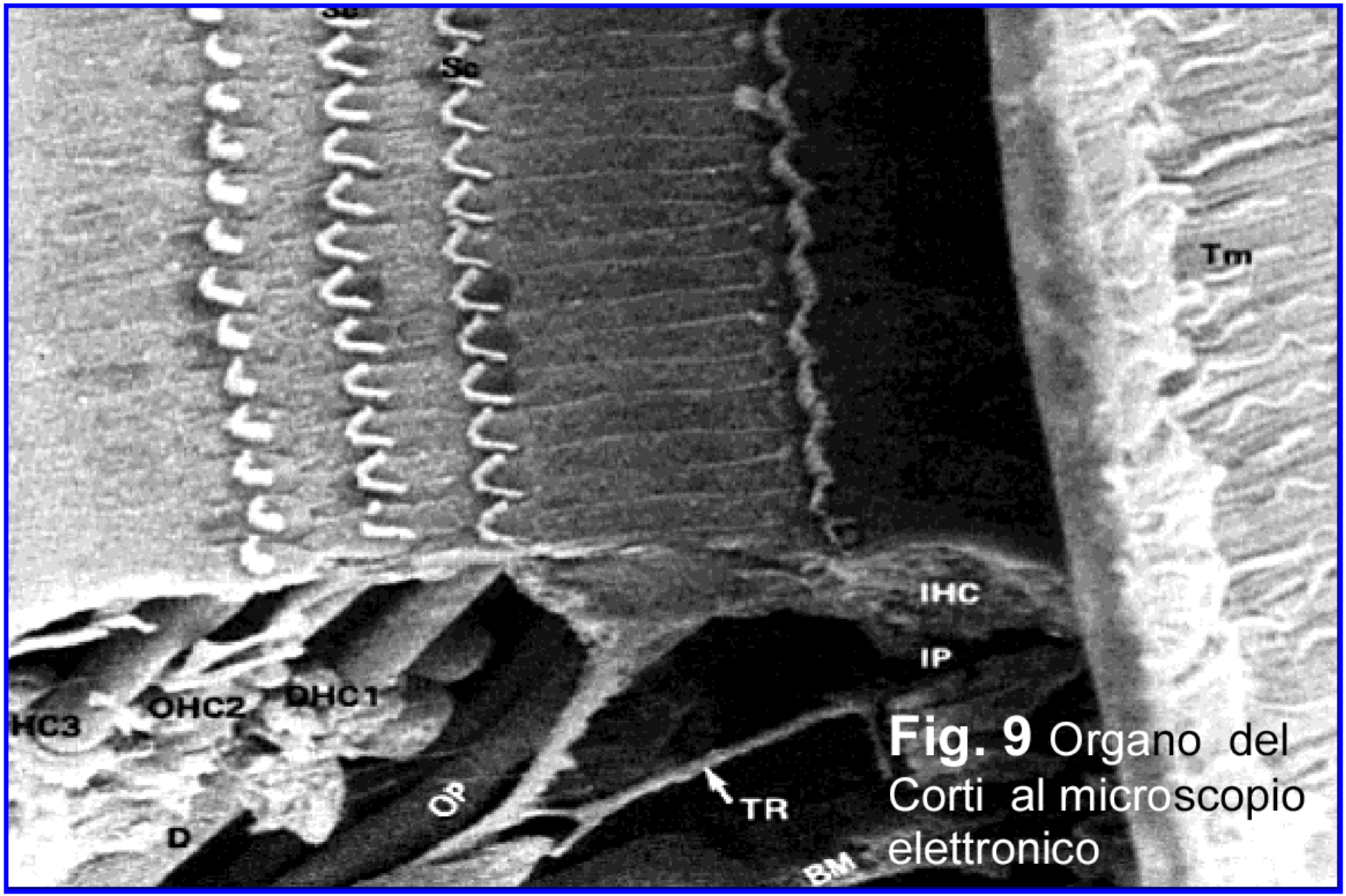
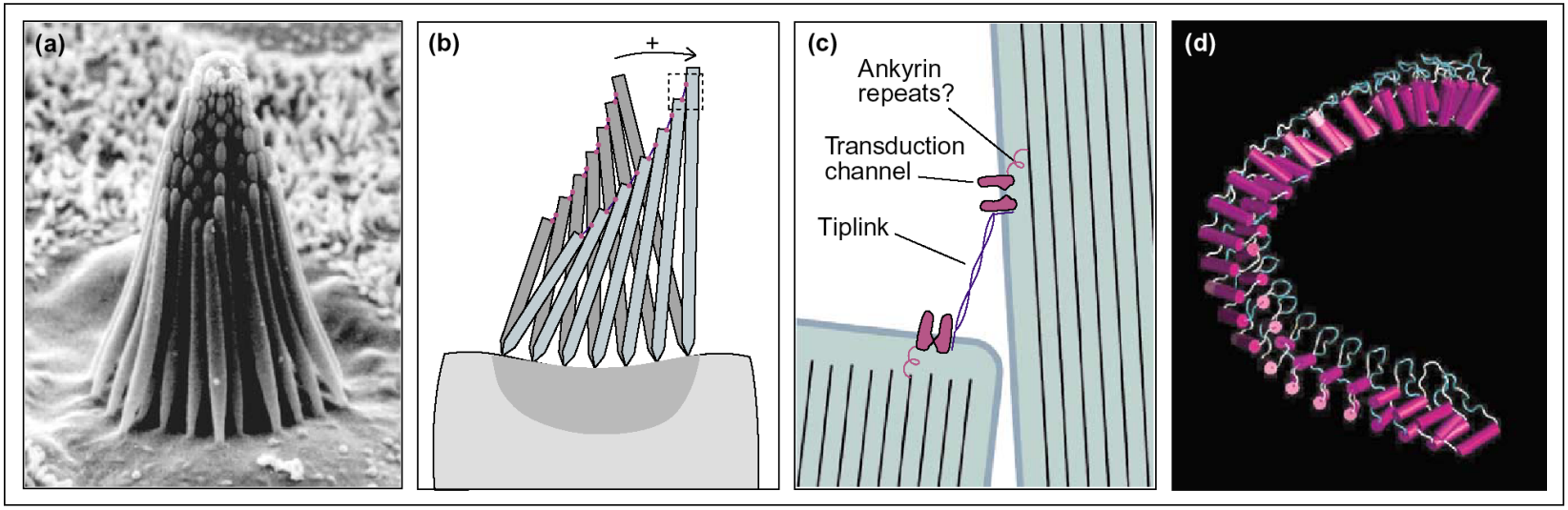
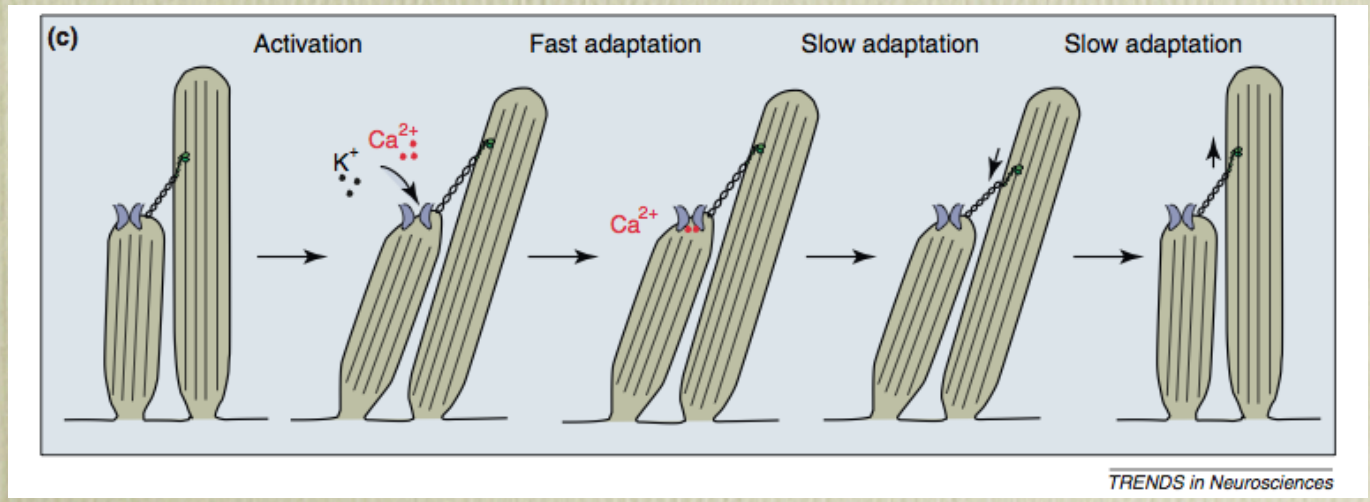


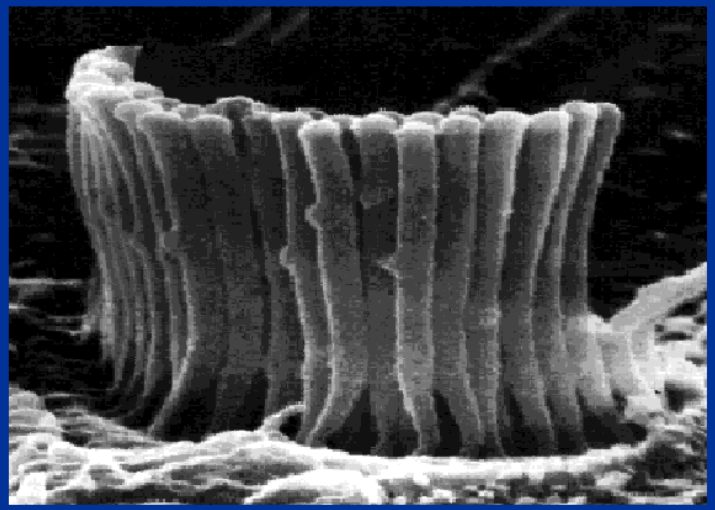

**Fig. 9** Organo del Corti al microscopio elettronico



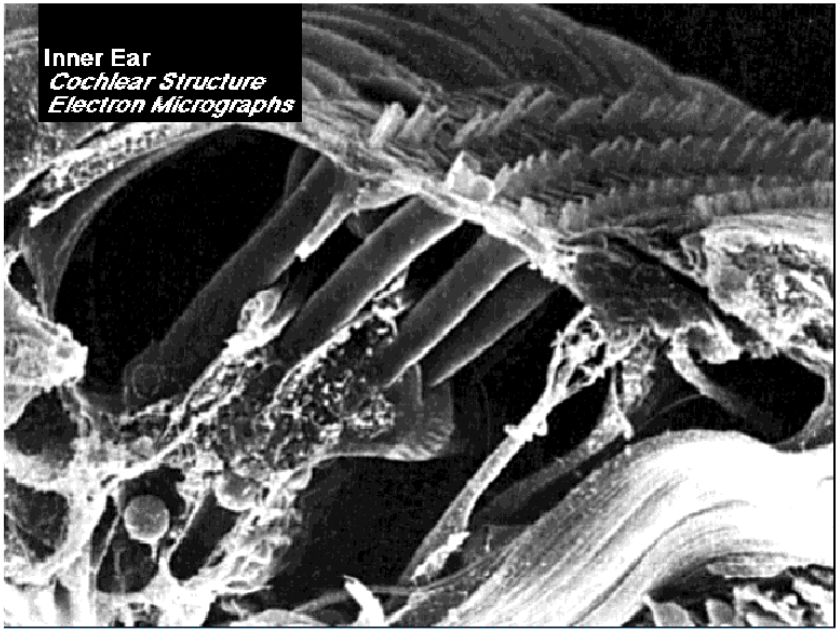

Mechanotransduction by vertebrate hair cells. **(a)** A single hair bundle from a frog vestibular hair cell. Stereocilia heights increase uniformly towards the kinocilium. **(b)** Positive deflection of the hair bundle increases the distance between adjacent stereocilia tips. **(c)** Transduction apparatus in the stereocilia tips. The tip link, probably composed of cadherin 23, extends between adjacent membranes and is associated with one or two transduction channels at each end. The transduction channel, probably incorporating TRPA1, is elastically linked to the actin cytoskeleton. (Reproduced with permission from Sotomayor *et al*. 2005 [27].) **(d)** The crystal structure of a polyankyrin domain similar to that in TRPA1, in this case with 24 ankyrin repeats. Molecular dynamics modeling suggests that it is an elastic element.



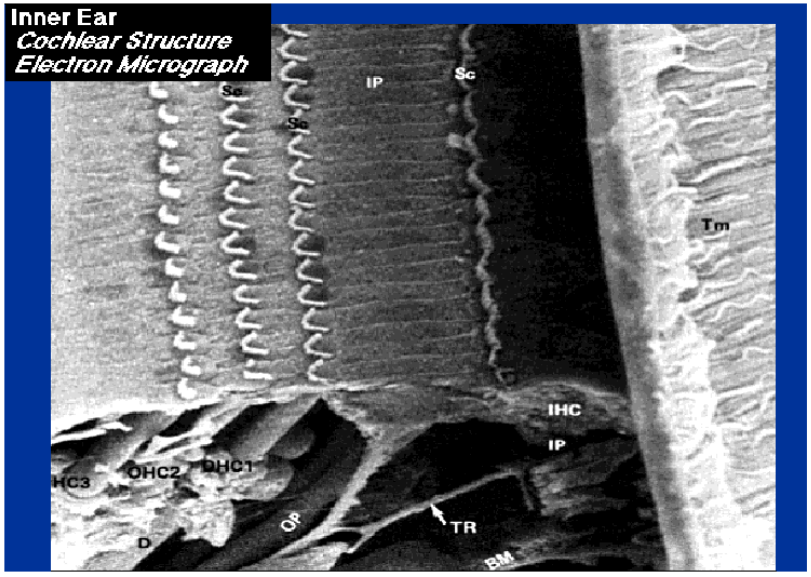
**Inner Ear**
*Inner Hair Cell Stereocilia*



**Inner Ear**
*Cochlear Structure*
*Electron Micrographs*



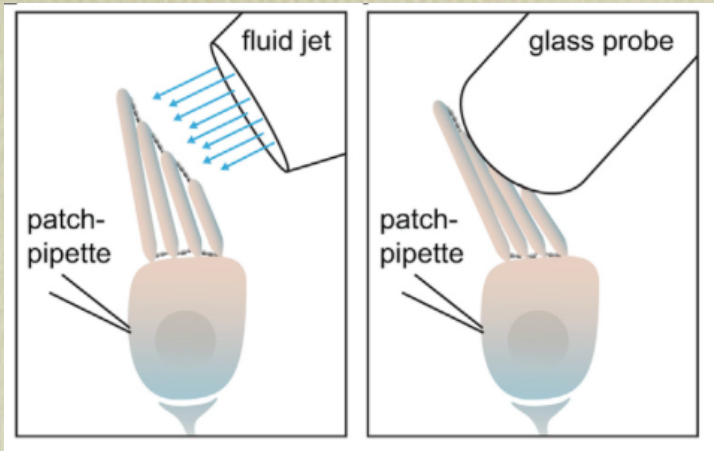
**Inner Ear**
*Cochlear Structure*
*Electron Micrograph*



## Box 1. Outstanding questions

- What is the molecular identity of the mechanotransduction channel?
- What are the mechanical properties of tip links, and what is the atomic structure of the adhesion interface between CDH23 and PCDH15?
- Which molecule(s) form the gating spring for the transducer channel?
- What is the mechanism of fast adaptation? What is the mechanism of slow adaptation and what roles do Myo1c and Myo7a play in this process? Are other myosin motor proteins involved?
- What is the full complement of proteins at the upper and lower end of tip links and how do they regulate tip-link function in mechanotransduction?
- How is the exquisite polarity of CDH23 and PCDH15 at tip links achieved, and how are proteins such as the transduction channel and harmonin targeted to opposite ends of the tip link?
- Which mechanisms define the numbers and rows of stereocilia and their organ-pipe arrangement?
- Which signaling mechanisms establish precise polarity of the hair bundle in the apical surface of a hair cell?

# MECHANOTRANSDUCTION CHANNEL IN VERTEBRATE HAIR CELLS




- Located in tips of lower cilia
- Calcium permeable
- conductance ≈ 100 pS
- permeable to some small organic cations

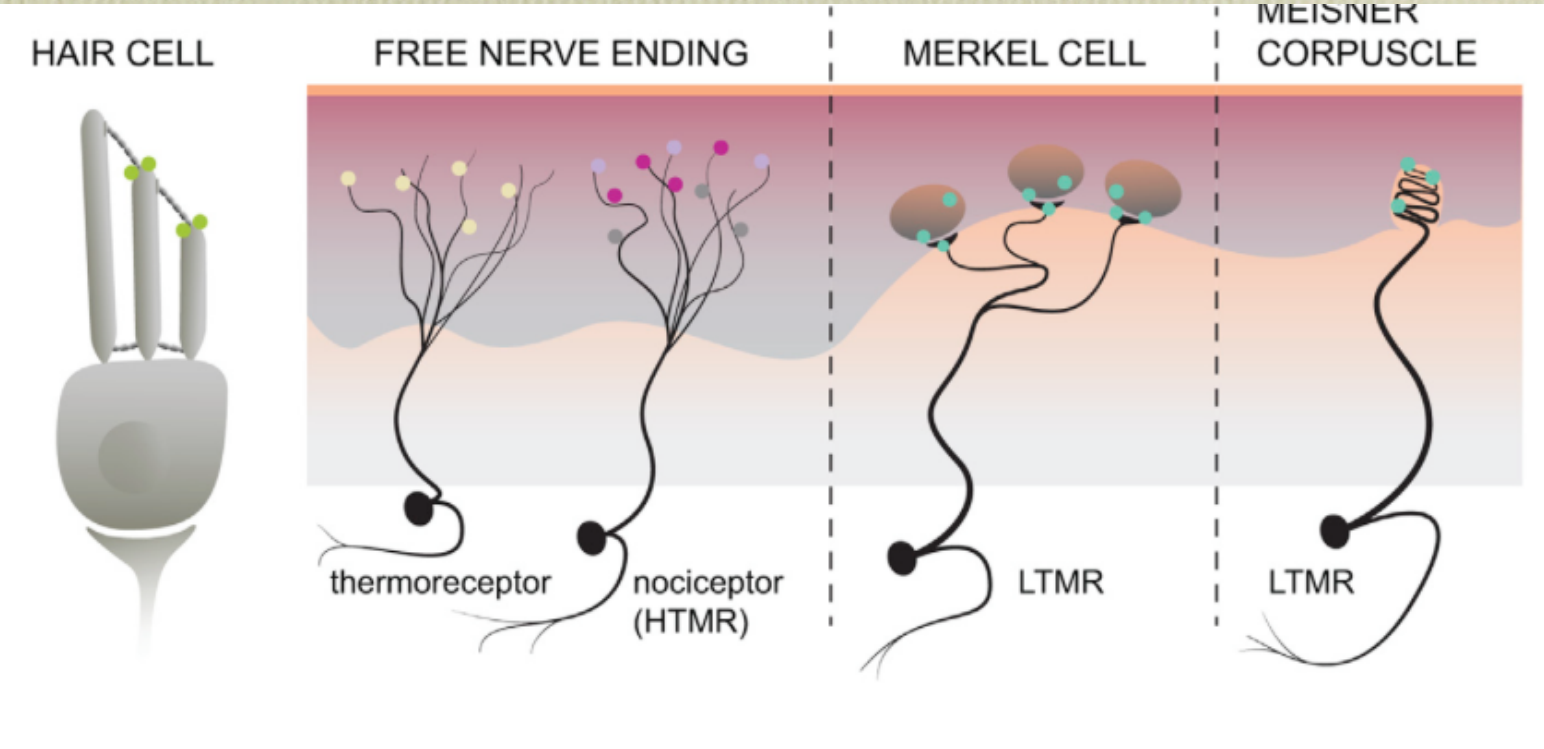
  and to the fluorescent lipophilic dye FM1-43

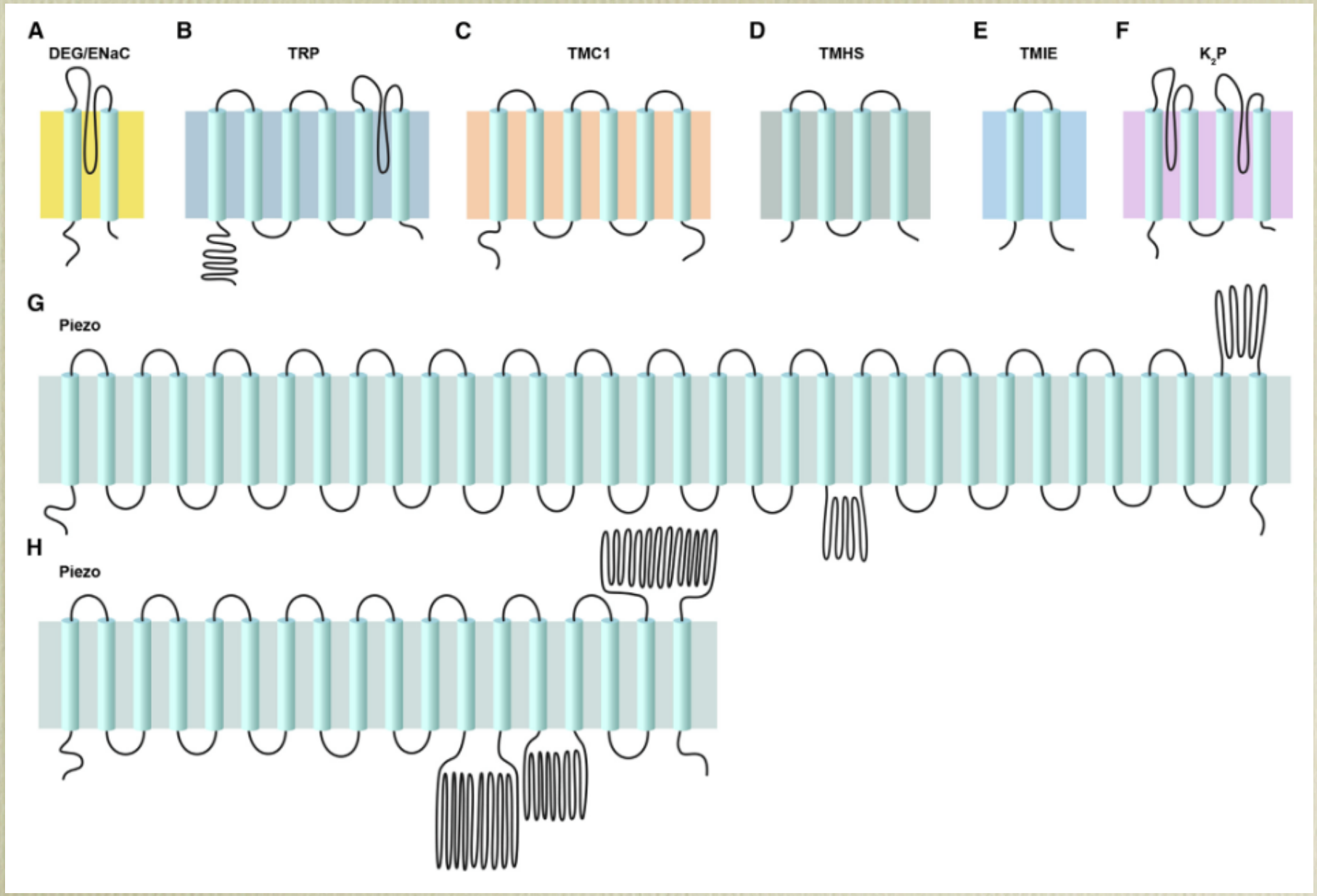
These characteristics rule out candidate channels of the DEG/ENaC family, which may mediate touch sensation in nematodes, they are typical of ion channels of the TRP superfamily. Moreover, TRP channels are found in a variety of sense organs, probably mediating pheromone transduction (TRPC2), sweet and bitter taste (TRPM5), warm and cool thermal sensation (TRPV1–4, TRPM8, TRPA1)

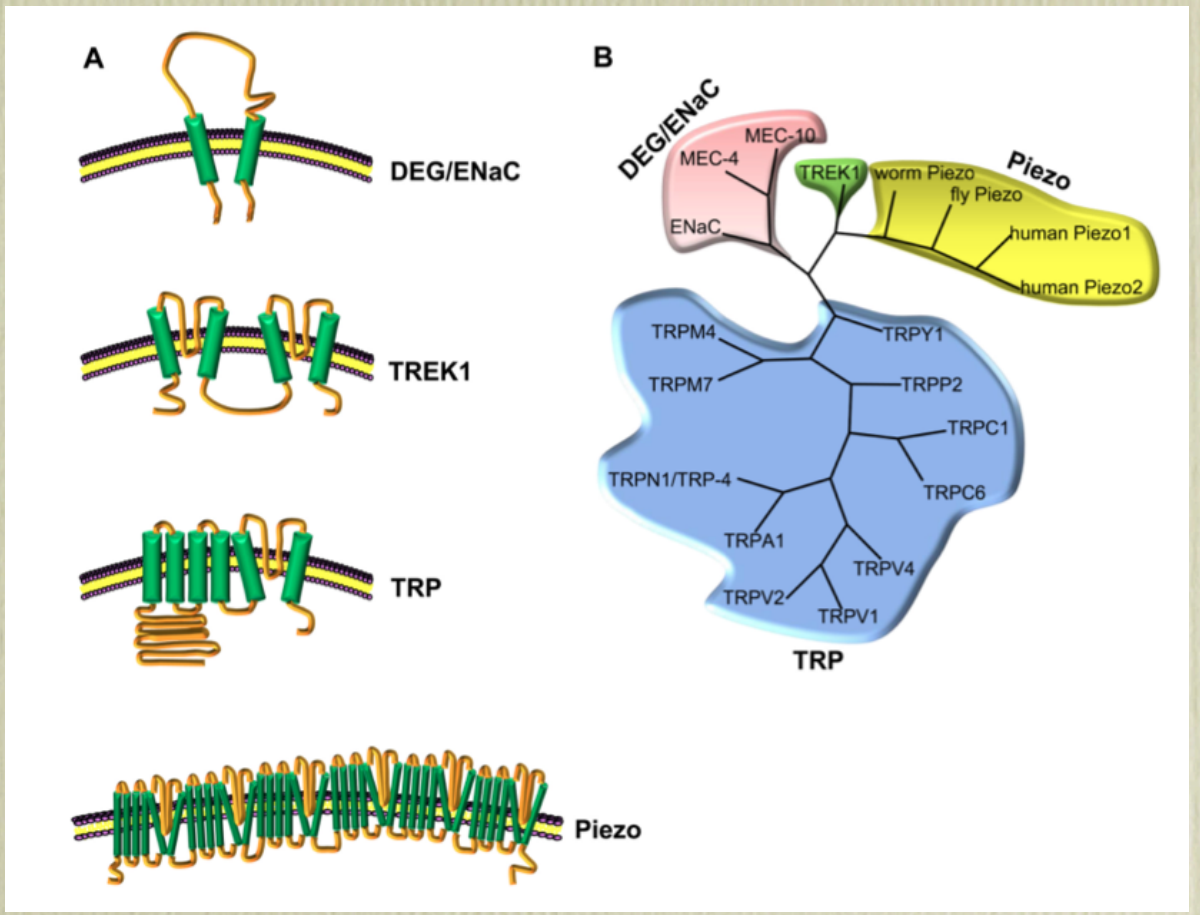
# Mechanically Activated Ion Channels

Sanjeev S. Ranade,[1] Ruhma Syeda,[1] and Ardem Patapoutian[1,*]

Neuron *87*, September 23, 2015 ©2015 Elsevier Inc.




A
DEG/ENaC
B
TRP
C
TMC1
D
TMHS
E
TMIE
F
$K_2P$
G
Piezo
H
Piezo


A
DEG/ENaC
TREK1
TRP
Piezo
B
DEG/ENaC
MEC-10
MEC-4
ENaC
TREK1
Piezo
worm Piezo
fly Piezo
human Piezo1
human Piezo2
TRPM4
TRPM7
TRPN1/TRP-4
TRPA1
TRPV2
TRPV1
TRPV4
TRPC6
TRPC1
TRPP2
TRPY1
TRP

# TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells

David P. Corey[1,2]*, Jaime García-Añoveros[4]*, Jeffrey R. Holt[5]*, Kelvin Y. Kwan[1,2]*, Shuh-Yow Lin[1,6]*, Melissa A. Vollrath[1,2]*, Andrea Amalfitano[8], Eunice L.-M. Cheung[1], Bruce H. Derfler[1,2], Anne Duggan[4], Gwénaëlle S. G. Géléoc[5], Paul A. Gray[1,3], Matthew P. Hoffman[9], Heidi L. Rehm[7], Daniel Tamasauskas[1,2] & Duan-Sun Zhang[1,2]

Nature, 2004

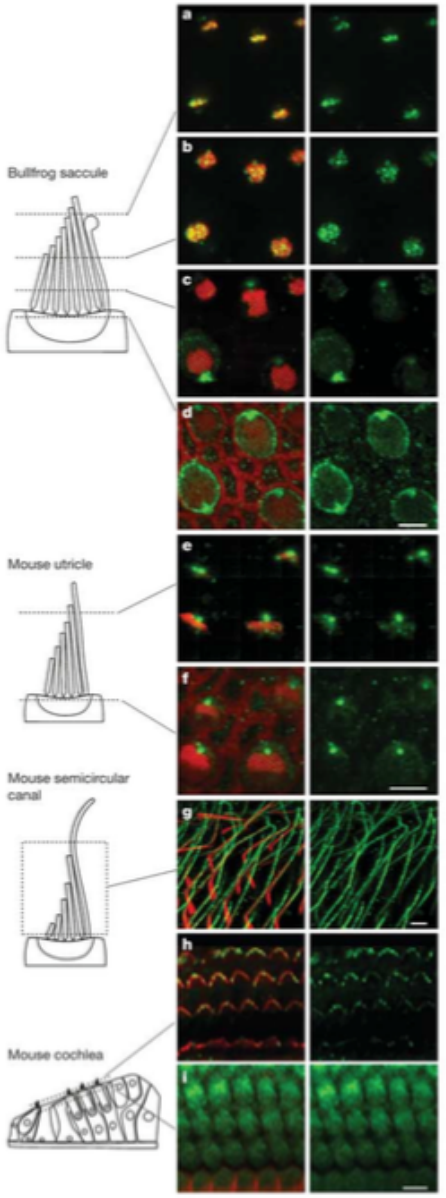
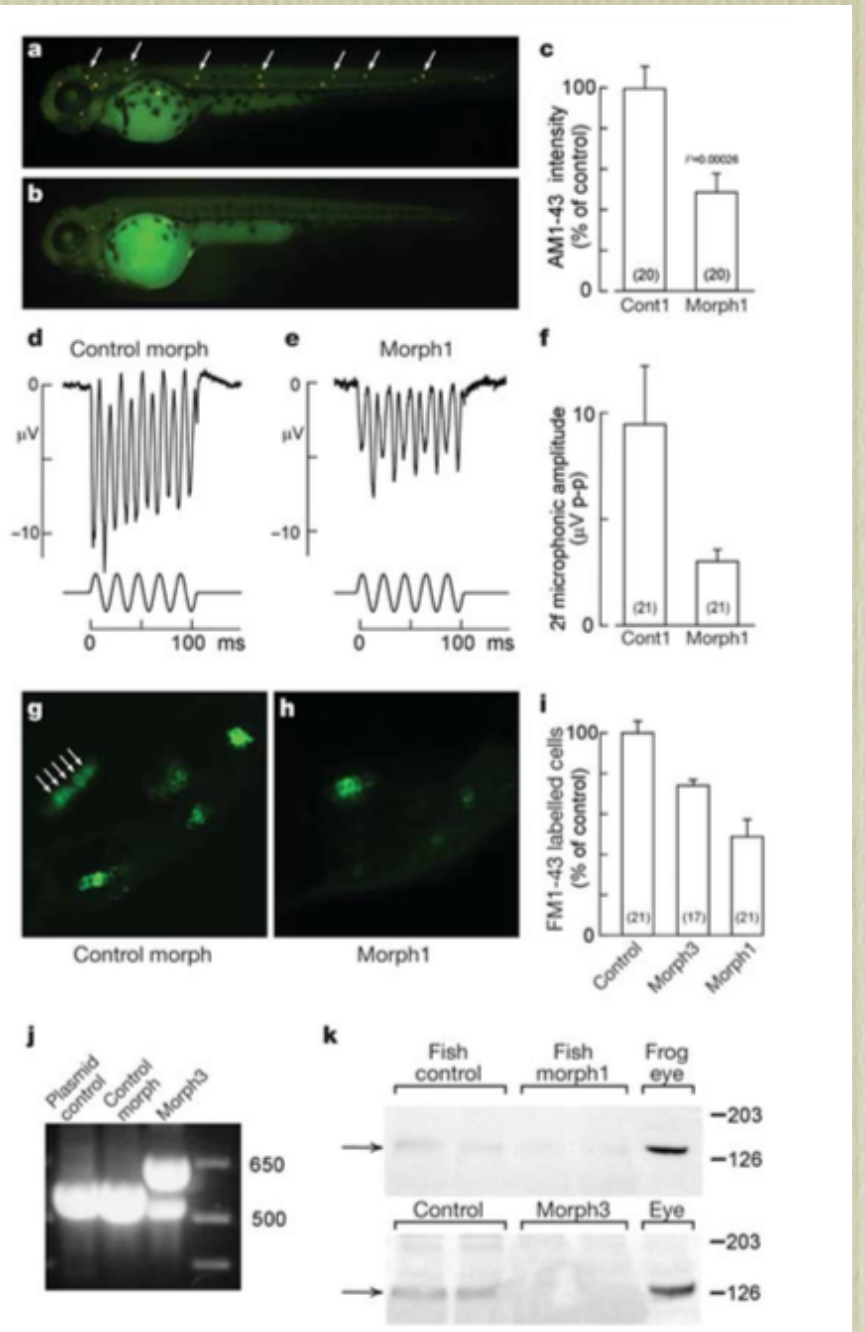



**Figure 2** Antibody labelling of TRPA1 in bullfrog and mouse inner ears. Red, actin; green, TRPA1 antibody 0203mt. Right panel is TRPA1 antibody alone. **a**–**d**, Adult bullfrog saccule; optical sections as indicated. **e**, **f**, Hair cells from the mouse utricle; optical sections through a whole mount showing tips or bases of stereocilia. **g**, Hair bundles from the mouse semicircular canal. **h**, Hair cells from the mouse cochlea at P7. **i**, Label also appears in the cell bodies of hair cells. Scale bar, 5 μm.



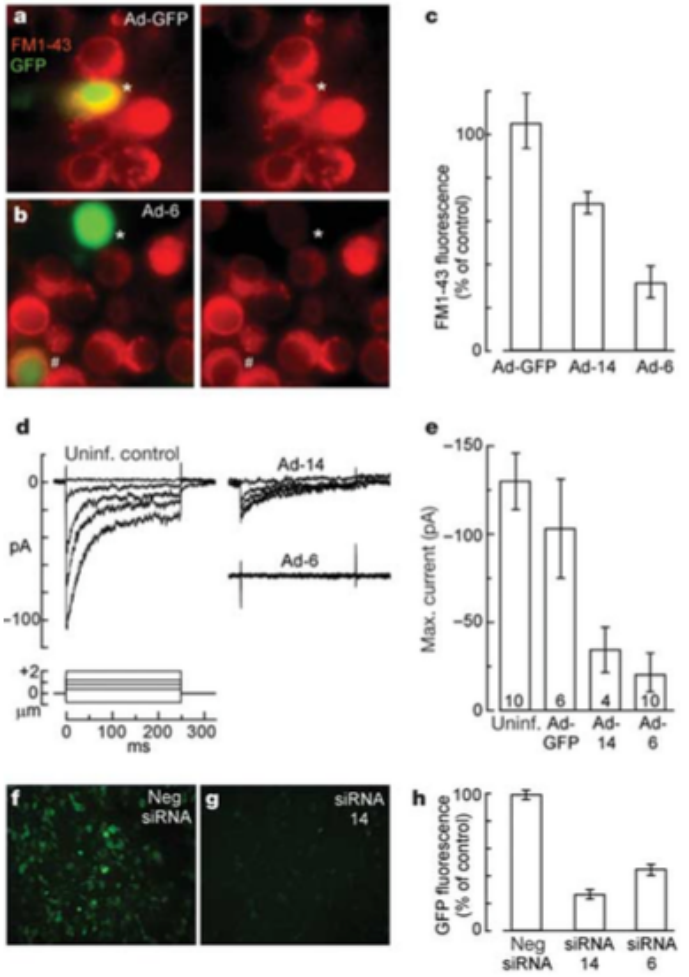




**Figure 5** Inhibition of transduction in mouse with adenoviruses encoding siRNAs. **a**, Utricular hair cells labelled with FM1-43 to mark transducing cells; optical section through the cell body. A hair cell (asterisk) infected with Ad-GFP (green) accumulated FM1-43. **b**, Ad-6-infected cells are green; only one (hash) accumulated FM1-43. **c**, Summary of FM1-43 accumulation in infected cells (average intensity per cell) relative to uninfected controls. Data are mean ± s.e.m. **d**, Typical transduction currents in uninfected cells and cells infected with Ad-14 or Ad-6. **e**, Summary of peak currents. Data are mean ± s.e.m., *N* is as indicated. **f**, HEK cells transfected with GFP::mmTRPA1 and a negative control siRNA construct. **g**, HEK cells transfected with GFP::mmTRPA1 and siRNA-14. **h**, Green fluorescence intensity above background, with co-transfection with the control siRNA, siRNA-14, or siRNA-6. Data are mean ± s.d.; $N = 5$.

Neuron 50, 277–289, April 20, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.neuron.2006.03.042

# TRPA1 Contributes to Cold, Mechanical, and Chemical Nociception but Is Not Essential for Hair-Cell Transduction

Kelvin Y. Kwan,[1,*] Andrew J. Allchorne,[2] Melissa A. Vollrath,[1] Adam P. Christensen,[3] Duan-Sun Zhang,[1] Clifford J. Woolf,[2] and David P. Corey[1]

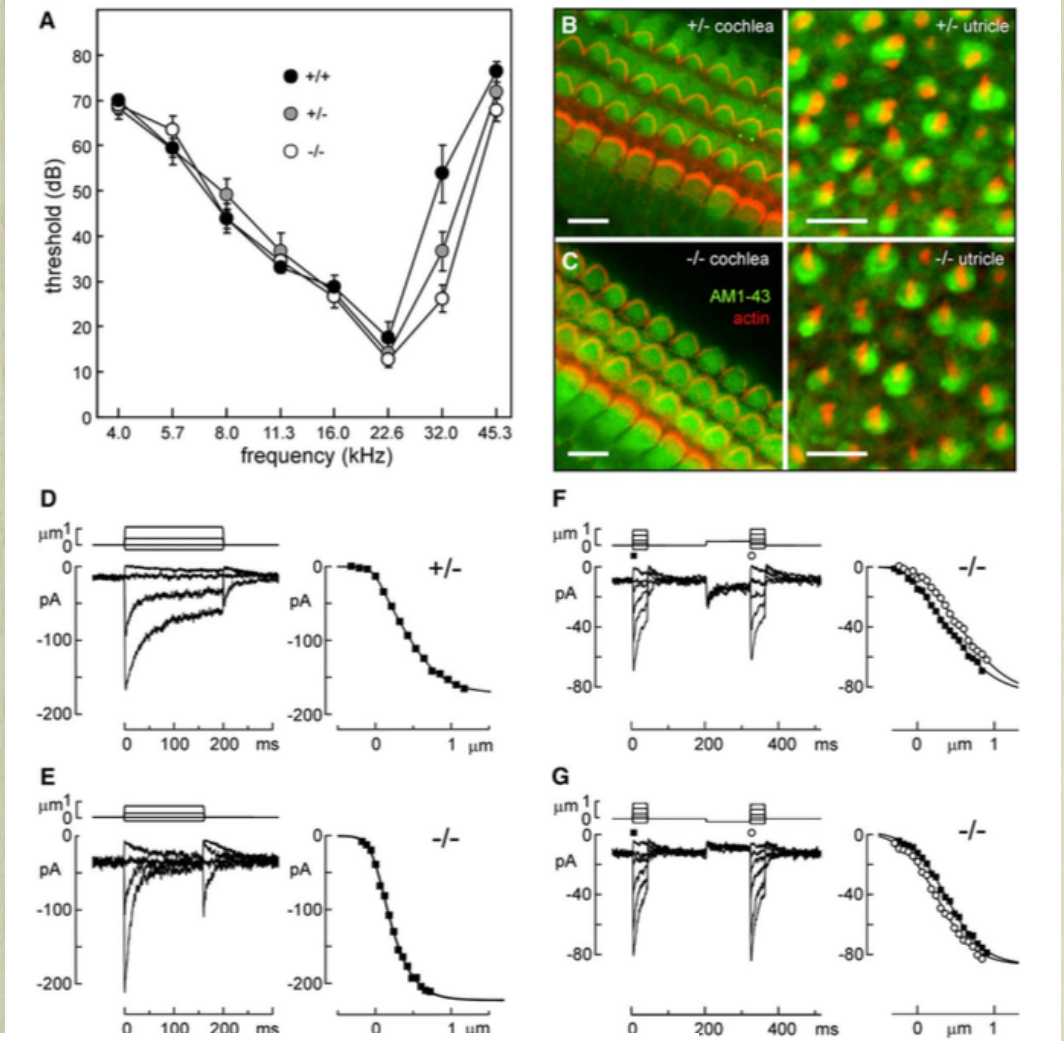



Table 1. Properties of Transduction and Adaptation

| | $I_{max}$ (pA) | $P_0$ (%) | Operating Range (nm) | $\tau_A$ (ms) | Extent (%) | n |
|---|---|---|---|---|---|---|
| wild-type | 155 ± 16 | 14 ± 1 | 749 ± 59 | 30 ± 2 | 76 ± 3 | 31 |
| *Trpa1*$^{+/-}$ | 131 ± 27 | 7 ± 1 | 841 ± 192 | 28 ± 8 | 79 ± 6 | 5 |
| *Trpa1*$^{-/-}$ | 129 ± 18 | 12 ± 3 | 812 ± 71 | 37 ± 7 | 71 ± 5 | 10 |

Values are mean ± SE. $P_0$ is percent of current activated at rest; operating range is 10%–90% of $I_{max}$; $\tau_A$ is adaptation time constant measured from current decay for a half-maximal displacement; extent of adaptation measured from curve fitted to decay. Wild-type values from Vollrath and Eatock (2003).

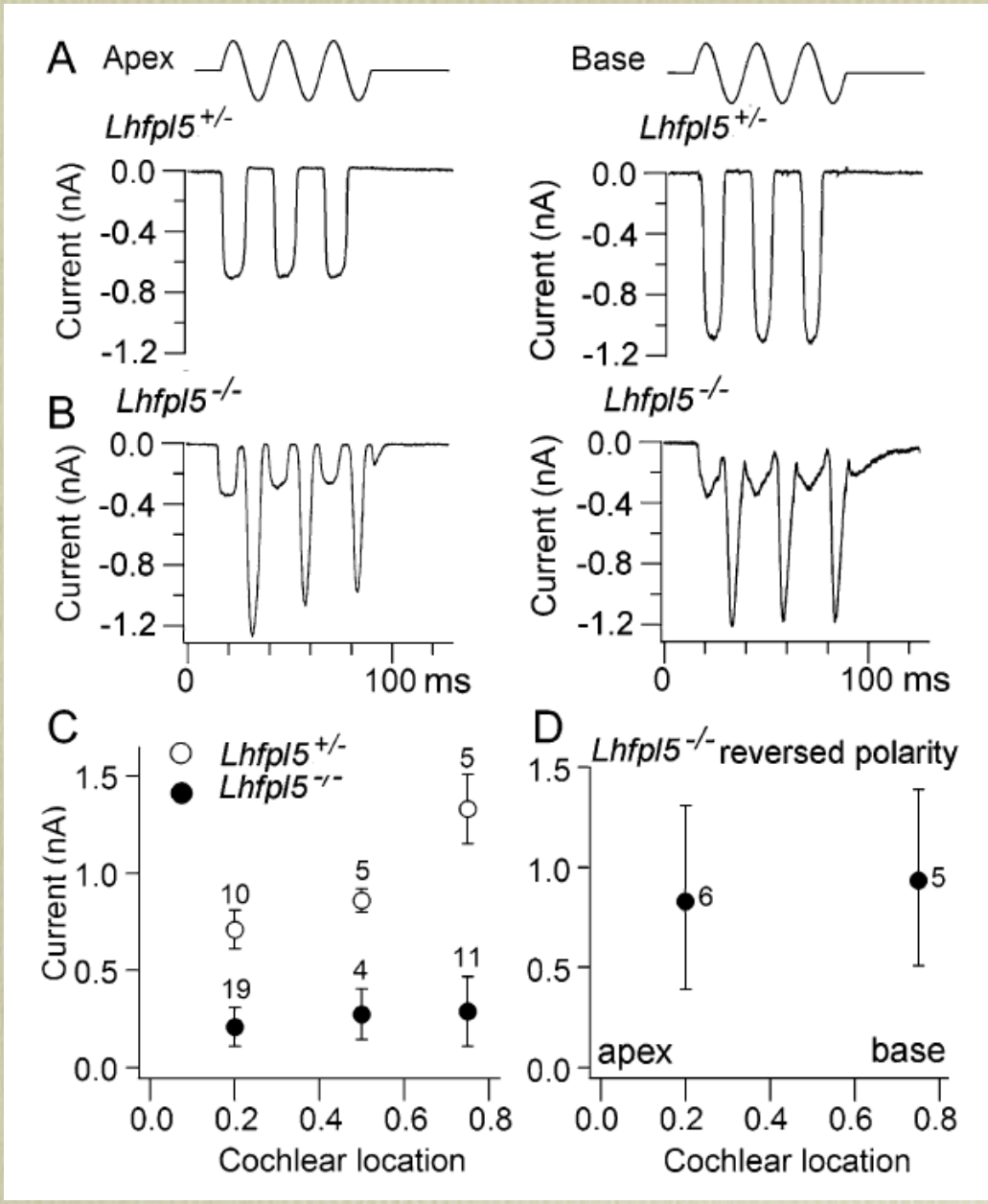
# Subunit determination of the conductance of hair-cell mechanotransducer channels

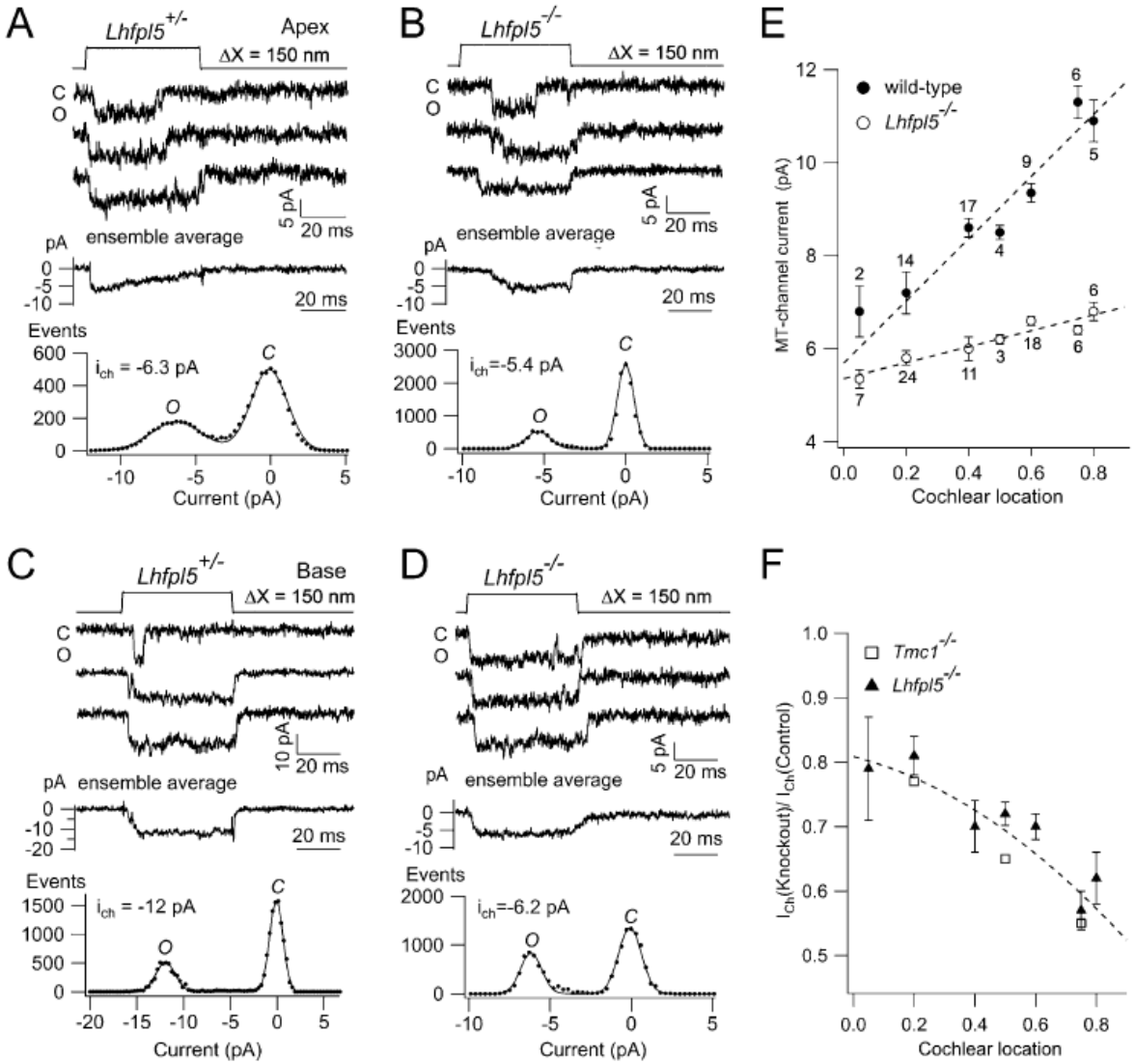
PNAS, 2015

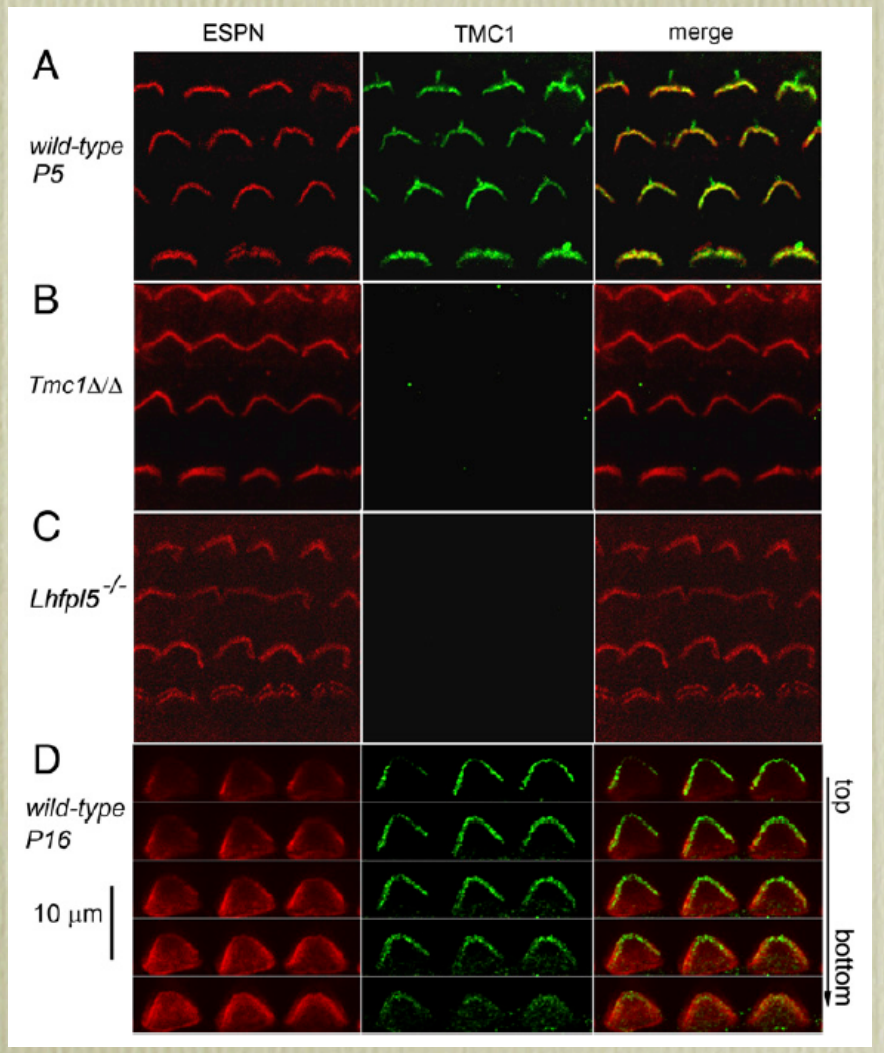
Maryline Beurg[a], Wei Xiong[b], Bo Zhao[b], Ulrich Müller[b], and Robert Fettiplace[a,1]

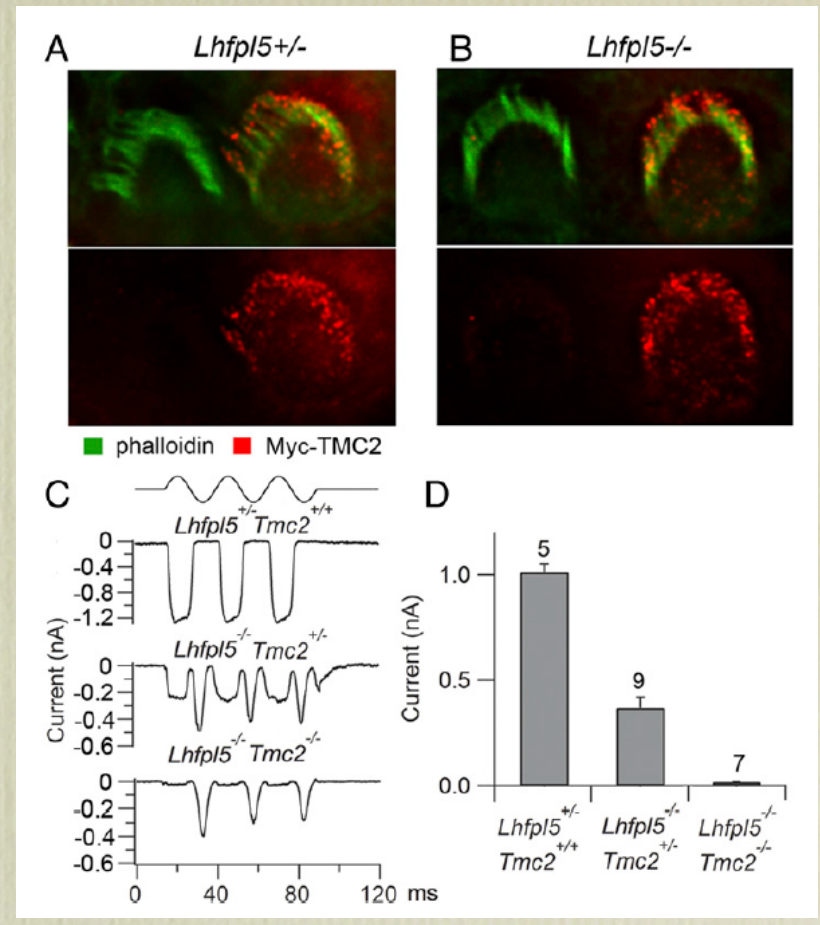
## Significance

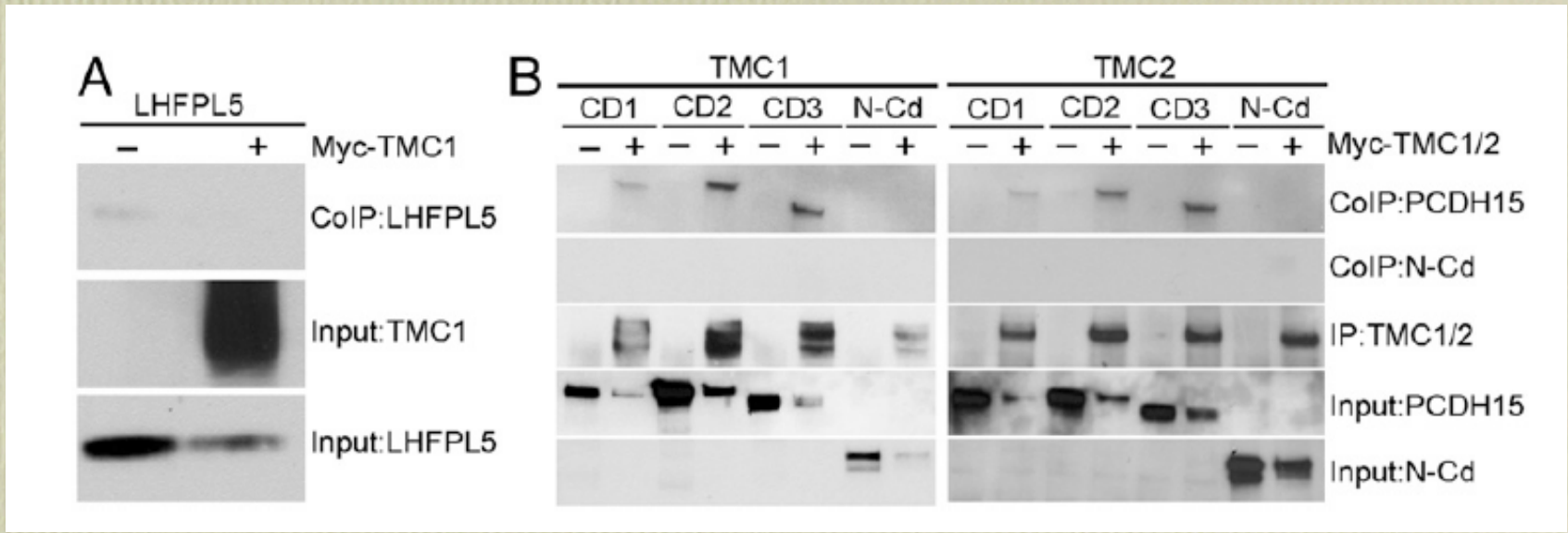
Cochlear hair cells are sensory receptors of the inner ear that detect sound via opening of mechanically sensitive transduction channels at the tips of the eponymous hairs. The conductance of the channel increases two-fold along the cochlea, but neither its molecular structure nor mechanism of tonotopic variation is known. We show that when either of two deafness-linked proteins, transmembrane channel-like protein isoform 1 (TMC1) and tetraspan membrane protein of hair cell stereocilia (TMHS, also known as lipoma HMGIC fusion partner-like 5, LHFPL5) is knocked out, the conductance variation is lost. Furthermore, the effect of LHFPL5 is attributable to down-regulation of TMC1, suggesting that titrating the TMC1 content of the channel modulates its conductance. Evidence indicates that both proteins interact with the mechanotransduction channel and also with protocadherin-15, a component of the extracellular tip link that applies force to the channel.


A
Apex
Base
Lhfpl5 +/-
Lhfpl5 +/-
Current (nA)
0.0
-0.4
-0.8
-1.2
B
Lhfpl5 -/-
Lhfpl5 -/-
0
100 ms
C
Lhfpl5 +/-
Lhfpl5 -/-
1.5
1.0
0.5
0.0
10
19
5
4
5
11
0.0
0.2
0.4
0.6
0.8
Cochlear location
D
Lhfpl5 -/- reversed polarity
6
5
apex
base


A
Lhfpl5+/-
Apex
ΔX = 150 nm
C
O
5 pA
20 ms
pA
ensemble average
0
-5
-10
20 ms
Events
600
400
200
0
ich = -6.3 pA
O
C
-10
-5
0
5
Current (pA)
B
Lhfpl5-/-
ΔX = 150 nm
C
O
5 pA
20 ms
pA
ensemble average
0
-5
-10
20 ms
Events
3000
2000
1000
0
ich=-5.4 pA
O
C
-10
-5
0
5
Current (pA)
E
wild-type
Lhfpl5-/-
MT-channel current (pA)
12
10
8
6
4
2
14
17
9
6
5
4
24
11
3
18
6
7
0.0
0.2
0.4
0.6
0.8
Cochlear location
C
Lhfpl5+/-
Base
ΔX = 150 nm
C
O
10 pA
20 ms
pA
ensemble average
0
-10
-20
20 ms
Events
1500
1000
500
0
ich = -12 pA
O
C
-20
-15
-10
-5
0
5
Current (pA)
D
Lhfpl5-/-
ΔX = 150 nm
C
O
5 pA
20 ms
pA
ensemble average
0
-5
-10
20 ms
Events
2000
1000
0
ich=-6.2 pA
O
C
-10
-5
0
5
Current (pA)
F
Tmc1-/-
Lhfpl5-/-
ICh(Knockout)/ ICh(Control)
1.0
0.9
0.8
0.7
0.6
0.5
0.0
0.2
0.4
0.6
0.8
Cochlear location


ESPN
TMC1
merge
A
wild-type
P5
B
Tmc1Δ/Δ
C
Lhfpl5-/-
D
wild-type
P16
10 μm
top
bottom


A
Lhfpl5+/-
B
Lhfpl5-/-
phalloidin
Myc-TMC2
C
Lhfpl5+/- Tmc2+/+
Lhfpl5-/- Tmc2+/-
Lhfpl5-/- Tmc2-/-
Current (nA)
0
-0.4
-0.8
-1.2
-0.2
-0.6
0
40
80
120 ms
D
Current (nA)
1.0
0.5
0.0
5
9
7
Lhfpl5+/- Tmc2+/+
Lhfpl5-/- Tmc2+/-
Lhfpl5-/- Tmc2-/-


A
LHFPL5
– +
Myc-TMC1
CoIP:LHFPL5
Input:TMC1
Input:LHFPL5
B
TMC1
TMC2
CD1 CD2 CD3 N-Cd
CD1 CD2 CD3 N-Cd
– + – + – + – +
– + – + – + – +
Myc-TMC1/2
CoIP:PCDH15
CoIP:N-Cd
IP:TMC1/2
Input:PCDH15
Input:N-Cd

## In the Right Place at the Right Time: Is TMC1/2 the Transduction Channel for Hearing?

Artur A. Indzhykulian[1,*] and David P. Corey[1,*]

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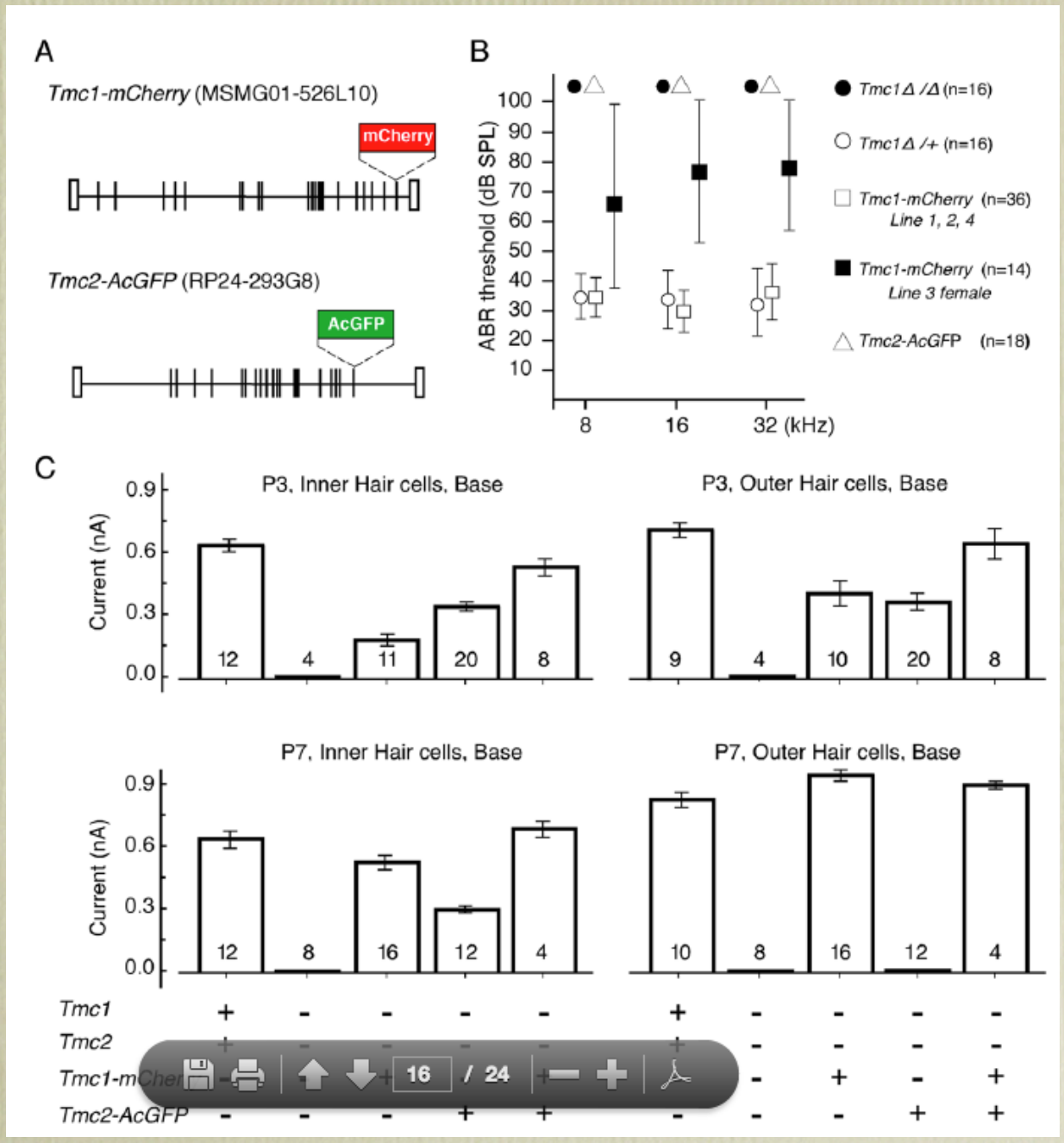
## TMC1 and TMC2 Localize at the Site of Mechanotransduction in Mammalian Inner Ear Hair Cell Stereocilia

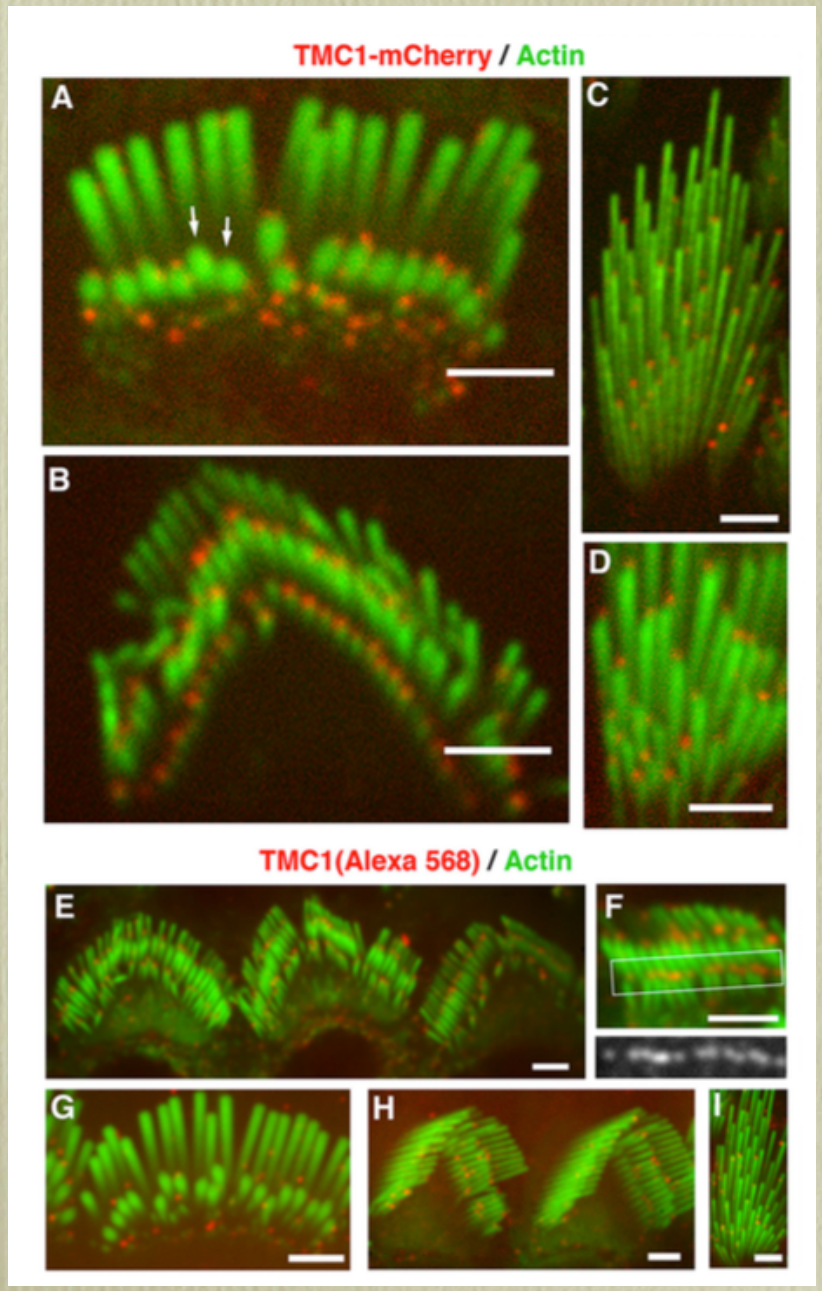
**Kiyoto Kurima[1,*], Seham Ebrahim[2,*], Bifen Pan[3], Miloslav Sedlacek[2], Prabuddha Sengupta[4], Bryan A. Millis[2], Runjia Cui[2], Hiroshi Nakanishi[1], Taro Fujikawa[2], Yoshi**

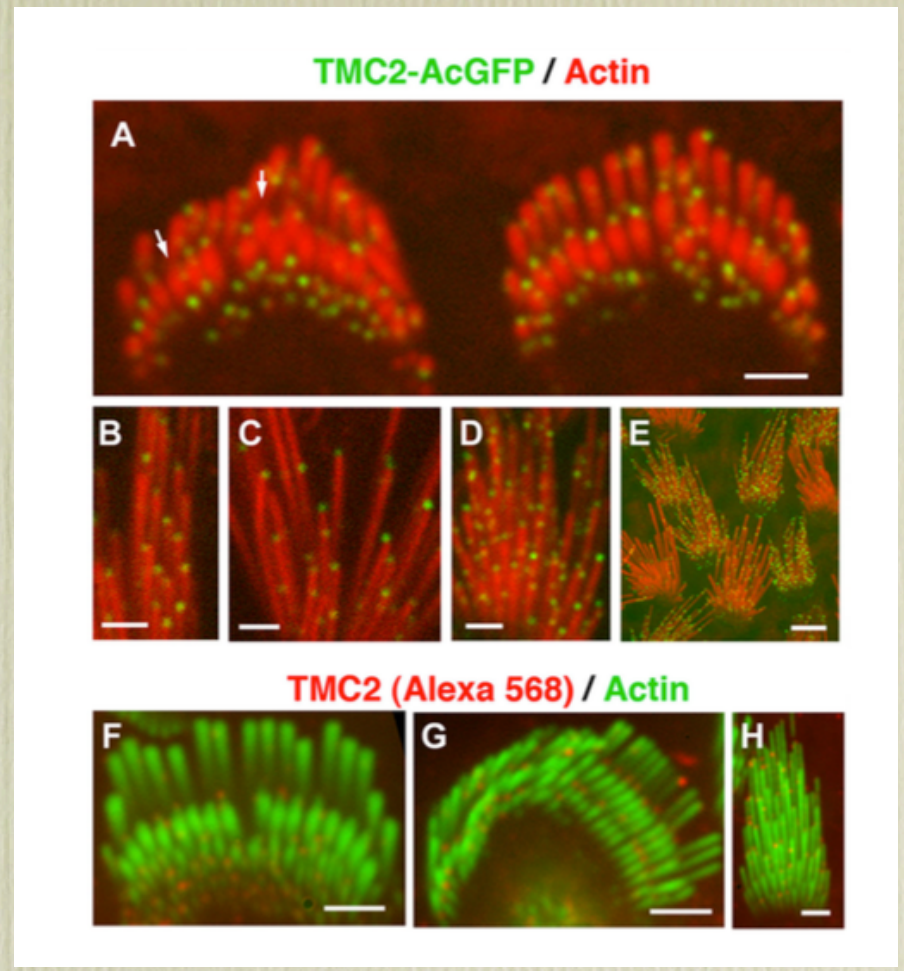
nd

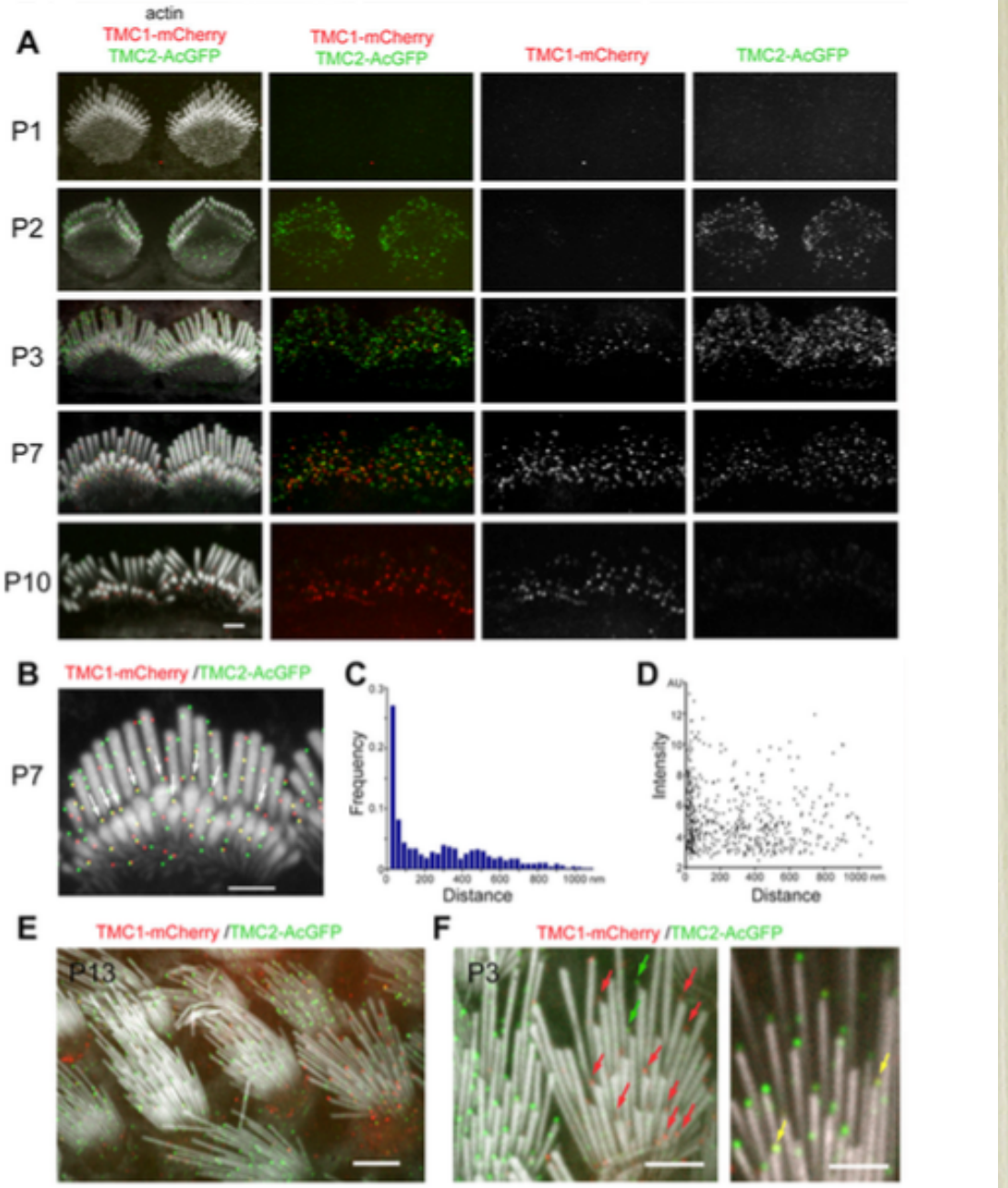
## Summary

Mechanosensitive ion channels at stereocilia tips mediate mechanoelectrical transduction (MET) in inner ear sensory hair cells. Transmembrane channel-like 1 and 2 (TMC1 and TMC2) are essential for MET and are hypothesized to be components of the MET complex, but evidence for their predicted spatiotemporal localization in stereocilia is lacking. Here we determine the stereocilia-localization of the TMC proteins in mice expressing TMC1-mCherry and TMC2-AcGFP. Functionality of the tagged proteins was verified by transgenic rescue of MET currents and hearing in $Tmc1^{\Delta/\Delta};Tmc2^{\Delta/\Delta}$ mice. TMC1-mCherry and TMC2-AcGFP localize along the length of immature stereocilia. However, as hair cells develop, the two proteins localize predominantly to stereocilia tips. Both TMCs are absent from the tips of the tallest stereocilia, where MET activity is not detectable. This distribution was confirmed for the endogenous proteins by immunofluorescence. These data are consistent with TMC1 and TMC2 being components of the stereocilia MET channel complex.


A
Tmc1-mCherry (MSMG01-526L10)
mCherry
Tmc2-AcGFP (RP24-293G8)
AcGFP
B
ABR threshold (dB SPL)
100
90
80
70
60
50
40
30
20
10
8
16
32 (kHz)
Tmc1Δ/Δ (n=16)
Tmc1Δ/+ (n=16)
Tmc1-mCherry (n=36)
Line 1, 2, 4
Tmc1-mCherry (n=14)
Line 3 female
Tmc2-AcGFP (n=18)
C
P3, Inner Hair cells, Base
P3, Outer Hair cells, Base
P7, Inner Hair cells, Base
P7, Outer Hair cells, Base
Current (nA)
0.9
0.6
0.3
0.0
12
4
11
20
8
9
4
10
20
8
12
8
16
12
4
10
8
16
12
4
Tmc1
Tmc2
Tmc1-mCherry
Tmc2-AcGFP
16 / 24


TMC1-mCherry / Actin
A
B
C
D
TMC1(Alexa 568) / Actin
E
F
G
H
I


TMC2-AcGFP / Actin
A
B
C
D
E
TMC2 (Alexa 568) / Actin
F
G
H


A
actin
TMC1-mCherry
TMC2-AcGFP
TMC1-mCherry
TMC2-AcGFP
TMC1-mCherry
TMC2-AcGFP
P1
P2
P3
P7
P10
B
TMC1-mCherry /TMC2-AcGFP
P7
C
Frequency
Distance
D
Intensity
Distance
E
TMC1-mCherry /TMC2-AcGFP
P13
F
TMC1-mCherry /TMC2-AcGFP
P3

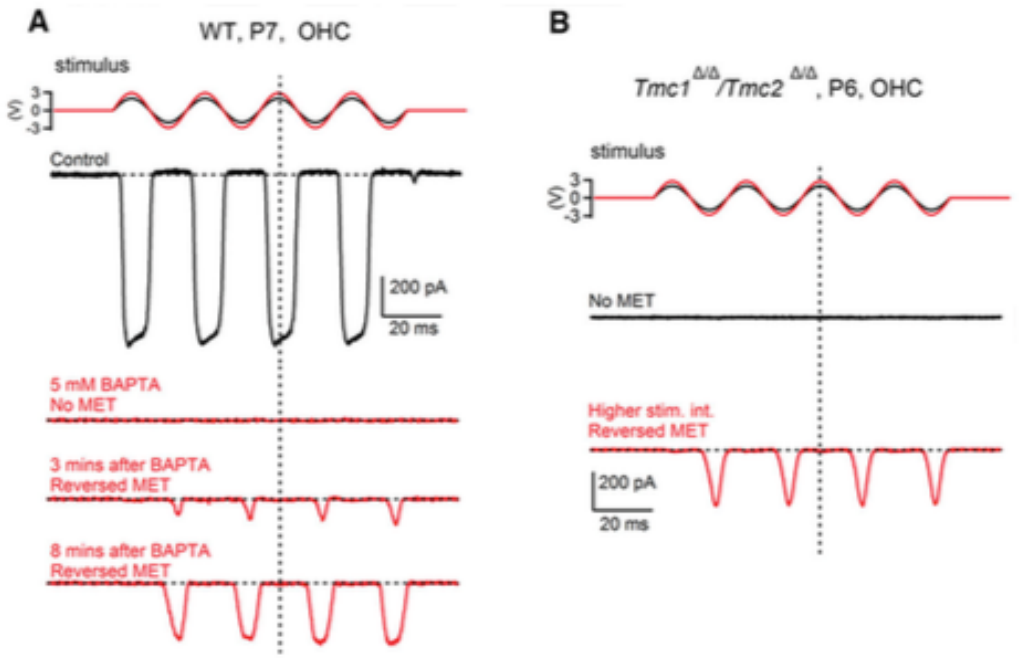



**Figure 6. Reverse-polarity currents in WT and *Tmc1*$^{\Delta/\Delta}$;*Tmc2*$^{\Delta/\Delta}$ hair cells**

(A) Example of MET current (black trace) recorded from a WT outer hair cell (from mid-apical turn of the cochlea, P7 mouse) in response to a sine wave stimulus (black) with a fluid jet device. Upon application of 5 mM BAPTA the MET current of the same cell is abolished (red trace) and followed with the progressive appearance of the reverse polarity currents. (B) Representative MET current recordings from a *Tmc1*$^{\Delta/\Delta}$;*Tmc2*$^{\Delta/\Delta}$ outer hair cell. No conventional MET currents were detected during regular stimulation (black trace). A higher stimulus (red sine wave) evoked reverse-polarity currents (red trace). All recordings in panels A and B are averages of 3–8 individual traces (n=5 cells).

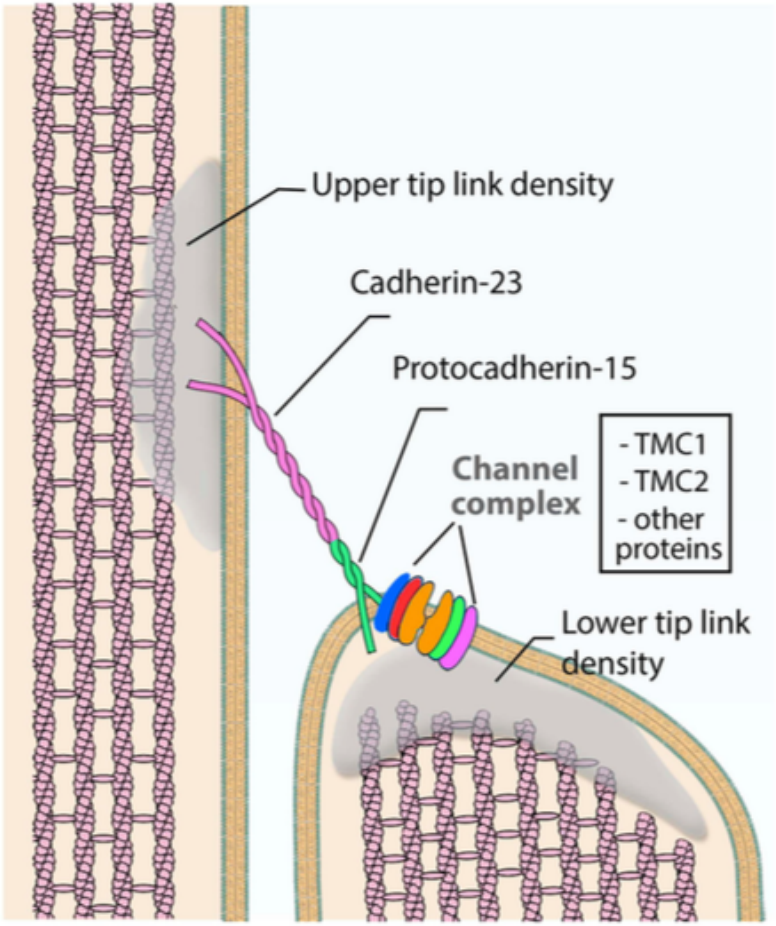



**Figure 7. Schematic diagram of stereocilia MET channel complex proteins**
Diagram of the stereocilia MET channel complex illustrating the localization of known associated proteins. Localization of TMC1 and TMC2 is consistent with these proteins being components of the complex.

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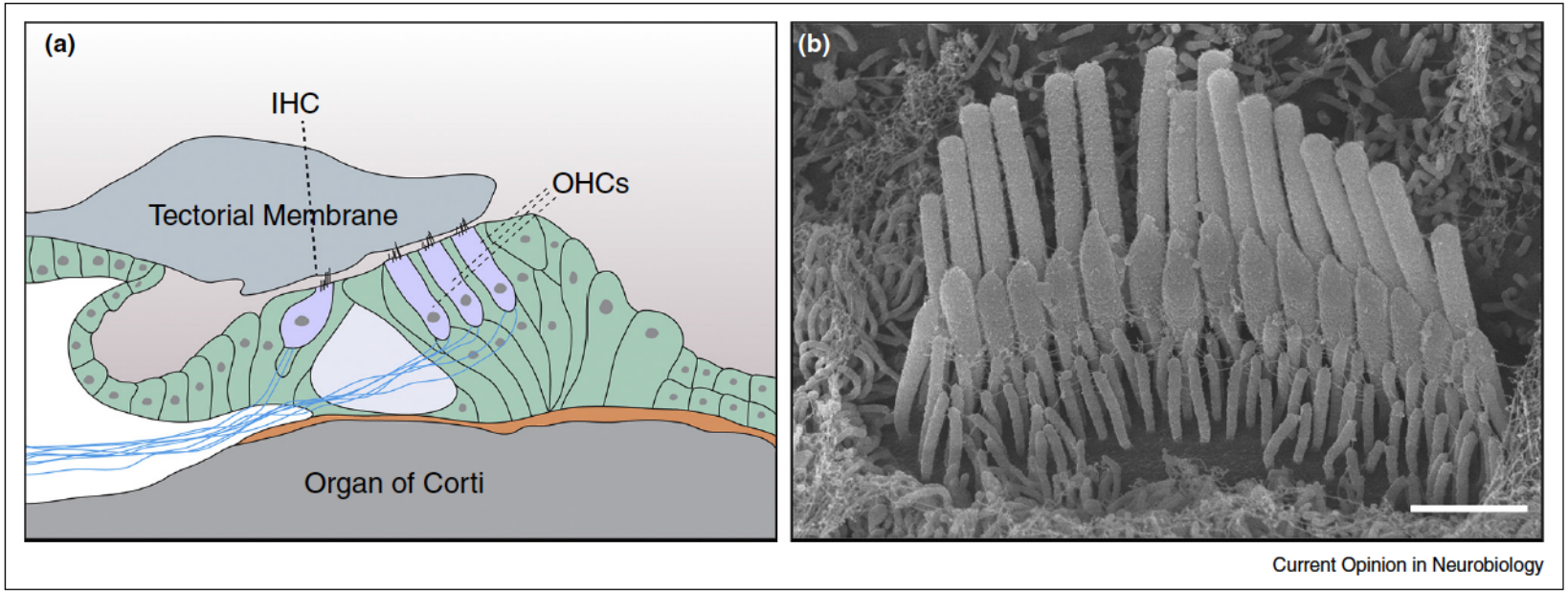
Current Opinion in Neurobiology

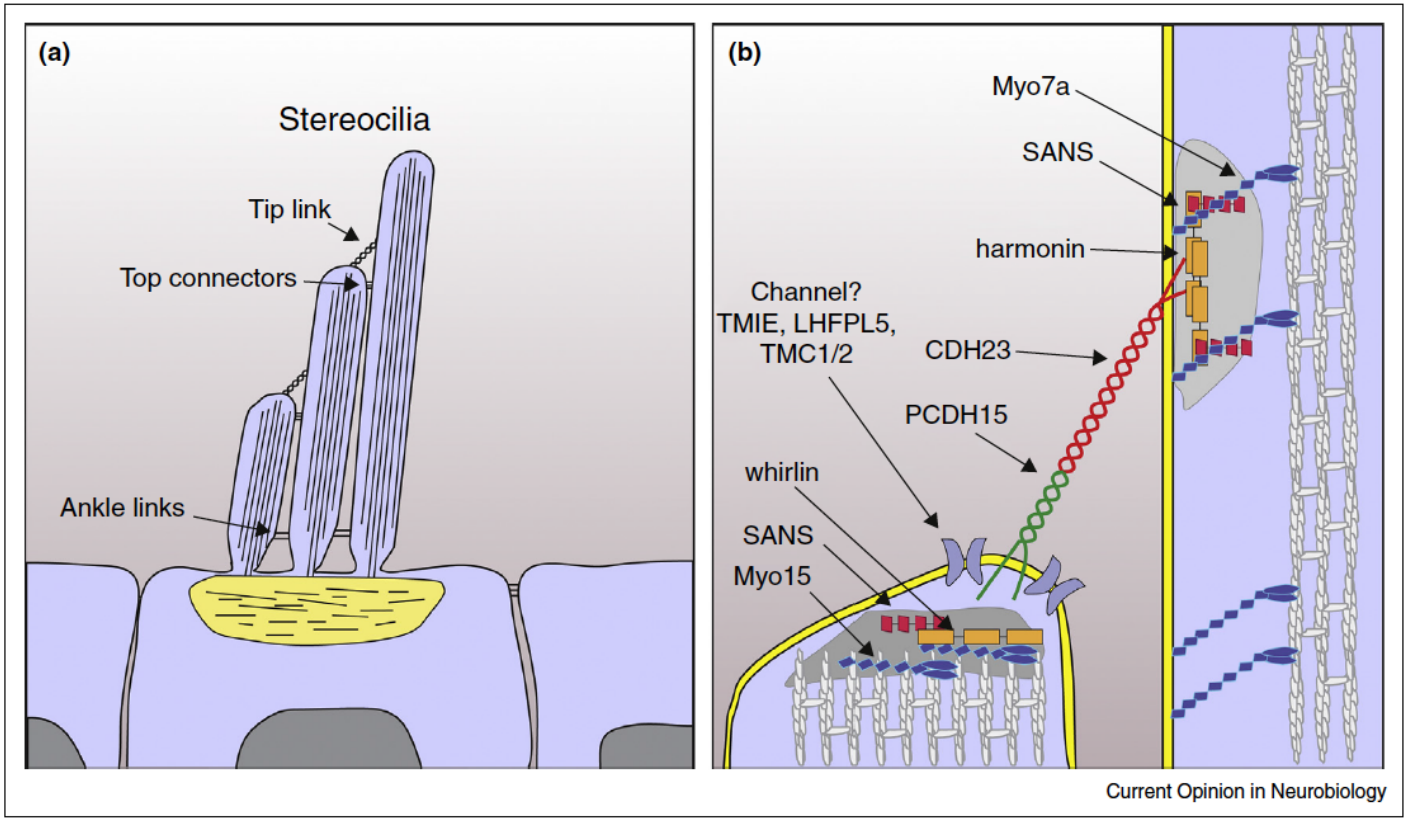
# The elusive mechanotransduction machinery of hair cells

Bo Zhao and Ulrich Müller

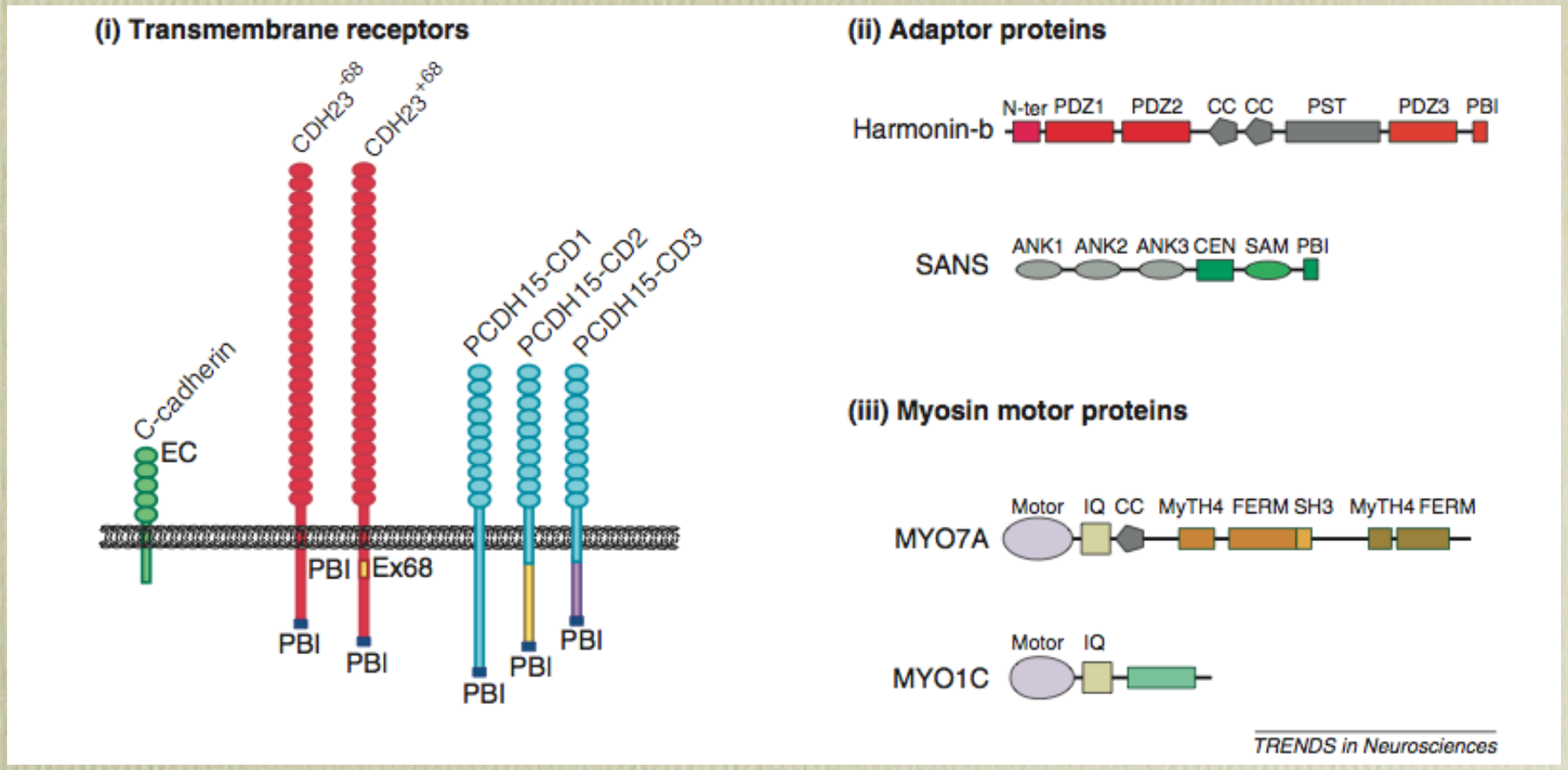
2015

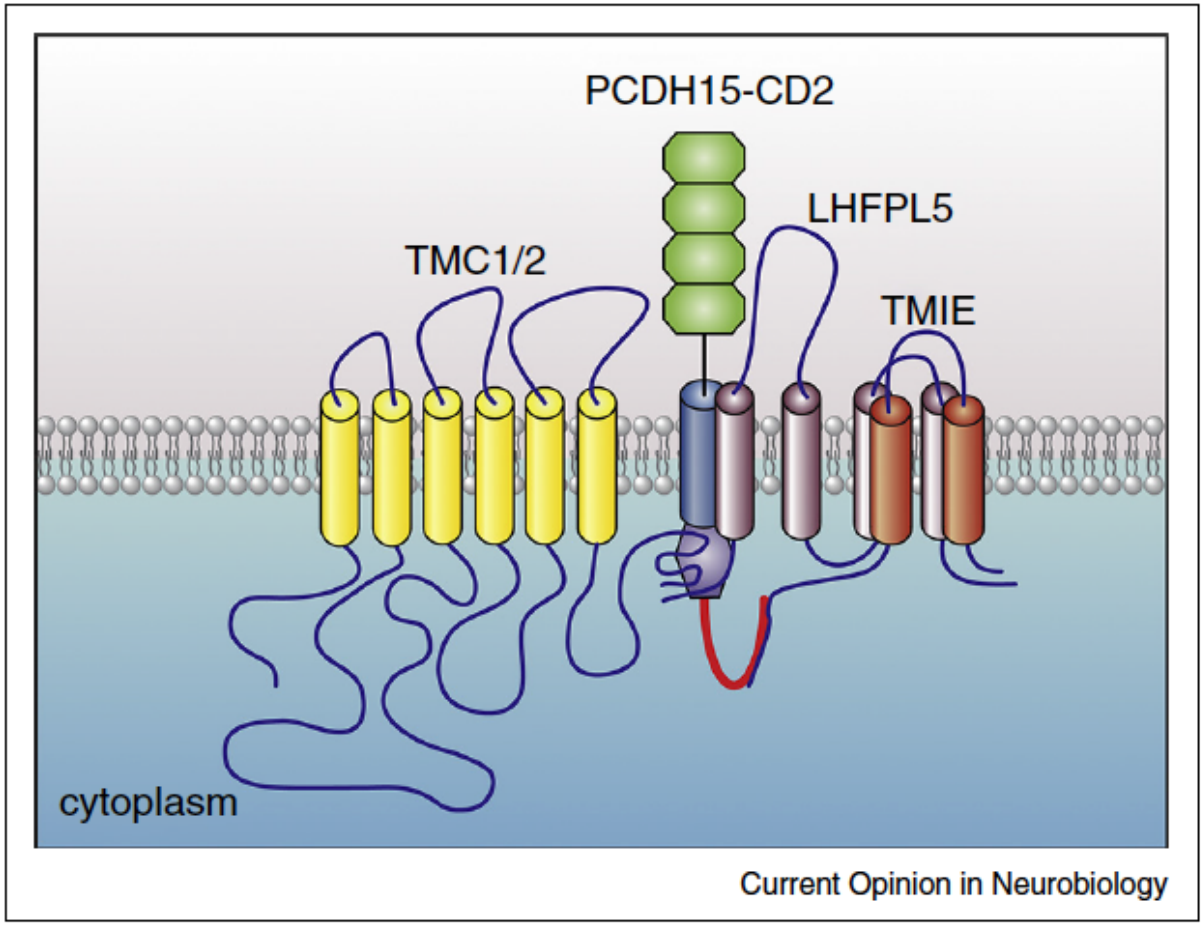



Anatomy of mammalian organ of corti. (**a**) The sensory epithelia in the organ of Corti in the mammalian cochlea contain three rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs). OHCs are important for the amplification of sound signals and receive efferent innervation, while IHCs are innervated by afferent neurons that carry sound information to the nervous system. Other structural features of the organ of Corti such as the basilar membrane and the tectorial membrane are indicated. (**b**) Scanning electron micrograph showing the stereocilia of an IHC that are organized in rows of decreasing heights (picture courtesy of Nicolas Grillet). Scale bar: 1 μm.




Model of the tip-link complex in hair cells. (**a**) Diagram of a hair cell highlighting the hair bundle and the tip-link filaments that connect the stereocilia in the direction of their mechanical sensitivity. Top-connectors and ankle-links are additional filaments that connect the stereocilia. (**b**) Key molecules associated with tip links. Parallel homodimers of CDH23 interact with parallel homodimers of PCDH15 to form the upper and lower parts of tip links. The USH1 proteins harmonin, Myo7a and SANS form a complex that localizes near CDH23 at the upper tip-link region. LHFPL5, TMIE, and TMC1/2 localize at the lower end of tip links near PCDH15 where transduction channels are located. Whirlin and Myo15 are also concentrated near tip links but are not discussed in the text because their link to transduction is unclear.


(i) Transmembrane receptors
CDH23 -68
CDH23 +68
PCDH15-CD1
PCDH15-CD2
PCDH15-CD3
C-cadherin
EC
PBI
Ex68
PBI
PBI
PBI
PBI
PBI
(ii) Adaptor proteins
Harmonin-b
N-ter PDZ1 PDZ2 CC CC PST PDZ3 PBI
SANS
ANK1 ANK2 ANK3 CEN SAM PBI
(iii) Myosin motor proteins
MYO7A
Motor IQ CC MyTH4 FERM SH3 MyTH4 FERM
MYO1C
Motor IQ
TRENDS in Neurosciences




Model of the transduction channel complex of hair cells. TMC1/2 and LHFPL5 interact with the common region of PCDH15, while TMIE interact with the unique C-terminus of the PCDH15-CD2 isoform as well as with LHFPL5.

Neuron, Vol. 53, 9–12, April 7, 2007 Copyright ©2007 Elsevier Inc. DOI 10.1016/j.neuron.2006.12.014

# Pain TRPs

Minireview

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Massachusetts General Hospital and
Harvard Medical School
Charlestown, Massachusetts 02129

Table 1. Mammalian Sensory TRPs

| Channel Name | Major Tissue Distribution | Sensory Modality | Regulatory Mechanism |
|---|---|---|---|
| TRPV Subfamily | | | |
| TRPV1 | DRG, trigeminal ganglia (TG), urinary bladder | T $\geq$ 43°C, acid, capsaicin, resiniferatoxin, phorbol ester, N-arachidonyl dopamine, arachidonic acid metabolites, endocannabinoids, 2-aminoethoxydiphenyl borate (2-APB) | (+) PKA, PKC, PI3K, p38, Src, PLC, $PLA_2$/lipoxygenase, CaMKII, BK, NGF, $PGE_2$, ATP, ethanol, nicotine, acid, 2-APB |
| | | | (–) $PIP_2$, calmodulin, calcineurin, adenosine |
| TRPV2 | DRG, spinal cord (SC), brain, spleen, intestine | T $\geq$ 52°C, 2-APB | (+) translocation (by IGF-1) |
| TRPV3 | DRG, TG, SC, brain, keratinocytes, tongue | T $\geq$ 30°C–39°C, 2-APB, camphor | (+) 2-APB, camphor |
| TRPV4 | DRG, TG, brain, keratinocytes, kidney, lung, spleen, testis, endothelium, liver, heart, inner-ear hair cells | T $\geq$ 25°C, hypotonicity, noxious mechanical stimulus, acid, phorbol ester, endocannabinoids, arachidonic acid metabolites | (+) PLA2/cytochrome P450, Src, $PGE_2$ |
| TRPM Subfamily | | | |
| TRPM5 | taste tissue, small intestine, liver, lung, | taste (sweet, bitter, umami) | (+) $PLC_\beta 2$, intracellular $Ca^{++}$, $PIP_2$ |
| TRPM8 | DRG, TG, prostate | T $\leq$ 23°C–28°C, menthol, icilin, $PIP_2$ | (+) $PIP_2$ |
| | | | (–) intracellular acidification, 2-APB |
| TRPA Subfamily | | | |
| TRPA1 | DRG, fibroblasts, hair cells | T $\leq$ 18°C, icilin, cannabinoids, mustard oil, BK, cinnamaldehyde, mechanical stimulus (hair cells) | (+) $PLC_\beta$ |
| TRPC Subfamily | | | |
| TRPC2 (pseudogene in human) | Vomeronasal organ, testis, spleen, liver, heart, brain | pheromone (mouse only) | (+) DAG |

# Skin: keratinocytes concur to sensory transduction?

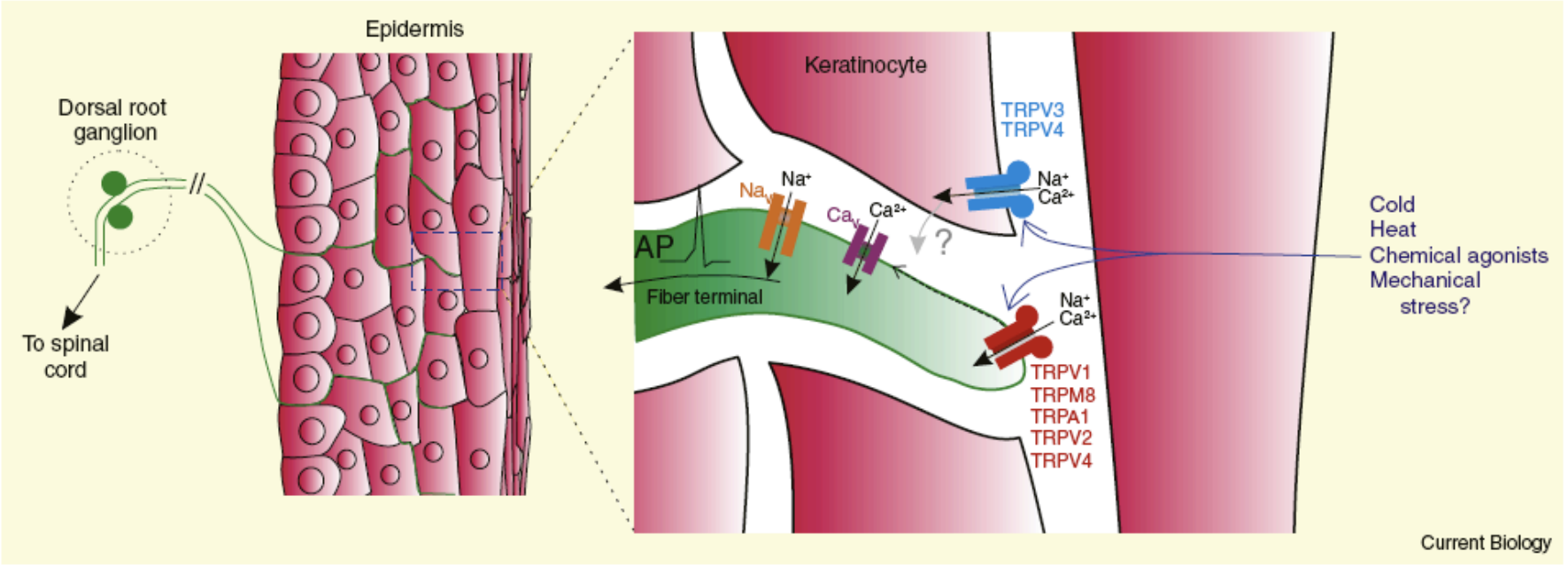


Figure 3. Model for the role of TRP channels detecting thermal, chemical and mechanical stimuli in the skin.

Free sensory nerve endings are located in the skin (left) and are coupled via the dorsal root sensory ganglia to the spinal cord for further information processing in the brain. An enlargement of the outer skin laminae is shown at the right. Physical and chemical stimuli can directly activate TRP channels in the free sensory nerve endings, causing depolarization of these fibers, activation of voltage-gated $Na_V$, $Ca_V$ channels and generation of action potentials. In addition, TRPV3 and TRPV4 are expressed in keratinocytes, from which signal transduction to the DRG neurons may occur via a yet unresolved signal transduction pathway.

unexpected sensory cells….

CELL BIOLOGY

# The sensation of stretch

**Piezo proteins have been shown to form large ion channels that serve a sensory function in fruitflies. The findings help to explain how Piezos convert mechanical force into biological signals.** SEE ARTICLE P.176 & LETTER P.209

Published in final edited form as:
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## Piezos are pore-forming subunits of mechanically activated channels

**Bertrand Coste[1,*], Bailong Xiao[1,*], Jose S. Santos[2], Ruhma Syeda[2], Jörg Grandl[1,#], Kathryn S. Spencer[1], Sung Eun Kim[1], Manuela Schmidt[1], Jayanti Mathur[3], Adrienne E. Dubin[1], Mauricio Montal[2], and Ardem Patapoutian[1,3,4]**

LETTER

doi:10.1038/nature10801

## The role of *Drosophila* Piezo in mechanical nociception

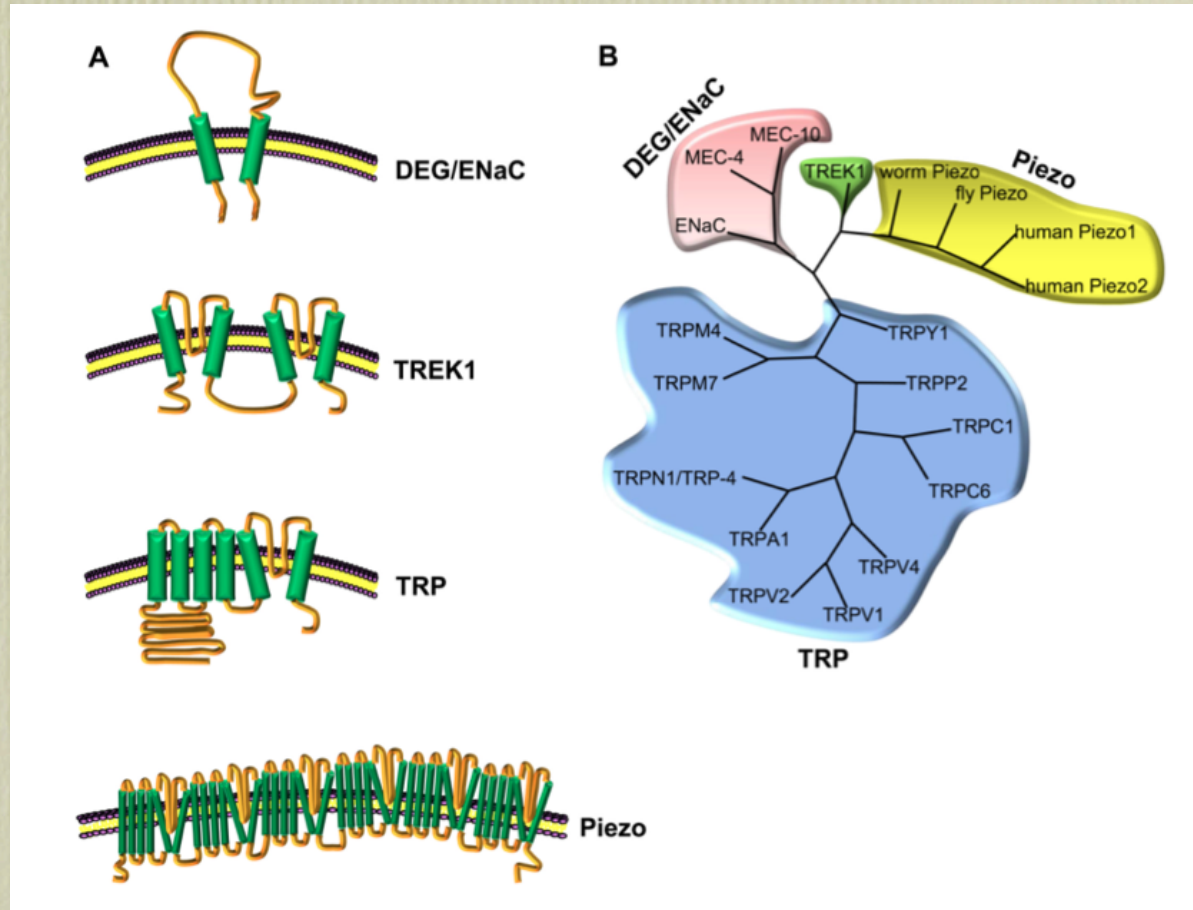
Sung Eun Kim[1], Bertrand Coste[1], Abhishek Chadha[1], Boaz Cook[1] & Ardem Patapoutian[1,2]

# Mechanosensitive Channels: In Touch with Piezo

**Mechanosensory transduction underlies touch, hearing and proprioception and requires mechanosensitive channels that are directly gated by forces; however, the molecular identities of these channels remain largely elusive. A new study has identified Piezo1 and Piezo2 as a novel class of mechanosensitive channels.**

NOT ONLY TRPs !

- Expressed in several eukaryotes (not yeast)
- 24-26 TM domains
- mpiezo1 tetramer ($1.2\text{-}10^6$ Da)
- Non-selective cationic channels sensitive to ruthenium red and Gd
- Fast inactivation
- Expressed DRG neurons

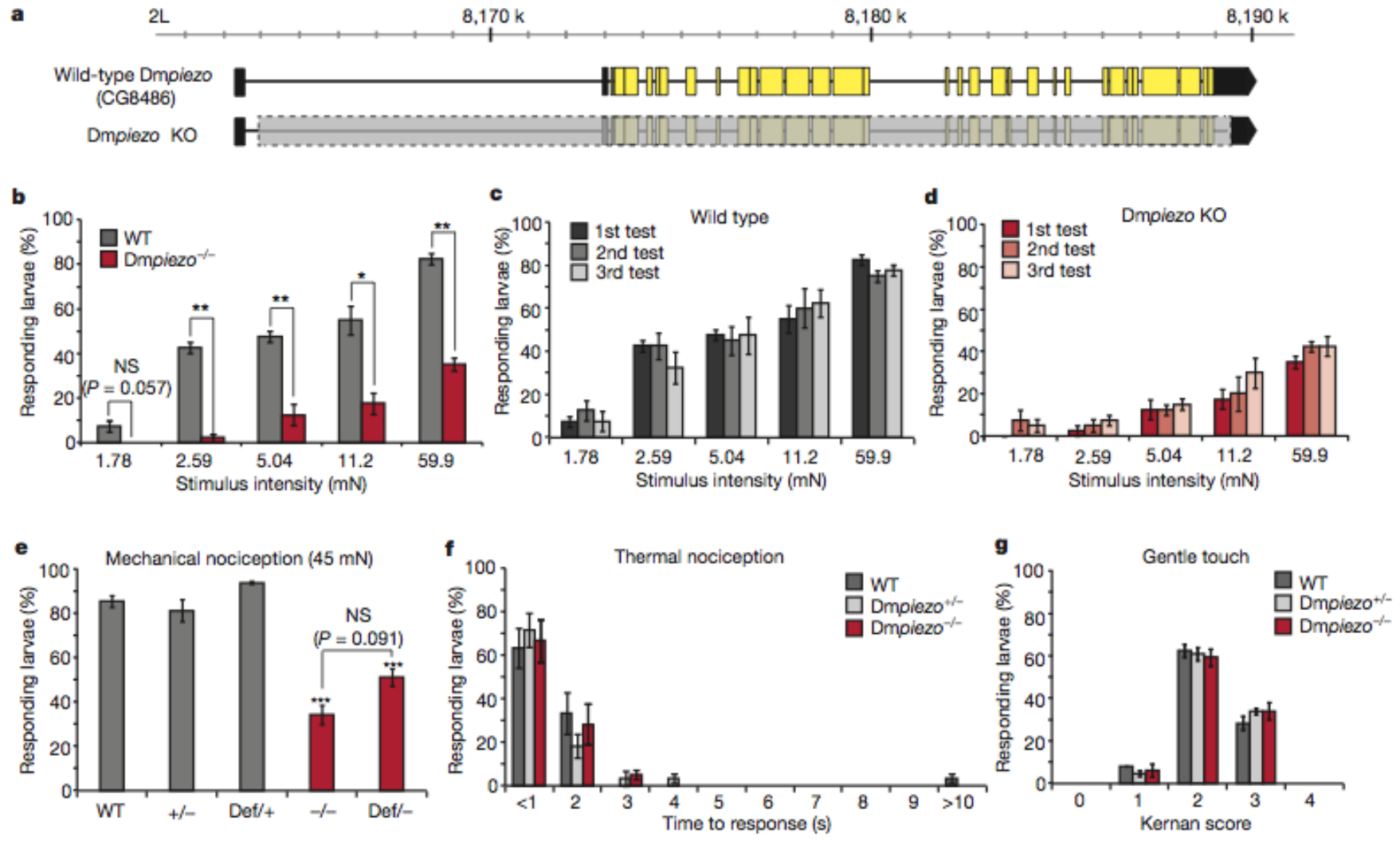


LETTER

doi:10.1038/nature10801

# The role of *Drosophila* Piezo in mechanical nociception

Sung Eun Kim[1], Bertrand Coste[1], Abhishek Chadha[1], Boaz Cook[1] & Ardem Patapoutian[1,2]



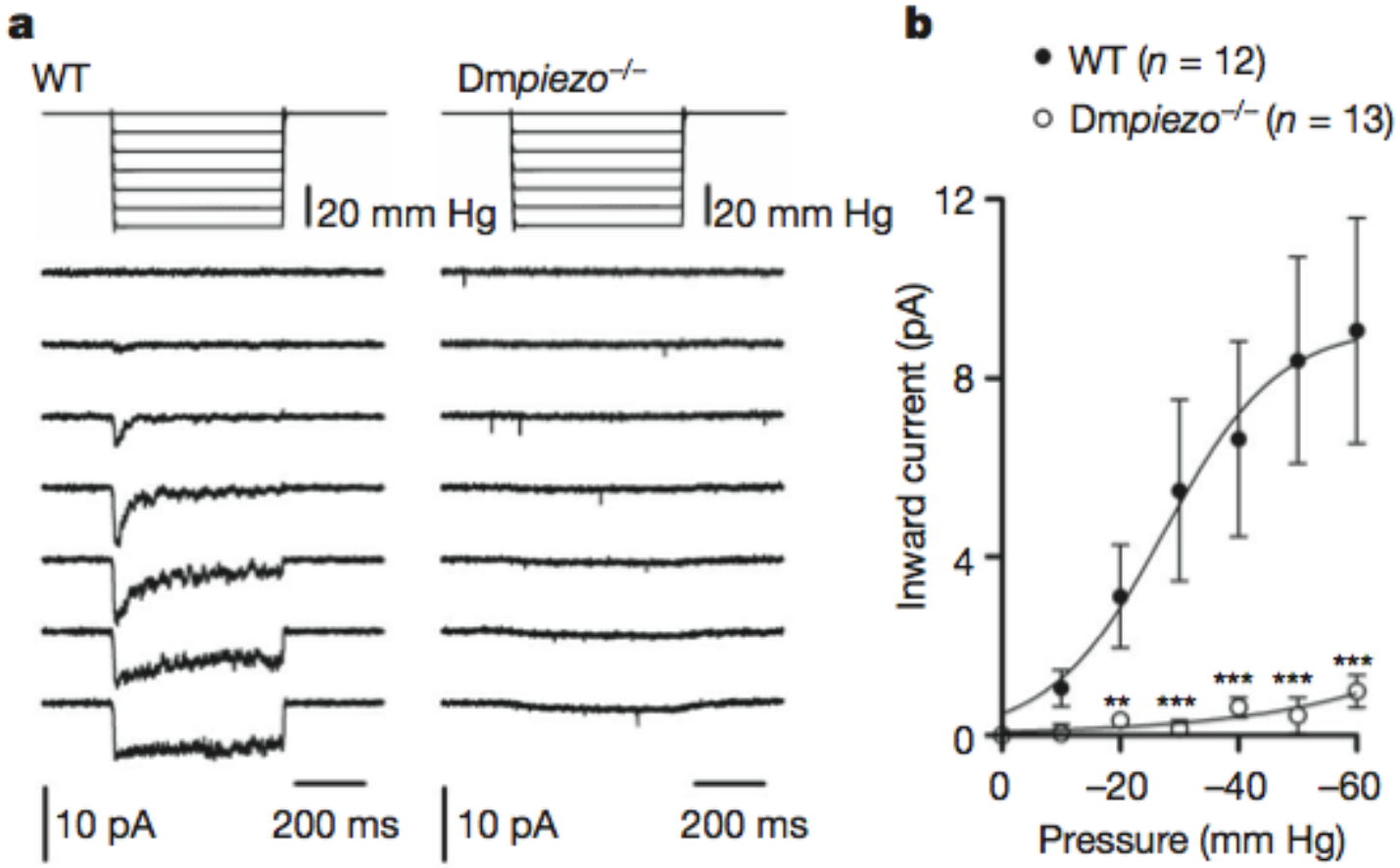



**Figure 3 | Dm*piezo* mediates mechanically activated currents in *ppk*-positive neurons.** **a**, Representative currents elicited by negative pipette pressure (0 to −60 mm Hg, Δ10 mm Hg) in cell-attached configuration at −80 mV in wild type (left) and Dm*piezo*$^{-/-}$ (right). **b**, Average peak current–pressure relationship of stretch-activated currents in wild type ($n = 12$ cells) and Dm*piezo*$^{-/-}$ ($n = 13$ cells). Data points are mean ± s.e.m. fitted with a Boltzmann equation. $^{**}P < 0.01$, $^{***}P < 0.001$, Mann–Whitney test.