# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities




WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

## Interested in publishing with us?
## Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

# The Glial Cell of Human Cutaneous Sensory Corpuscles: Origin, Characterization, and Putative Roles

*Ramón Cobo, Yolanda García-Mesa, Jorge García-Piqueras, Jorge Feito, José Martín-Cruces, Olivia García-Suárez and José A. Vega*

## Abstract

Sensory corpuscles of human skin are structures located at the peripheral end of the mechanoreceptive neurons and function as low-threshold mechanoreceptors (LTMRs). In its structure, in addition to the axon, there are glial cells, not myelinating, that are organized in different ways according to the morphotype of sensitive corpuscle, forming the so-called laminar cells of Meissner's corpuscles, the laminar cells of the inner core of Pacinian corpuscles, or cells of the inner core in Ruffini's corpuscles. Classically the glial cells of sensory corpuscles have been considered support cells and passive in the process of mechanotransduction. However, the presence of ion channels and synapses-like systems between them and the axon suggests that corpuscular glial cells are actively involved in the transformation of mechanical into electrical impulses. This chapter is an update on the origin, development, cytoarchitecture, and protein profile of glial cells of sensitive corpuscles especially those of human glabrous skin.

**Keywords:** terminal glial cells, lamellar cells, Meissner corpuscles, Pacinian corpuscles, human

## 1. Introduction

The human skin is supplied by sensory nerve fibers which form in the dermis complexes sensory structures known collectively as sensory corpuscles [1]. These sensory formations are connected to nerve fibers originating from intermediate- or large-sized neurons (see for a review [2]) that work as low-threshold mechanoreceptors (LTMRs). LTMRs are classified as Aβ, Aδ, or C based on their degree of myelination and action potential conduction velocities [2, 3] and functionally fall into two categories: rapidly adapting (RA) and slowly adapting (SA) mechanoreceptors, which each have two variants, type I and type II [4, 5]. RAI and RAII mechanoreceptors correspond to Meissner and Pacinian corpuscles, respectively; SAI mechanoreceptors are the Merkel cell-neurite complexes, and SAII mechanoreceptors are the dermal Ruffini's corpuscles [1]. This diversity of LTMRs suggests

differentiated ability to detect and discriminate diverse stimuli in relation to their connectivity to central nervous system nuclei [1, 2, 6, 7].

The peripheral processes of Aβ axons contact in the skin with specialized epithelial cells, i.e., Merkel cells to form Merkel cell-neurite complexes, or with glial Schwann-like cells to form a part of the sensory corpuscles, i.e., Meissner corpuscles, Ruffini's corpuscles, and Pacinian corpuscles [1, 3, 8, 9]. Structurally, the cutaneous sensory corpuscles consists of a dendritic zone (the extreme tip of the peripheral process of an Aβ LTMR), surrounded by nonmyelinating glial cells variably arranged, and both are surrounded by a more or less developed capsule of endoneurial/perineurial cells [9–13]. Filling the spaces among cells, there is a chemically complex extracellular matrix, sometimes organized as a basal lamina [14–17]. So, periaxonic cells that form sensory corpuscles are continuous with the cells of nerve trunks, demonstrating a close relationship between the components of nerves and sensory corpuscles [11].

The peripheral tip of the sensory Aβ axon is always coated by glial cells. These cells constitute a special population of peripheral glial cells denominated terminal glial cells or skin end-organ glia [18], but habitually they are a neglected entity in books and reviews in the topic and are not mentioned among peripheral glial cell types [19]. However, emerging data strongly suggest that glial cells of the sensory corpuscles play key roles in mechanotransduction.

In this review we summarize the current knowledge about the origin and development, cytoarchitecture, immunohistochemical profile, and putative roles of glial cells in sensory corpuscles especially in the genesis of mechanical potential action.

## 2. Origin of the sensory corpuscles glial cells

The glial cells forming a part of the cutaneous sensory corpuscles are regarded as nonmyelinating Schwann-related cells and share some molecular markers. During embryonic development, peripheral glial progenitors originated in the neural crest (NC) cells contact the surface of developing axons and differentiate into Schwann cell precursors (SCPs) [20]. Subsequently, SCPs originate immature Schwann cells (ISCs) that later generate adult peripheral glial cells types, including the glia found in cutaneous sensory end organs [18].

Neural crest boundary cells (NC-BCs) can also generate peripheral glia during embryonic development [21] which in the presence of neuregulins (NRs) are able to differentiate into SCPs [22] and then into ISCs before maturing into myelinating and nonmyelinating Schwann cells [23]. The immediate progeny of NC-BCs, together with other nerve-associated SCPs, migrate along the sensory nerves toward the skin to give rise to highly specialized glial cells (denominated specific sensory nerve fiber-associated glia in the skin) associated to nerve endings in the epidermis although these cells are distinct to the specialized glial subtype found within the cutaneous sensory corpuscles [24]. But according to Etxaniz and coworkers [25], in the skin BC derivatives give rise to at least three glial populations: Schwann cells (mainly nonmyelinating) associated with subcutaneous and dermal nerves and two types of terminal Schwann cells, associated with lanceolate endings or free nerve endings. It can be speculated that the glial cells of sensory corpuscles can derivate of that first type.

Furthermore, NC-derived stem cells are retained postnatally in the skin and peripheral nerves after differentiation the SCPs cells and do not completely lost multipotentiality [26] retaining certain characteristics of NC cells and remaining multipotent [27, 28].

In view of the diverse possible origins of the glial cells of sensory corpuscles, it is not possible to know exactly the cells from which they come. Probably these cells are a consequence of combinatory distinct molecular signatures and local factors during development [18].

## 3. Development of the sensory corpuscles glial cells

Sensory axons are critical inducing the development of sensory corpuscles, and reciprocal interactions between axons and target cells, especially peripheral glial cells, seem to initiate their morphogenesis [29]. SCPs comigrate with growing axons in peripheral nerves upon axonal signals such as NRG-1 [30, 31].

Some of the molecules that interplay those axon-peripheral glial cells relationships in developing sensory corpuscles are now also known. The neurotrophin (NT) family of growth factors is involved in the development of mechanoreceptors controlling the development of mechanosensory neurons. Mice lacking TrkB and its ligand brain-derived neurotrophic factor (BDNF), but not NT-4, do not develop Meissner-like corpuscles [32–34], whereas overexpression of BDNF [35] and NT-4 [36] leads to an increase in the size and density of those corpuscles. The role of NTs in regulating development of Pacinian corpuscles is more complex and controversial since multiple NT-Trk signals participate, resulting in a reduction of the number of Pacinian corpuscles in mice deficient for BDNF and NT-3 and TrkA and TrkB [37]. However, Pacinian corpuscles of postnatal TrkB-deficient mice were found largely normal [33, 38]. ER81 is also present in developing murine Pacinian corpuscles [39], and in the absence of this transcription factor, Pacinian corpuscles do not form because their afferents do not survive. NRG-1 interacts with ErbB2/ErbB3 receptors on Schwann cell lineage and is broadly involved in Schwann cell development [40]. Recently, it has been demonstrated that a RET-ER81-NRG-1 signaling pathway promotes axon communication with nonmyelinating Schwann cells. The glial cells forming inner core of murine Pacinian corpuscles display NRG receptors erbB2, erbB3, and erbB4, whereas the central axon is immunoreactive for NRG-1 and ablating Ret and Nrg-1 in mechanosensory neurons results in the absence of Pacinian corpuscles, while Meissner's corpuscles were unaffected [41–43]. Interestingly, the dependence of the corpuscular glial cells from the axons continues during adult life at least for the expression of some antigens. After denervation, glial cells of Meissner-like corpuscles lack some specific markers [44, 45] and strongly decrease the expression of TrkA [46], and the glial cells forming the inner core of Pacinian corpuscles undergo apoptotic death that can be prevented by administration of glial growth factor 2 [47].

In addition to the axon-glial cells interactions, probably local molecules participate in the development of sensory corpuscles including growth factors [48, 49], β-arrestin-1 [50], semaphorins [49, 51, 52], ankyrin-B [53], and also mechanical signals [54].

NC cells, SCPs, and ISCs share some markers (neuregulin receptors ErbB2 and ErbB3, L1, nestin, vimentin). Two markers used for labeling of mature Schwann cells, i.e., S100 protein and vimentin, are also present in ISCs but are absent or expressed at much lower levels in PSCs [30, 55]. Using these proteins as ISCs or mature Schwann and Schwann-related cell markers, we have determined the timetable of the development of sensory corpuscles. In murine Meissner-like corpuscles start to express immunoreactivity for S100 protein by postnatal day 7 (Pd7), vimentin by Pd12, and $p75^{LNGFR}$ (a marker for peripheral glia too) transitory from Pd7 to Pd19. Pacinian corpuscles show S100 protein in the inner core at Pd7, whereas vimentin starts expression at Pd19 and later [56]. In human, the first evidence

of Pacinian corpuscles was at 13 weeks of estimated gestational age (wega). At this time, and until 16 wega, the S100 protein positive from one or two layers of rounded cells then (16–18 wega) become flattened and show lamellar organization, thus originating a primitive inner core. Thereafter, between 20 and 24 wega, the S100 protein-positive cells emitted cytoplasmic expansions that invaded the outer region of the corpuscle forming a network. In the period between 24 and 36 wega, the edge of the inner core was still not totally defined until the fourth month of life, when the lamellae forming it become strongly packed and the inner core clefts are clearly distinguished. During development of Pacinian corpuscles, expression of vimentin started shortly later than that of S100P and did not vary along lifespan. On the other hand, at 23 wega hook-shaped axonal profiles are identified in the dermal papillae, but S100P-positive cells reach this place at 33 wega. By 36–40 wega, the S100 protein-positive lamellar cells of incipient Meissner's corpuscles can become progressively flattened, and around these cells also express vimentin, but their definite and typical arrangement occurs in the first weeks of life. Along the first semester of life, the S100P-positive cells become definitively flattened, reaching the adult morphology around 8 months [57].

## 4. Cytoarchitecture of glial cells in the different morphotypes of cutaneous sensory corpuscles

The arrangement of terminal glial cells in the different morphotypes of sensory corpuscles varies from one to another, either irregularly (Krause and Ruffini's corpuscles), regularly (Meissner corpuscles), or forming the lamellar system of the inner core (Pacinian corpuscles) [8, 9].

In Meissner's corpuscles, the terminal glial cells are currently denominated lamellar cells.

The organization of the lamellar has a typical flattened appearance due to the horizontal lamelation that form stacks of lamellae separated by axon branches [8, 58]. Habitually the nuclei of the cells are at the periphery of the corpuscle and are total or partially covered by a CD34-positive capsule of endoneurial origin [13] (**Figure 1**).

The inner core is the zone of Pacinian corpuscles that lies between the axon and the intermediate layer and consists of tightly packed lamellae of peripheral glial cells which are diversely organized in the preterminal, terminal, and ultraterminal zones of the corpuscle. In the preterminal zone, the axon is still covered by the myelin sheath; the terminal zone characteristically has a bilateral symmetric organization; and in the ultraterminal zone, glial cells lose bilaterally. The flattened lamellar cells forming the terminal zone of the inner core have the nuclei lying in the outer core of the inner core itself. The lamellar cells project processes from the outer margin into the inner core, and flattening give the appearance of concentric layers of lamellae arranged in bilateral symmetry, hemilamellae, and the tips of the lamellae are separated by two clefs that run along the entire length of the axon until the ultraterminal zone. Interestingly the lamellae of the inner core have numerous gap (tight) junctions as well as desmosome-like junctions (see for a review [8, 9, 59]) (**Figure 2**).

Regarding Ruffini's corpuscles, the glial cells forming the inner core have an irregular distribution within the capsule with variable relationship with the dendritic zone of the axon tip [8] (**Figure 3**).

The terminal glial cells forming the inner core of Pacinian corpuscles and the lamellar cells of the Meissner ones are covered by a basal lamina, and around there is a complex extracellular matrix, whose composition in now rather well known [14–17, 60].

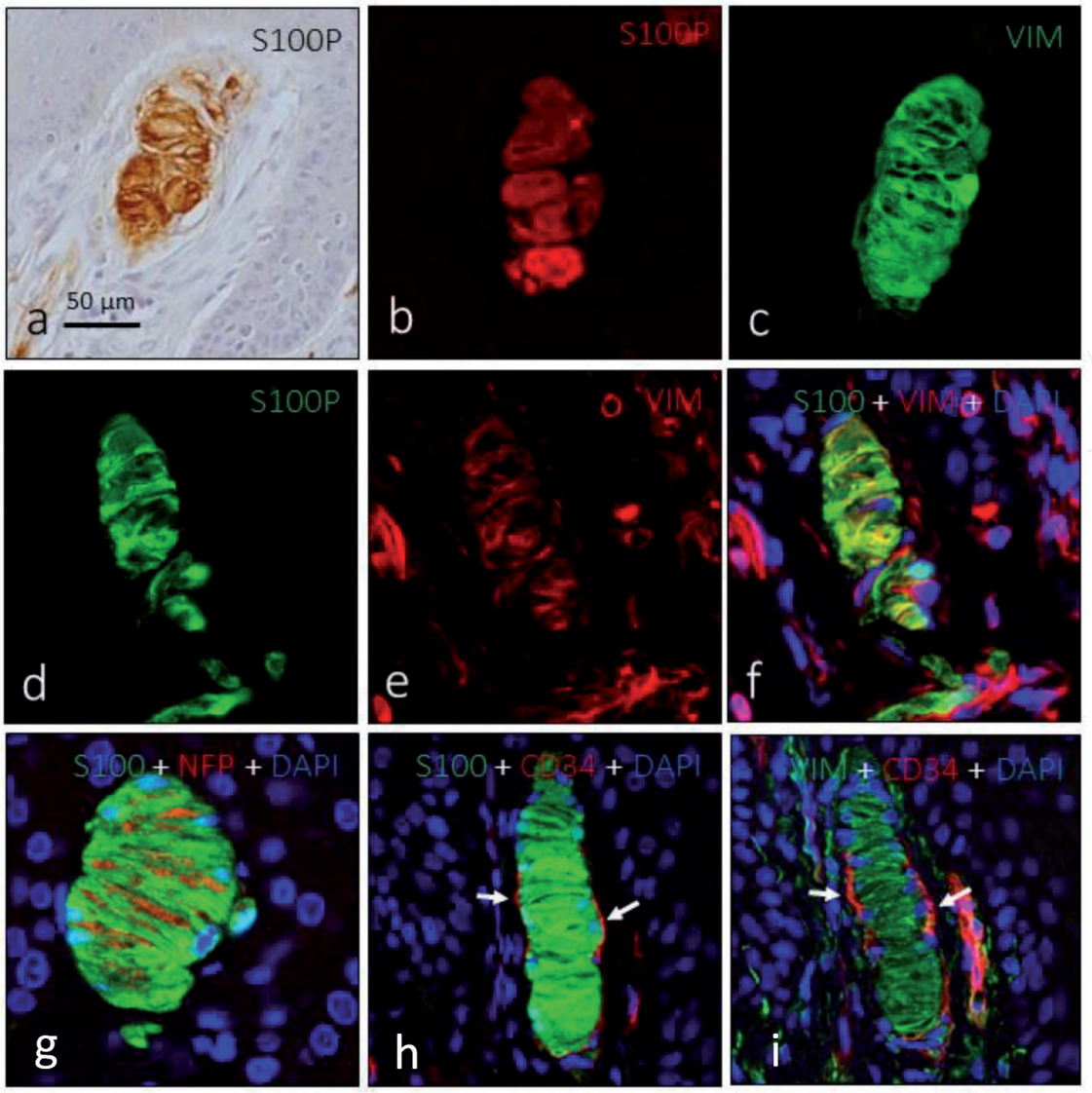



**Figure 1.**
*Immunohistochemical localizacion of S100 protein (S100P; a, b, g, h), vimentin (VIM; c, e, i), neurofilament proteins (red in g) and CD34 (red in h, i) in Meissner'w corpuscles. The lamellar cells display intense and selective cytoplasmic S100P and VIM which are colocalized (d-f). The lamellar are in close contact with the axon (red fluorescence in g) and an endoeneurial capsule (red fluorescence in h and i).*

## 5. Immunohistochemical profile

### 5.1 Cytoskeletal proteins and general markers

Glial fibrillary acidic protein (GFAP) is theoretically the intermediate filament protein filling the cytoplasm of Schwann and Schwann-related cells forming cutaneous sensory corpuscles. However, most authors consider that peripheral glial cells express vimentin as the main intermediate filament protein [61]. In agreement with this assumption, GFAP was always absent from rat [62] and human [63] cutaneous sensory corpuscles. In contrast, the cytoplasm of the peripheral glial cells of sensory corpuscles expresses vimentin [62–64]. However, GFAP immunoreactivity was detected in the innermost lamellae of the inner core of feline Pacinian corpuscles [65] and human pancreatic Pacinian corpuscles [66].

The $Ca^{2+}$-binding proteins represent one of the physiological mechanisms for maintaining intracellular $Ca^{2+}$ homeostasis [67]. Some of these proteins have been

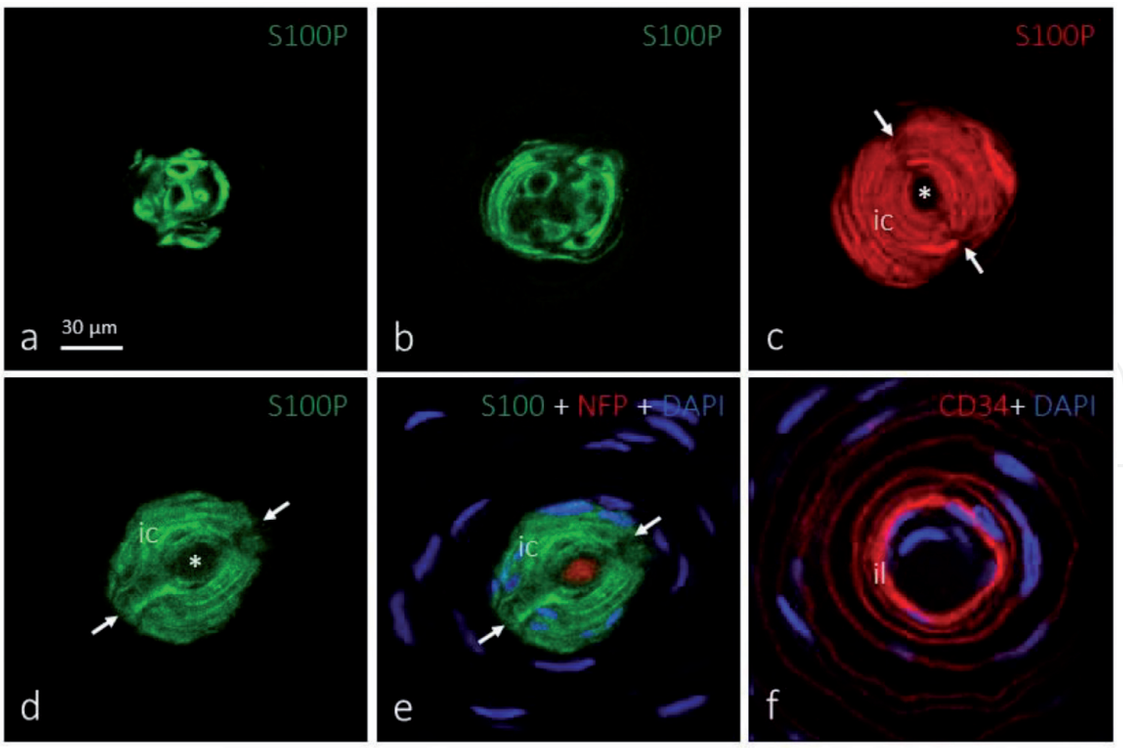



**Figure 2.**
*Immunohistochemical localization of S100 protein (S100; a-e), neurofilament protein (NFP; red fluorescence in e) and CD34 (red fluorescence in f). The glial cells forming the central zone of the inner core are characteristically arranged into two symmetrical hemilamellar systems separated by clefts (arrows in c-e) whereas in the ultraterminal zone of the inner core are irregularly disposed (a, b). The inner most lamellae of the inner core is in close contact with the axon (e) while de outer most lamellae is closely related with the so-called intermediate layer. ic: inner core; il: intermediate layer; asterisks indicate the zone occupied by the axon.*

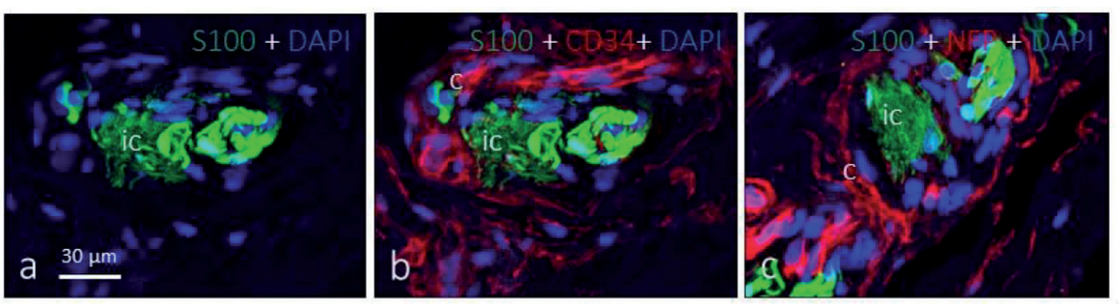



**Figure 3.**
*Immunohistochemical localization of S100 protein (a-c) and CD34 in human cutaneous Ruffini's corpuscles. The glial cells are irregularly arranged and display a strong S100P immunofluorescence (a-c). The capsule of these corpuscles is CD34 positive suggesting and endoneurial origin (b, c). c: capsule; ic: inner core.*

found in the glial cells of cutaneous sensory corpuscles, most of them belonging to the so-called "EF-hand" family. They include S100 protein, calbindin D28k, parvalbumin, and calretinin (sensory corpuscles) [10, 68, 69].

## 5.2 Growth factors and growth factor receptors

As far as we know, the only growth factors detected in the glial cells of sensory corpuscles are TGF-β in the lamellar cells of rat Meissner corpuscles [70] and BDNF in the inner core cells of digital Pacinian corpuscles of *Macaca fascicularis* [71]. However, the glial cells of sensory corpuscles display a wide range of receptors for different growth factors. Epidermal growth factor receptor was detected in the lamellar and the inner core cells of human Meissner and Pacinian corpuscles,

respectively [72], as well as low- and high-affinity receptors for NTs including $p75^{NNR}$ [73–76], TrkA [77], and TrkB [78, 79]. TGF-β receptors RI and RII are also present in the inner core lamellar cells of cat Pacinian corpuscles and the lamellar cells of Meissner corpuscles [70].

## 6. Are the corpuscular glial cells accessory cells or active cells?

### 6.1 The GABA-ergic/glutamatergic system in Pacinian corpuscles

The inner core of Pacinian corpuscles expresses immunoreactivity for glutamate receptors, vesicular-glutamate transporters, and the synaptic proteins synaptobrevin (VAMP2) and SNAP-23. Moreover, inner core cells release neurotransmitters (glutamate, GABA) when they are stimulated by glutamate, ATP, or even by mechanical motion [80]. This implies "synaptic-like" interaction between the axon and the glial cells of Pacinian corpuscles. This hypothesis, postulated by Pawson and co-workers [80, 81], argues that: "action potentials in response to dynamic stimuli are due to depolarization of the axon by cations entering mechano-gated channels that are opened due to mechanical motion; however, action potentials in the static portion of the Pacinian corpuscle rapidly adapting response are due to glutamatergic excitation, which are then inhibited by GABA released from the modified Schwann cells of the inner core." These results suggest that in the Pacinian corpuscles, GABA emanating from the capsule inhibits glutamate excitation (stemming either from the neurite itself or from the capsule), leading to a glial-neuronal "mechanochemical," rather than solely mechanical, RA response to sustained pressure. These elegant and attractive results should be confirmed in other mechanoreceptors and in different vertebrate species.

### 6.2 Ion channels

In the past, investigators proposed that the response of sensory corpuscles could be explained entirely by the mechanical properties periaxonic cells, especially the capsule. Then the discovery that some ion channels are gated by mechanical forces (mechanosensitive ion channels) suggests that mechanotransduction occurs through the activation of ion channels along the somatosensory neurons that reach the skin. The opening of these channels consent the entry of ions within the axon to produce the mechanotransduction [82–86]. Thus, deformations in the membrane of different cells that form the mechanoreceptors (i.e., axon, glial cells, and endoneurial and/or perineurial fibroblast) trigger the opening of mechanosensitive ion channels that transduce mechanical energy into electrical activity. Consistently, the cells forming the mechanoreceptors are thought to express ion channels activated by force or displacement to act as mechanodetectors and/or mechanotransducers. Thus, mechanotransduction can be defined as the conversion of a mechanical stimulus into an electrical signal, and in the sensory corpuscles, the first step of mechanotransduction takes place [87, 88].

Numerous types of mechanically gated ion channels were found in vertebrate sensory corpuscles, but most of them were localized in the axon. Nevertheless, evidence exists that some of them are also present in the glial cells. The inner core of murine [89] and human [90] Pacinian corpuscles displays immunoreactivity for ASIC2, a member of the acid-sensing ion channels included in the degenerin/epithelial $Na^+$ channel superfamily. In a subpopulation of human Meissner corpuscles, the lamellar cells also show ASIC2 immunoreactivity [91]. Some members of the superfamily of the transient receptor potential (TRP) ion channels have been

detected in glial cells of sensory corpuscles. TRPV4 was detected in the lamellar cells of human Meissner corpuscles [92]. On the other hand, voltage-sensitive $Na^+$ channels (α-subunit type I and type II voltage-gated $Na^+$ channel) present in the inner core lamellae and the axon might participate in both transduction and action potential generation [93].

Based on the above data in addition to the hypothesis of voltage-gated and non-voltage-gated channels, a possible classical neurotransmission cannot be excluded for the genesis of the action potential in sensory corpuscles. In the process of touch sensation, a mechanical stimulus is converted into electrical activity in peripheral sensory neurons, and this conversion may occur through the activation of ion channels that gate in response to mechanical stimuli.

## 7. Concluding remarks

The glial cells of the sensory corpuscles form a glial subpopulation, highly differentiated and with important functions in the mechanotransduction process that has been repeatedly forgotten in studies on peripheral glia. Its origin is not known exactly, and they could come from cells of the neural crest or the boundary cap cells. However, the chronology of its arrival and organization within the corpuscles has recently been established, as well as their interdependence with sensory axons. In the last decade, some mechano-gated ion channels have been discovered in corpuscular glial cells. This fact associated with the demonstration of a GABA-ergic/glutamatergic neurotransmission system in the Pacinian corpuscles suggests that the glial cells of the sensory corpuscles are not support cells but have an active role in the mechanotransduction process. Nevertheless, whether or not this occurs only in Pacinian corpuscles or in all sensory corpuscles remains to be demonstrated.

## Acknowledgements

This study was supported in part by a grant from Gerencia Regional de Salud de Castilla y León (GRS 1615/A/17). YG-M was supported by a grant "Severo Ochoa" from the Government of the Principality of Asturias (Ref. BP17-044). The authors thank Dr. Marta Guervos (Servicios Comunes de Investigación, Microscopia Confocal, Universidad de Oviedo) and Marta Sánchez-Pitiot (Grupo de Histopatología Molecular, Instituto Universitario de Oncología del Principado de Asturias) for their technical assistance.

*DOI: http://dx.doi.org/10.5772/intechopen.91815*

IntechOpen

## Author details

Ramón Cobo[1], Yolanda García-Mesa[1], Jorge García-Piqueras[1], Jorge Feito[1,2,3], José Martín-Cruces[1], Olivía García-Suárez[1] and José A. Vega[1,4*]

1 Departamento de Morfología y Biología Celular, Grupo SINPOS, Universidad de Oviedo, Oviedo, Spain

2 Departamento de Anatomía e Histología Humanas, Universidad de Salamanca, Spain

3 Servicio de Anatomía Patológica, Complejo Hospitalario, Universitario de Salamanca, Salamanca, Spain

4 Facultad de Ciencias de la Salud, Universidad Autónoma, Santiago, Chile

*Address all correspondence to: javega@uniovi.es

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

## References

[1] Zimmerman A, Bai L, Ginty DD. The gentle touch receptors of mammalian skin. Science. 2014;**346**:950-954

[2] Abraira VE, Ginty DD. The sensory neurons of touch. Neuron. 2013;**79**:618-639

[3] Rice FL, Albrecht PJ. Cutaneous mechanisms of tactile perception: Morphological and chemical organization of the innervation to the skin. In: Somatosensation GE, Kaas JA, editors. The Senses: A Comprehensive Reference. Vol. 6. Amsterdam: Elsevier; 2008. pp. 1-31

[4] Jones LA, Smith AM. Tactile sensory system: Encoding from the periphery to the cortex. Wiley Interdisciplinary Reviews. Systems Biology and Medicine. 2014;**6**:279-287

[5] Olson W, Dong P, Fleming M, Luo W. The specification and wiring of mammalian cutaneous low-threshold mechanoreceptors. Wiley Interdisciplinary Reviews: Developmental Biology. 2016;**5**:389-404

[6] Oaklander AL, Siegel SM. Cutaneous innervation: Form and function. Journal of the American Academy of Dermatology. 2006;**53**:1027-1037

[7] McGlone F, Reilly D. The cutaneous sensory system. Neuroscience and Biobehavioral Reviews. 2010;**34**:148-159

[8] Munger BL, Ide C. The structure and function of cutaneous sensory receptors. Archives of Histology and Cytology. 1988;**51**:1-34

[9] Zelena J. Nerves and Mechanoreceptors: The Role of Innervation in the Development and Maintenance of Mammalian Mechanoreceptors. New York: Chapman & Hall; 1994

[10] Vega JA, Haro JJ, Del Valle ME. Immunohistochemistry of human cutaneous Meissner and Pacinian corpuscles. Microscopy Research and Technique. 1996;**34**:351-361

[11] Vega JA, García-Suárez O, Montaño JA, Pardo B, Cobo JM. The Meissner and Pacinian sensory corpuscles revisited: New data from the last decade. Microscopy Research and Technique. 2009;**72**:299-309

[12] García-Piqueras J, García-Suárez O, Rodríguez-González MC, Cobo JL, Cabo R, Vega JA, et al. Endoneurial-CD34 positive cells define an intermediate layer in human digital Pacinian corpuscles. Annals of Anatomy. 2017;**211**:55-60

[13] García-Piqueras J, Cobo R, Cárcaba L, García-Mesa Y, Feito J, Cobo J, et al. The capsule of human Meissner corpuscles: Immunohistochemical evidence. Journal of Anatomy. 2020. DOI: 10.1111/joa.13139

[14] Dubový P, Bednárová J. The extracellular matrix of rat pacinian corpuscles: An analysis of its fine structure. Anatomy and Embryology. 1999;**200**:615-623

[15] García-Piqueras J, Carcaba L, García-Mesa Y, Feito J, García B, Viña E, et al. Chondroitin sulfate in human cutaneous Meissner and Pacinian sensory corpuscles. Anatomical Record (Hoboken, N.J.). 2019;**302**:325-331

[16] García-Piqueras J, García-Mesa Y, Feito J, García B, Quiros LM, Martín-Biedma B, et al. Class I and class II small leucine-rich proteoglycans in human cutaneous pacinian corpuscles. Annals of Anatomy. 2019;**224**:62-72

[17] García-Piqueras J, García-Suárez O, García-Mesa Y, García-Fernandez B, Quirós LM, Cobo R, et al. Heparan

sulfate in human cutaneous Meissner's and Pacinian corpuscles. Anatomical Record (Hoboken, N.J.). 2020. DOI: 10.1002/ar.24328

[18] Kastriti ME, Adameyko I. Specification, plasticity and evolutionary origin of peripheral glial cells. Current Opinion in Neurobiology. 2017;**47**:196-202

[19] Jessen KR, Mirsky R. Schwann cell precursors; multipotent glial cells in embryonic nerves. Frontiers in Molecular Neuroscience. 2019;**12**:69

[20] Furlan A, Adameyko I. Schwann cell precursor: A neural crest cell in disguise? Developmental Biology. 2018;**444**(Suppl 1):S25-S35

[21] Maro GS, Vermeren M, Voiculescu O, Melton L, Cohen J, Charnay P, et al. Neural crest boundary cap cells constitute a source of neuronal and glial cells of the PNS. Nature Neuroscience. 2004;**7**:930-938

[22] Petersen J, Adameyko I. Nerve-associated neural crest: Peripheral glial cells generate multiple fates in the body. Current Opinion in Genetics & Development. 2017;**45**:10-14

[23] Aquino JB, Hjerling-Leffler J, Koltzenburg M, Edlund T, Villar MJ, Ernfors P. In vitro and in vivo differentiation of boundary cap neural crest stem cells into mature Schwann cells. Experimental Neurology. 2006;**198**:438-449

[24] Gresset A, Coulpier F, Gerschenfeld G, Jourdon A, Matesic G, Richard L, et al. Boundary caps give rise to neurogenic stem cells and terminal glia in the skin. Stem Cell Reports. 2015;**5**:278-290

[25] Etxaniz U, Pérez-San Vicente A, Gago-López N, García-Dominguez M, Iribar H, Aduriz A, et al. Neural-competent cells of adult human dermis belong to the Schwann lineage. Stem Cell Reports. 2014;**3**:774-788

[26] Dyachuk V, Furlan A, Shahidi MK, Giovenco M, Kaukua N, Konstantinidou C, et al. Neurodevelopment. Parasympathetic neurons originate from nerve-associated peripheral glial progenitors. Science. 2014;**345**:82-87

[27] Widera D, Heimann P, Zander C, Imielski Y, Heidbreder M, Heilemann M, et al. Schwann cells can be reprogrammed to multipotency by culture. Stem Cells and Development. 2011;**20**:2053-2064

[28] Calavia M, Viña E, Menéndez-González M, López-Muñiz A, Alonso-Guervós M, Cobo J, et al. Evidence of nestin-positive cells in the human cutaneous Meissner and Pacinian corpuscles. CNS & Neurological Disorders Drug Targets. 2012;**11**:869-877

[29] Saxod R. Ontogeny of the cutaneous sensory organs. Microscopy Research and Technique. 1996;**34**:313-333

[30] Jessen KR, Mirsky R. The origin and development of glial cells in peripheral nerves. Nature Reviews. Neuroscience. 2005;**6**:671-682

[31] Nave KA, Salzer JL. Axonal regulation of myelination by neuregulin 1. Current Opinion in Neurobiology. 2006;**16**:492-500

[32] IchikawaH,MatsuoS,Silos-SantiagoI, Sugimoto T. Developmental dependency of Meissner corpuscles on trkB but not trkA or trkC. Neuroreport. 2000;**11**:259-262

[33] González-Martínez T, Germanà GP, Monjil DF, Silos-Santiago I, de Carlos F, Germanà G, et al. Absence of Meissner corpuscles in the digital pads of mice lacking functional TrkB. Brain Research. 2004;**1002**:120-128

[34] González-Martínez T, Fariñas I, Del Valle ME, Feito J, Germanà G, Cobo J, et al. BDNF, but not NT-4, is necessary for normal development of Meissner corpuscles. Neuroscience Letters. 2005;**377**:12-15

[35] LeMaster AM, Krimm RF, Davis BM, Noel T, Forbes ME, Johnson JE, et al. Overexpression of brain-derived neurotrophic factor enhances sensory innervation and selectively increases neuron number. The Journal of Neuroscience. 1999;**19**:5919-5931

[36] Krimm RF, Davis BM, Noel T, Albers KM. Overexpression of neurotrophin 4 in skin enhances myelinated sensory endings but does not influence sensory neuron number. The Journal of Comparative Neurology. 2006;**498**:455-465

[37] Sedý J, Szeder V, Walro JM, Ren ZG, Nanka O, Tessarollo L, et al. Pacinian corpuscle development involves multiple Trk signaling pathways. Developmental Dynamics. 2004;**231**:551-563

[38] Pérez-Piñera P, García-Suarez O, Germanà A, Díaz-Esnal B, de Carlos F, Silos-Santiago I, et al. Characterization of sensory deficits in TrkB knockout mice. Neuroscience Letters. 2008;**433**:43-47

[39] Sedý J, Tseng S, Walro JM, Grim M, Kucera J. ETS transcription factor ER81 is required for the Pacinian corpuscle development. Developmental Dynamics. 2006;**235**:1081-1089

[40] Birchmeier C, Nave KA. Neuregulin-1, a key axonal signal that drives Schwann cell growth and differentiation. Glia. 2008;**56**:1491-1497

[41] Luo W, Enomoto H, Rice FL, Milbrandt J, Ginty DD. Molecular identification of rapidly adapting mechanoreceptors and their developmental dependence on ret signaling. Neuron. 2009;**64**:841-856

[42] Fleming MS, Li JJ, Ramos D, Li T, Talmage DA, Abe SI, et al. A RET-ER81-NRG1 signaling pathway drives the development of Pacinian corpuscles. The Journal of Neuroscience. 2016;**36**:10337-10355

[43] González-Martínez T, Germana A, Catania S, Cobo T, Ochoa-Erena FJ, de Carlos F, et al. Postnatal developmental changes in the expression of ErbB receptors in murine Pacinian cospucles. Neuroscience Letters. 2007;**420**:90-95

[44] Del Valle ME, Cabal A, Alvarez-Mendez JC, Calzada B, Haro JJ, Collier W, et al. Effect of denervation on lamellar cells of Meissner-like sensory corpuscles of the rat. An immunohistochemical study. Cellular and Molecular Biology. 1993;**39**:801-807

[45] Albuerne M, López S, Naves FJ, Martinez-Almagro A, Represa J, Vega JA. S100α and S100β proteins in human cutaneous sensory corpuscles: Effects of nerve and spinal cord injury. The Anatomical Record. 1998;**251**:351-359

[46] Márquez J, Pérez-Pérez M, Naves FJ, Vega JA. Effect of spinal cord and peripheral nerve injury on human cutaneous sensory corpuscles. An immunohistochemical study. Journal of the Peripheral Nervous System. 1997;**2**:49-59

[47] Kopp DM, Trachtenberg JT, Thompson WJ. Glial growth factor rescues Schwann cells of mechanoreceptors from denervation-induced apoptosis. The Journal of Neuroscience. 1997;**17**:6697-6706

[48] Schecterson LC, Bothwell M. Novel roles for neurotrophins are suggested by BDNF and NT-3 mRNA expression in developing neurons. Neuron. 1992;**9**:449-466

[49] Dontchev VD, Letourneau PC. Growth cones integrate signaling from multiple guidance cues. The Journal of Histochemistry and Cytochemistry. 2003;**51**:435-444

[50] Komori N, Neal J, Cain SD, Logan J, Wirsig C, Miller KE. Presence of beta-arrestin-1 immunoreactivity in the cutaneous nerve fibers of rat glabrous skin. Brain Research. 2003;**988**:121-129

[51] Curley JL, Catig GC, Horn-Ranney EL, Moore MJ. Sensory axon guidance with semaphorin 6A and nerve growth factor in a biomimetic choice point model. Biofabrication. 2014;**6**:035026

[52] McCormick AM, Jarmusik NA, Leipzig ND. Co-immobilization of semaphorin3A and nerve growth factor to guide and pattern axons. Acta Biomaterialia. 2015;**28**:33-44

[53] Engelhardt M, Vorwald S, Sobotzik JM, Bennett V, Schultz C. Ankyrin-B structurally defines terminal microdomains of peripheral somatosensory axons. Brain Structure & Function. 2013;**218**:1005-1016

[54] Koser DE, Thompson AJ, Foster SK, Dwivedy A, Pillai EK, Sheridan GK, et al. Mechanosensing is critical for axon growth in the developing brain. Nature Neuroscience. 2016;**19**:1592-1598

[55] Aquino JB, Sierra R. Schwann cell precursors in health and disease. Glia. 2018;**66**:465-476

[56] Albuerne M, De Lavallina J, Esteban I, Naves FJ, Silos-Santiago I, Vega JA. Development of Meissner-like and Pacinian sensory corpuscles in the mouse demonstrated with specific markers for corpuscular constituents. The Anatomical Record. 2000;**258**:235-242

[57] Feito J, García-Suárez O, García-Piqueras J, García-Mesa Y, Pérez-Sánchez A, Suazo I, et al. The development of human digital Meissner's and Pacinian corpuscles. Annals of Anatomy. 2018;**219**:8-24

[58] Vega JA, López-Muñiz A, Calavia MG, García-Suárez O, Cobo J, Otero J, et al. Clinical implication of Meissner's corpuscles. CNS & Neurological Disorders Drug Targets. 2012;**11**:856-868

[59] Bell J, Bolanowski S, Holmes MH. The structure and function of Pacinian corpuscles: A review. Progress in Neurobiology. 1994;**42**:79-128

[60] Vega JA, Esteban I, Naves FJ, del Valle ME, Malinovsky L. Immunohistochemical localization of laminin and type IV collagen in human cutaneous sensory nerve formations. Anatomy and Embryology. 1995;**191**:33-39

[61] Bianchini D, De Martini I, Cadoni A, Zicca A, Tabaton M, Schenone A, et al. GFAP expression of human Schwann cells in tissue culture. Brain Research. 1992;**570**:209-217

[62] Vega JA, Malinovsky L, Del Valle ME, Hernandez LC, Dubovy P, Perez-Casas A. Immunohistochemical study of sensory formations from the glabrous skin of the rat. Zeitschrift fur mikroskopisch-anatomische Forschung. 1990;**104**:779-787

[63] Haro JJ, Vega JA, Del Valle ME, Calzada B, Zaccheo D, Malinovsky L. Immunohistochemical study of sensory nerve formations in the human glabrous skin. European Journal of Morphology. 1991;**29**:271-284

[64] Vega JA, Del Valle ME, Haro JJ, Naves FJ, Calzada B, Uribelarrea R. The inner-core, outer-core and capsule of the human Pacinian corpuscles: An immunohistochemical study. European Journal of Morphology. 1994;**32**:11-18

[65] Vega JA, Dubovy P, del Valle-Soto ME, Hernandez LC, Perez-Casas A, Malinovsky L. Immunohistochemical study of Pacinian corpuscles using monoclonal antibodies for neurofilament protein, glial fibrillary acidic protein and S-100 protein. Cellular and Molecular Biology. 1989;**35**:627-633

[66] García-Suárez O, Calavia MG, Pérez-Moltó FJ, Alvarez-Abad C, Pérez-Piñera P, Cobo JM, et al. Immunohistochemical profile of human pancreatic pacinian corpuscles. Pancreas. 2010;**39**:403-410

[67] Andressen C, Bliimke I, Celio MR. Calcium-binding proteins: Selective markers of nerve cells. Cell and Tissue Research. 1993;**271**:181-208

[68] Del Valle ME, Vazquez E, Naves FJ, Represa JJ, Malinovsky L, Vega JA. Immunohistochemical localization of calcium-binding proteins in the human cutaneous sensory corpuscles. Neuroscience Letters. 1994;**168**:247-250

[69] Gonzalez-Martinez T, Perez-Piñera P, Díaz-Esnal B, Vega JA. S-100 proteins in the human peripheral nervous system. Microscopy Research and Technique. 2003;**60**:633-638

[70] Stark B, Carlstedt T, Risling M. Distribution of TGF-β, the TGF-β type I receptor and the R-II receptor in peripheral nerves and mechanoreceptors; observations on changes after traumatic injury. Brain Research. 2001;**913**:47-56

[71] Cabo R, Alonso P, San José I, Vázquez G, Pastor JF, Germanà A, et al. Brain-derived neurotrophic factor and its receptor TrkB are present, but segregated, within mature cutaneous Pacinian corpuscles of Macaca fascicularis. Anatomical record (Hoboken, N.J.). 2015;**298**:624-629

[72] Vega JA, Vazquez E, Naves FJ, Calzada B, Del Valle ME, Represa JJ. Expression of epidermal growth factor receptor (EGFr) immunoreactivity in human cutaneous nerves and sensory corpuscles. The Anatomical Record. 1994;**240**:125-130

[73] Ribeiro da Silva A, Kenigsberg RL, Cuello AC. Light and electron microscopic distribution of nerve growth factor receptor-like immunoreactivity in the skin of the rat lower lip. Neuroscience. 1991;**43**:631-646

[74] Vega JA, Del Valle ME, Haro JJ, Calzada B, Suarez-Garnacho S, Malinovsky L. Nerve growth factor receptor immunoreactivity in Meissner and Pacinian corpuscles of the human digital skin. The Anatomical Record. 1993;**236**:730-736

[75] Vega JA, Haro JJ, De Lamo A, Ordieres M, Del Valle ME, Calzada B. Distribution of low affinity nerve growth factor receptors (NGFr) immunoreactivity in the human digital skin. European Journal of Dermatology. 1993;**2**:509-516

[76] Schatteman GC, Langer T, Lanahn AA, Bothwell MA. Distribution of 75-kD low affinity nerve growth factor receptor in the primate peripheral nervous system. Somatosensory & Motor Research. 1993;**10**:415-432

[77] Vega JA, Vazquez E, Naves FJ, Del Valle ME, Calzada B, Represa JJ. Immunohistochemical localization of the high affinity NGF receptor (p140kDa-trkA) in adult dorsal root and sympathetic ganglia, and in the nerves and sensory corpuscles supplying digital skin. The Anatomical Record. 1994;**240**:579-588

[78] Stark B, Risling M, Carlstedt T. Distribution of the neurotrophin receptors p75 and trkB in peripheral

mechanoreceptors; observations on changes after injury. Experimental Brain Research. 2001;**136**:101-107

[79] Calavia MG, Feito J, López-Iglesias L, de Carlos F, García-Suárez O, Pérez-Piñera P, et al. The lamellar cells in human Meissner corpuscles express TrkB. Neuroscience Letters. 2010;**468**:106-109

[80] Pawson L, Pack AK, Bolanowski SJ. Possible glutaminergic interaction between the capsule and neurite of Pacinian corpuscles. Somatosensory & Motor Research. 2007;**24**:85-95

[81] Pawson L, Prestia LT, Mahoney GK, Güçlü B, Cox PJ, Pack AK. GABAergic/glutamatergic-glial/neuronal interaction contributes to rapid adaptation in pacinian corpuscles. The Journal of Neuroscience. 2009;**29**:2695-2705

[82] Tsunozaki M, Bautista DM. Mammalian somatosensory mechanotransduction. Current Opinion in Neurobiology. 2009;**19**:362-369

[83] Lumpkin EA, Marshall KL, Nelson AM. The cell biology of touch. The Journal of Cell Biology. 2010;**191**:237-248

[84] Gu Y, Gu C. Physiological and pathological functions of mechanosensitive ion channels. Molecular Neurobiology. 2014;**50**:339-347

[85] Paluch EK, Nelson CM, Biais N, Fabry B, Moeller J, Pruitt BL, et al. Mechanotransduction: Use the force(s). BMC Biology. 2015;**13**:47

[86] Ranade SS, Syeda R, Patapoutian A. Mechanically activated ion channels. Neuron. 2015;**87**:1162-1179

[87] Roudaut Y, Lonigro A, Coste B, Hao J, Delmas P, Crest M. Touch sense: Functional organization and molecular determinants of mechanosensitive receptors. Channels (Austin). 2012;**6**:234-245

[88] Fleming MS, Luo W. The anatomy, function, and development of mammalian Aβ low-threshold mechanoreceptors. Frontiers in Biology (Beijing). 2013;**8**(4). DOI: 10.1007/s11515-013-1271-1

[89] Montaño JA, Calavia MG, García-Suárez O, Suarez-Quintanilla JA, Gálvez A, Pérez-Piñera P, et al. The expresssssion of ENa(+)C and ASIC2 proteins in Pacinian corpuscles is differently regulated by TrkB and its ligands BDNF and NT-4. Neuroscience Letters. 2009;**463**:114-118

[90] Calavia MG, Montaño JA, García-Suárez O, Feito J, Guervós MA, Germanà A, et al. Differential localization of acid-sensing ion channels 1 and 2 in human cutaneus pacinian corpuscles. Cellular and Molecular Neurobiology. 2010;**30**:841-848

[91] Cabo R, Alonso P, Viña E, Vázquez G, Gago A, Feito J, et al. ASIC2 is present in human mechanosensory neurons of the dorsal root ganglia and in mechanoreceptors of the glabrous skin. Histochemistry and Cell Biology. 2015;**143**:267-276

[92] Alonso-González P, Cabo R, San José I, Gago A, Suazo IC, García-Suárez O, et al. Human digital Meissner corpuscles display immunoreactivity for the multifunctional ion channels Trpc6 and Trpv4. Anatomical Record (Hoboken, N.J.). 2016. 2016;**300**:1022-1031

[93] Pawson L, Bolanowski SJ. Voltage-gated sodium channels are present on both the neural and capsular structures of Pacinian corpuscles. Somatosensory & Motor Research. 2002;**19**:231-237