Chapter

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

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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].

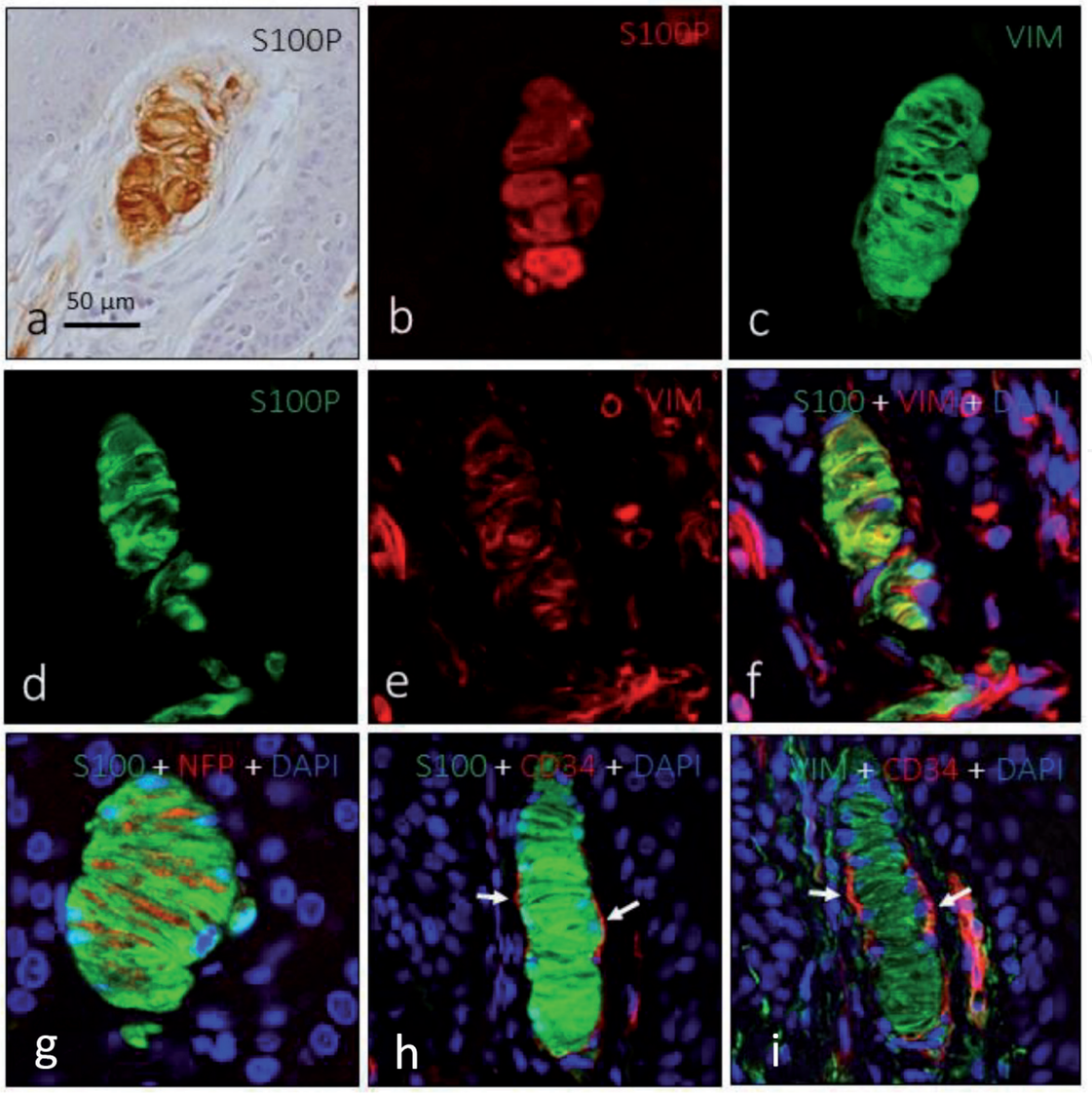

Figure 1.
Immunohistochemical localizacion of S100 protein (S100P; a, b, g, h), vimentin (VIM; c, e, i), neurofilament proteins (red in g) and CD34 (red in h, i) in Meissner'w corpuscles. The lamellar cells display intense and selective cytoplasmic S100P and VIM which are colocalized (d-f). The lamellar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

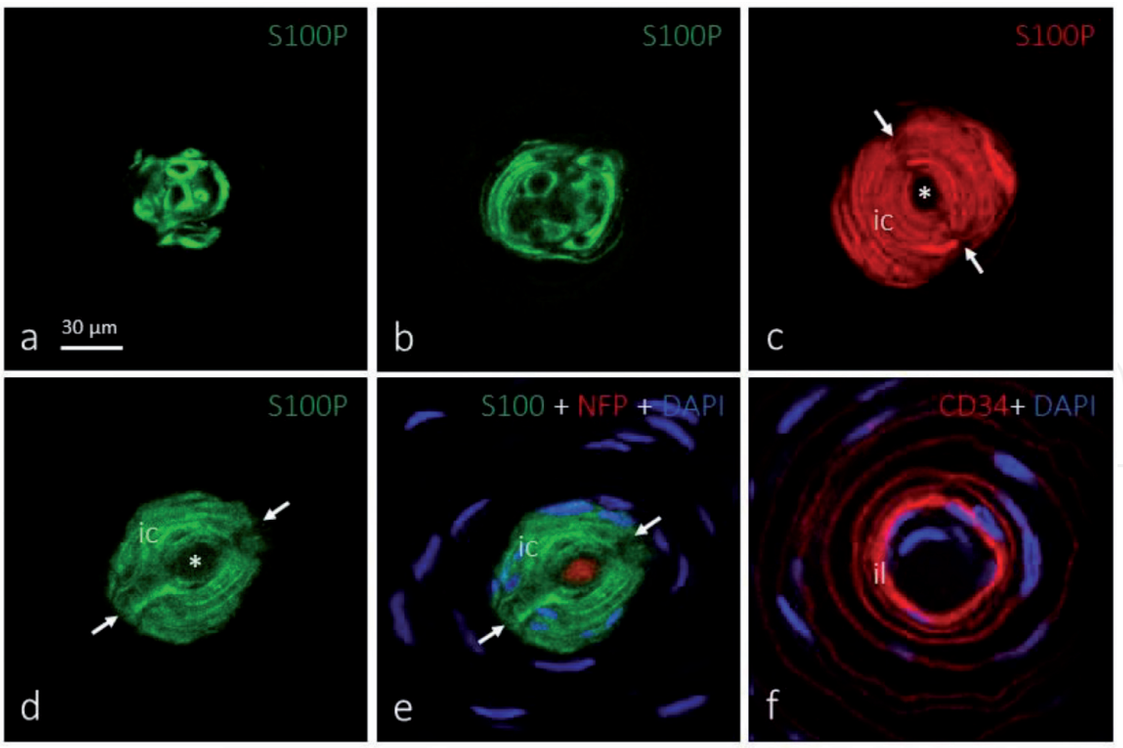

Figure 2.
Immunohistochemical localization of S100 protein (S100; a-e), neurofilament protein (NFP; red fluorescence in e) and CD34 (red fluorescence in f). The glial cells forming the central zone of the inner core are characteristically arranged into two symmetrical hemilamellar systems separated by 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.

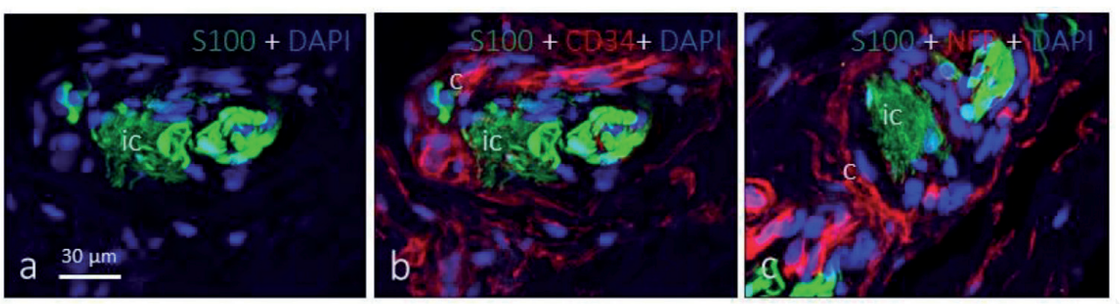

Figure 3.
Immunohistochemical localization of S100 protein (a-c) and CD34 in human cutaneous Ruffini's corpuscles. The glial cells are irregularly arranged and display a strong S100P immunofluorescence (a-c). The capsule of these corpuscles is CD34 positive suggesting and endoneurial origin (b, c). c: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

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