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Odontoblast: A Mechano-Sensory Cell

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ABSTRACT Odontoblasts are organized as a single layer of specialized cells responsible for dentine formation and presumably for playing a role in tooth pain transmission. Each cell has an extension running into a dentinal tubule and bathing in the dentinal fluid. A dense network of sensory unmyelinated nerve fibers surrounds the cell bodies and processes. Thus, dentinal tubules subjected to external stimuli causing dentinal fluid movements and odontoblasts/nerve complex response may represent a unique mechano-sensory system giving to dentine-forming cells a pivotal role in signal transduction. Mediators of mechano-transduction identified in odontoblast include mechano-sensitive ion channels (high conductance calcium-activated potassium channel—K_{Ca}—and a 2P domain potassium channel—TREK-1) and primary cilium. In many tissues, the latter is essential for microenvironment sensing but its role in the control of odontoblast behavior remains to be elucidated. Recent evidence for excitable properties and the concentration of key channels to the terminal web suggest that odontoblasts may operate as sensor cells. *J. Exp. Zool. (Mol. Dev. Evol.) 312B:416–424, 2009.*

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Mechanical forces are crucial for the regulation of cell behavior including at least growth, volume, shape, migration, gene expression and tissue development (review: Syntichaki and Tavernarakis, 2004; Ingber, 2006; Lumpkin and Caterina, 2007). The process by which cells convert mechanical energy into electrical or chemical signals is called mechano-transduction and concerns all living organisms. For instance, bone mechano-sensitivity owing to physical loading is implicated in regulating bone density and cells involved this process are acutely able to sense their biomechanical environment and transduce into cellular signals that are subsequently propagated to the nucleus where gene transcription is modified (Rubin et al., 2006). This mechano-sensory transduction network involved mediators such as stretch-activated ion channels, integrins, primary cilium, growth factor receptors, cytoskeleton, or extracellular matrix (ECM).

In tooth, odontoblasts are responsible for dentine formation (Ruch et al., '95) and presumably for playing a role in tooth pain transmission (Matthews et al., '96). Their spatial situation in the dentine/pulp complex—namely cell processes extending to a liquid phase (dentinal fluid) into calcified tubules and cell bodies included in the soft pulp tissue—suggests that they are potentially best placed to sense both external stimuli and/or transient changes in pulp microcirculation. Therefore, the control of dentine deposition in normal and pathological conditions may involve not only inductive molecules released from dentine/pulp matrix (Smith et al., '95; Tziafas, 2004) but also a direct mechano-transduction process. This point of view is enhanced by recent data demonstrating that odontoblasts are able to generate action potentials (Allard et al., 2006). In addition, the clustering of key molecules at the site of odontoblast–sensory nerve contact leads us to believe that odontoblasts could be involved in the sensory

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transduction process in tooth. This review will therefore be focused on the mechano-sensory system corresponding to the relationships between dentine, odontoblasts and nerve fibers and the cell structures implicated in signal transduction (mechano-sensitive ion channels, primary cilium).

ODONTOBLAST: A KEY CELL OF PULP/ DENTINE COMPLEX

Odontoblasts originate from neural crest derived mesenchymal cells. Their terminal differentiation is characterized by the withdrawal from the cell cycle, elongation and cytological polarization giving to the cells a tall and columnar aspect (Couve, '86; Ruch et al., '95). They are organized as a layer of palisade cells along the interface between the dental pulp and dentine (Fig. 1a). As dentinogenesis progresses, odontoblast extensions, which represent the secretory pole of the cells, become included in the calcified matrix forming dentinal tubules, whereas the cell bodies are embedded in the soft pulp tissue. Thereafter, odontoblasts continuously secrete the circumpulpal dentine at a slow rate (modulated by occlusal abrasion) and this dynamic process gives to these cells a unique spatial situation (Baume, '80). Dentinal tubules, extending from the borderline between enamel and dentine to the odontoblast layer, contain cell processes bathed in the dentinal fluid (Fig. 1b). Consequently, odontoblasts could act as a selective barrier that controls the relationship between dentine and pulp and vice versa under physiological and pathological conditions. This point of view is enhanced by the interrelationships (desmosome-like, tight and gap junctions) between odontoblasts themselves and with the underlying pulp cells forming the Höhl layer (Holland, '76; Callé, '85; Ushiyama, '89).

Odontoblast process and dentinal fluid

Odontoblast process contains cytoskeletal elements including intermediate filaments (vimentin), microtubules (tubulin) mainly localized in the core of the process and actin filaments associated with the plasma membrane (Sigal et al., '85; Nishikawa and Kitamura, '86). The latter displays $\alpha v\beta 3$ integrins suspected to be involved in the continuous reorganization of actin that accompanies process elongation and cell bodies moving toward the pulp core (Lucchini et al., 2004; Staquet et al., 2006). Since Tomes' description in 1856 (Tomes, 1856), considerable debates have been raised concerning the distance to which this process extends within the tubule. This seems to be particularly influenced by the methodologies used (scanning or transmission electron microscope, fluorescence labelling, radioactive tracers, confocal laser microscopy), the analyzed region (crown or root dentine) and age of specimen (for

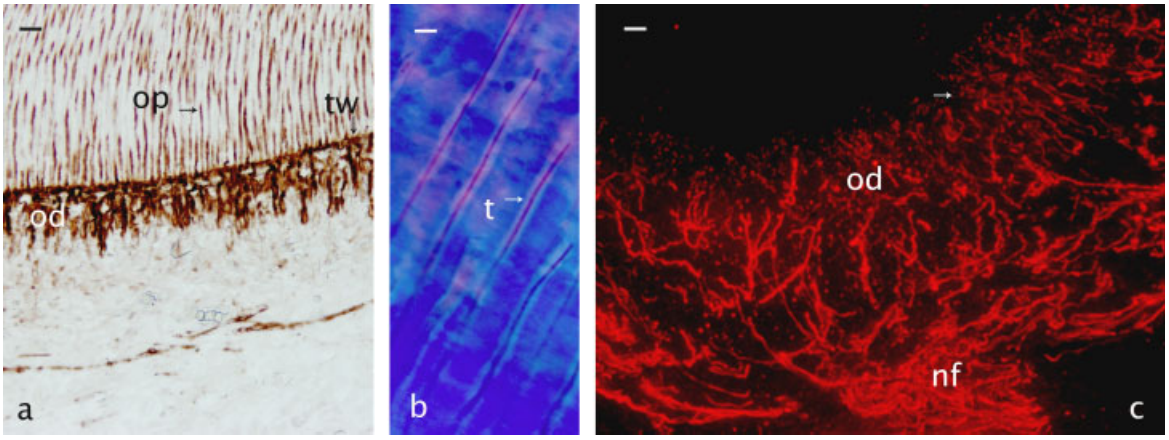

Fig. 1. Pulpal dentinal border of a human tooth. Odontoblasts (od) organized as a single layer with cell processes (op) extending in the dentinal tubules (t). (**a**) Immunoperoxidase detection of β tubulin in decalcified tooth (fixation in 4% paraformaldehyde; demineralization in 10% acetic acid) showing a strong expression in odontoblast cell bodies (od) and processes (op). tw, terminal web. (**b**) Decalcified section of dentine (Bouin's fixation) showing dentinal tubules (t) from the inner third of crown dentine (Masson's trichrome staining). Content of the tubules corresponds to odontoblast cell extensions. The space between processes and tubule walls (arrow) corresponds to the removal of peritubular dentine resulting from the demineralization procedure. (**c**) Frozen section of a carefully isolated pulp showing a dense distribution of nerve fibers (nf) in the odontoblast layer of the crown. The nerve endings and varicosities (arrow) run into the layer (immunodetection of peripherin, marker of intermediate filaments of trigeminal axons). Bar: (a) 20 μm; (b) 10 μm; (c) 10 μm.

review: Holland, '85; Pashley, '96; Tsuchiya et al., 2002). Nevertheless, it is clear that odontoblast processes are long and straight in the crown region and extensively branched and shorter in the root (Byers and Sugaya, '95). In addition, the use of fluorescence staining combined with transmission electron microscope strongly suggests that odontoblast processes do not extend beyond the inner dentine in human (Yoshiba et al., 2002). At light microscopic level on decalcified sections, the space routinely identified between tubule walls and processes (Fig. 1b) results from the removal of peritubular dentine and should be considered as a technical artifact. Indeed, at the ultrastructural level, cross sections of nondecalcified inner dentine clearly show that processes closely associated with axons happen to fill the lumens of the tubules, thus demonstrating a morphological barrier between dentine and pulp (Thomas, '79; Holland, '85; Yoshiba et al., 2002). In addition, the lanthanum perfusion as electron dense tracer is unable to pass between odontoblasts showing that these cells act also as a physiological barrier (Bishop, '92). Interestingly, an elegant experiment using fluoro-gold applied to enamel or dentine (Byers and Lin, 2003) revealed that the tracer is able to penetrate these mineralized tissues and concentrate in the odontoblast layer, underlining the major role of odontoblasts in regulating the transfer of molecules or ions from enamel and dentine to pulp. In this context, movements of the dentinal fluid (acting as hydraulic links) filling the upper part of tubules down to odontoblasts tip could be assumed as the earliest step of signal induction. Efflux of dentinal fluid flow within tubules at exposed dentine has been carefully analyzed in vivo and in vitro (Linden and Brännstrom, '67; Vongsavan and Matthews, '91; Pashley, '96; Charoenlarp et al., 2007; Chidchuangchai et al., 2007; Linsuwanont et al., 2008). Taken together, these findings have clearly demonstrated the relationship between dentine permeability and dentine sensitivity and support the widely accepted hydrodynamic theory of dentine sensitivity (Brännstrom and Astrom, '72). This theory states that changes in dentine fluid flow induce irritation of the pulpal end of the tubules including nerves, blood vessels and odontoblasts. Thus, dentinal fluid shifts across dentine in response to the application of painful stimuli could cause sufficient shear forces to stimulate odontoblast cell membrane. The origin and composition of dentinal fluid (often collected from cut dentine surfaces) have been poorly documented and remain controversial in spite of the help of dyes and ^{I31}I isotopes (Bartelstone et al., '47; Haljamäe and Röckert, '70; Tanaka, '80). At the ultrastructural level, it was identified (Thomas, '79; Yoshiba et al., 2002) as a densely packed fine granular material (result of the preparatory procedures). However, the use of sophisticated methods (micro-puncture and microprobe analysis) clearly showed an elevated concentration of potassium and lower values for sodium or calcium compared with serum (Larsson et al., '88), confirming that dentinal fluid is not derived from blood as a capillary transudate (Bishop, '92) in contrast with previous concepts.

Odontoblast/nerves relationships

Besides their fundamental role in dentinogenesis, odontoblasts were recently shown to express neural glycoproteins usually involved either in architectonic brain development or axon navigation. Expression of these genes in odontoblasts was first identified from a subtractive cDNA library of cultured human odontoblasts (Buchaille et al., 2000) and further investigations showed a putative role of reelin and semaphorins (3A, 7A) between odontoblasts and nerve fibers (Luukko et al., 2005; Maurin et al., 2004, 2005; Fried et al., 2007). Indeed, trigeminal nerve fibers form a dense and profuse network of sensory axons branching extensively in the odontoblastic region of the crown (Fig. 1c). Afferent unmyelinated nerve endings (A delta and C-fibers) are associated with odontoblasts, some penetrating the predentine and dentine but do not extend beyond the inner part of the tissue (Hildebrand et al., '95; Byers et al., 2003). These fibers mostly mediate painful sensations including mechano-sensitive stimuli (Luukko et al., 2005). They were shown to be closely related to odontoblast cell membrane with a narrow gap in between (Ibuki et al., '96) but no synaptic structures or any gap junction could be detected between them. During tooth development, dental axon guidance and patterning are under the control of neuroregulatory molecules (NGF, GDNF, BDNF, semaphorin 3A, netrins, ephrins) and ECM proteins (laminin, fibronectin, tenascin). The final guidance steps of dentine innervation (Loes et al., 2001; Luukko et al., 2005; Fried et al., 2007) involve semaphorin 7A (Maurin et al., 2005) and reelin, a large ECM glycoprotein that could promote intimate adhesion between odontoblasts and nerve varicosities (Maurin et al., 2004). At the sites of close contact, clusters of

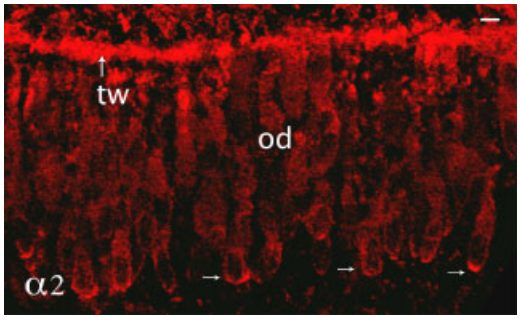

Fig. 2. Frozen section of crown portion of human pulp exposed to anti-sodium channel α2 subunit antibodies. A marked fluorescence reveals a concentration of sodium channels at the terminal web (tw) of the odontoblast layer and underlines the membranes of the basal pole of odontoblasts (arrows). Confocal laser microscopy (Zeiss LSM 510). Bar: 8 μm.

Na^+ channel α subunits were recently shown to be mainly concentrated at the apical pole (terminal web) of mature odontoblasts (Fig. 2) and β2 subunits (functioning also as cell adhesion molecules) were colocalized with peripherin filaments expressed by trigeminal axons (Allard et al., 2006). Thus, this close association suggests that odontoblasts and nerve terminals may directly interact and this event has been presupposed as the earliest step of tooth pain transmission.

Introducing the primary cilium of odontoblasts

Primary cilium exists in almost every eukaryotic cell type including odontoblasts and this structure emerges from the apical surface of the cell into the extracellular space as an antenna (Wheatley et al., '96). It forms a single organelle consisting of a membrane-bound cylinder surrounding a microtubule doublets backbone: the axoneme. The latter develops from the centrosome and is coordinately regulated with the cell cycle. The primary cilium is assembled and maintained by intraflagellar transport machinery in which protein complexes move from the base to the tip and backward along the doublet microtubules used as a track, underneath the ciliary membrane (for review: Badano et al., 2006). Originating from the proximal end of the basal body, a ciliary rootlet forms a cytoskeleton-like structure made of thick striated bundle extending toward the cell nucleus.

In many tissues, the primary cilium is an essential microenvironmental sensory organelle through which various mechanical, biochemical or light signals are sensed (Pazour and Witman, 2003; Praetorius and Spring, 2005; Nauli et al., 2008). In addition to this involvement in signal reception, the primary cilium participates in sensory transduction including chemical concentration of molecules, developmental morphogens (Shh signalling, for example) as well as osmolarity or light intensity. The plasma membrane of the cilium displays receptors specific to the functions of the tissue in which it is located (Pazour and Witman, 2003; Whitfield, 2004). Thus, it is becoming increasingly clear that the primary cilium plays a critical role by controlling important aspects of cellular physiology and development. Thus, it is not surprising that mutations in genes that encode cilium components generate major human genetic diseases and syndromes (Badano et al., 2006).

In odontoblasts, a primary cilium has been regularly described at the ultrastructural level, in the vicinity of the Golgi apparatus, emerging out of the cell and the use of detyrosinated α tubulin antibody, a ciliary marker (Fig. 3), reveals the axoneme (Baume, '80; Magloire et al., 2004). Presently, the knowledge base available is too limited to determine the crucial role (sensing, linking, cell polarity) of the cilium of odontoblasts compared with bone cells where it contributes to the balance between osteogenic (increase in osteopontin gene expression, upregulation of Runx2) and bone resorptive responses (Xiao et al., 2006; Malone et al., 2007). In chondrocytes it contributes to the translation of ECM deformations into intracellular signals (McGlashan et al., 2006). Considering the basal situation of primary cilia in odontoblast cell bodies constituting the periphery of the pulp tissue, it could be suggested that odontoblasts can use their cilia to sense the pulp microenvironment including capillaries em-

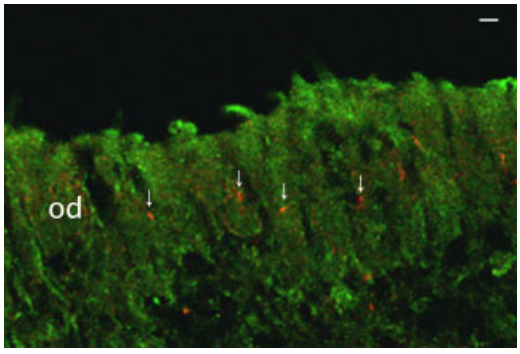

Fig. 3. Frozen section of crown portion of human pulp exposed to acetylated α tubulin antibodies (red) and β tubulin (green). A positive fluorescence reveals primary cilia (arrows) aligned in the odontoblast layer (od). Confocal laser microscopy (Zeiss LSM 510). Bar: 5 μm.

bedded in ECM components. In this context, primary cilia could participate in the regulation of the architecture of primary or secondary dentine formation as odontoblasts move centripetally toward the pulp core throughout the life of the tooth.

ODONTOBLAST: A SENSOR CELL

Mechano-sensitive ion channels

Cell membrane properties have been described in in vitro cultures of pulp cells, in freshly isolated odontoblasts from pulp cells and in surviving odontoblasts from pulp thick slices preparation. Thus, voltage-gated sodium, potassium and chloride-selective channels have been described in the odontoblast membrane (Davidson, '93, '94; Guo and Davidson, '98; Allard et al., 2000, 2006; Shibukawa and Suzuki, 2001; Magloire et al., 2003). In addition, several lines of evidence give to calcium channels ($Ca_v1.2$) a central role in odontoblast behavior both at the physiological and the pathological level (Seux et al., '94; Lundgren and Linde, '97, '98; Davidson and Guo, 2000; Shibukawa and Suzuki, 2003; Westenbroek et al., 2004). Interestingly, Allard et al. (2000) demonstrated in human that high conductance calcium-activated potassium channels (K_{Ca}) displayed mechano-sensitivity (activation in response to membrane stretch) in cultured odontoblasts, underlining their role in the transduction of mechanical stimuli into electrical cell signals (Figs. 4 and 5). In vivo, these channels are colocalized with L-type calcium channels ($Ca_v1.2$) and concentrated at the apical pole of the cells (terminal web) that actively participate in the directional transportation of calcium to the mineralization front of the dentine (Lundgren and Linde, '88, '97). Thus, odontoblasts might control via K_{Ca} channels a variety of metabolic processes including dentine formation. These channels could also be involved in tooth pain sensation. In response to mechanical stimuli, the combination of increased intracellular Ca^{2+} membrane stretch could cause K_{Ca} channel opening in odontoblasts and consequently depolarization of nerve endings (or odontoblasts) for firing in the sensory tract (or in odontoblasts). This could explain why K^+-containing agents placed into deep dentinal cavities induce short tooth pain sensations (Markowitz et al., '91; Markowitz and Pashley, 2008).

Besides K_{Ca} channels, mechano-sensitive TREK-1 potassium channels (TWIK-related K^+ channel) have been detected in odontoblast cell membrane (Magloire et al., 2003). They belong to the family of potassium channel subunits with two pore domains and four transmembrane segments named K_{2P} channels (Lesage and Lazdunski, 2000). In mammals, they are opened at resting membrane potentials in physiological conditions and gated by a variety of chemical and physical stimuli including stretch, cell swelling, intracellular acidosis, heat,

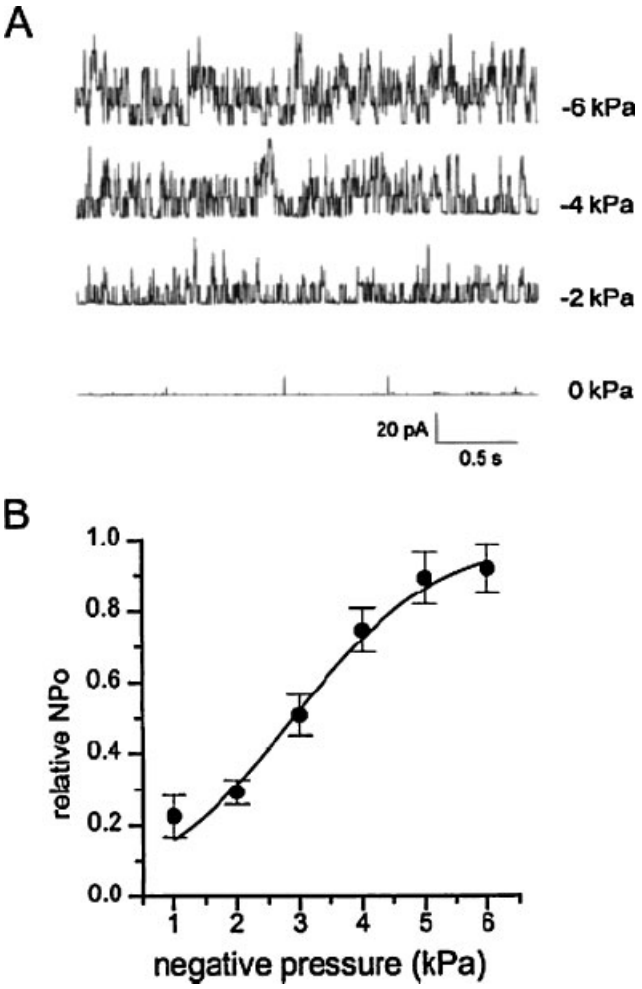

Fig. 4. Effect of application of negative pressure (expressed in kilopascal: kPa) of increasing amplitude on K_{Ca} channel activity recorded from single channel currents in cell-attached patches. (**A**) K_{Ca} channel currents recorded in the presence of different pressure levels in the pipette (indicated next to each current trace). The membrane potential was held at +20 mV (pA, pico-ampere; s, second). In this patch, NP_o was close to zero in control and increased in the presence of −2, −4 and −6 kPa negative pressure amplitudes (NP_o evidences a channel activity where N is the number of channels in the patch and P_o the open state probability). (**B**) Relationship (fitted with a Boltzmann equation) between channel activity and negative pressure. Maximum activation occurred at about −6 kPa (originally appeared in Allard et al., 2000).

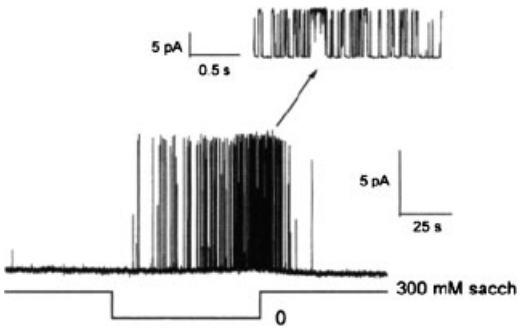

Fig. 5. Effect of an osmotic shock on K_{Ca} channel activity in a cell-attached patch. The patch potential was held at + 20 mV. In control, cells were bathed in a K^+-rich solution containing 300 mM saccharose and no channel opening was detected. Upon superfusion of the cell with a K^+-rich solution free of saccharose, after a delay of about 10 sec K_{Ca} channels began to open. On returning to the hypertonic external solution, K_{Ca} channels completely shut after a delay of 25 sec (originally appeared in Allard et al., 2000).

polyunsaturated fatty acids and volatile general anesthetic (Patel and Honoré, 2001). TREK-1 channels are considered as thermo-sensors, present in C-fiber nociceptors (Maingret et al., 2000) and assumed to be main mediator targets of pain (Murbatian et al., 2005). In teeth, they are strongly expressed in the membrane of coronal odontoblasts, absent in the root dentine-forming cells, and this pattern is closely related to the nerve fiber distribution showing a decreasing gradient of expression from cusp to root. Consequently, TREK-1 channels when stretch-activated could participate in the signal transduction to afferent nerve endings.

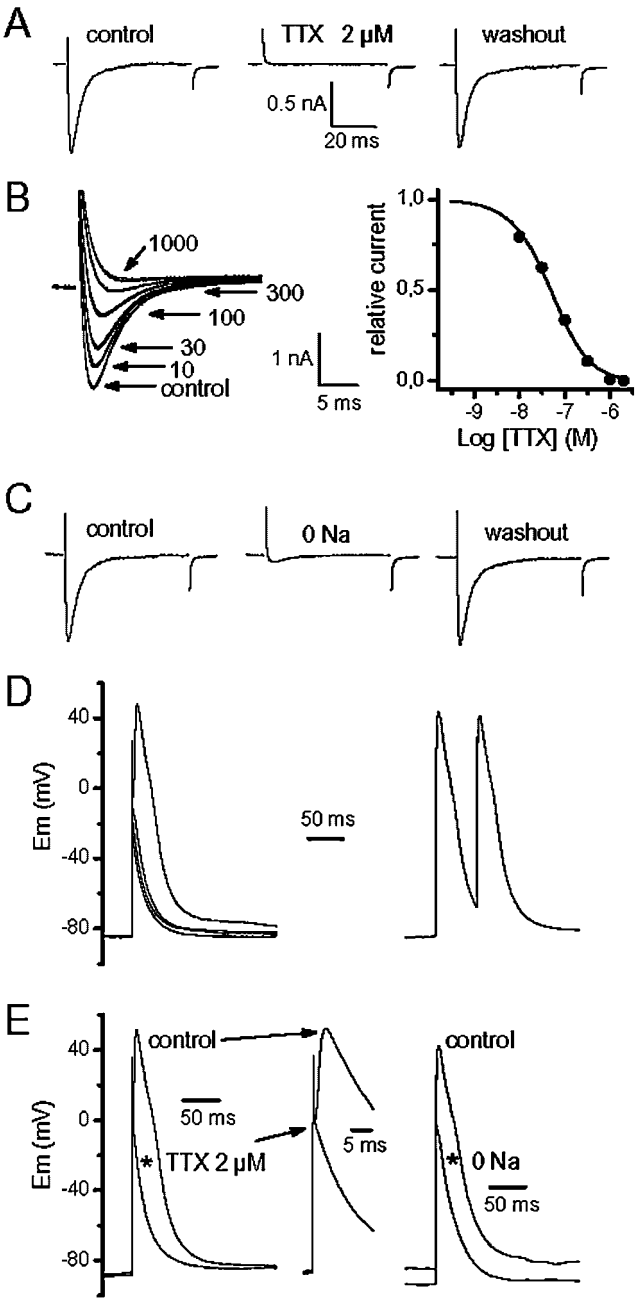

Fig. 6. Investigation of the electrical excitability of cultured odontoblasts. Voltage-gated tetrodotoxin-sensitive (TTX) sodium currents in voltage clamped cells. (**A**–**C**) Effect of TTX and removal of Na^+ on inward currents and voltage response. TTX completely and reversibly abolished the inward current elicited by a depolarizing pulse to 0 mV. This shows that odontoblasts express functional voltage-gated Na^+ channels. (**D**) Voltage responses obtained in response to injection of depolarizing currents (left panel). The right panel shows two consecutive spikes evoked by injection of two current pulses. (**E**) Spikes are totally inhibited by the addition of TTX in the bath or substitution of choline for Na^+ in the external solution. This confirms that the spike results from the activation of the voltage-gated TTX-sensitive Na^+ current. The stars indicate the voltage response evoked after the addition of 2 µM TTX (left panel) and after substitution of 140 mM choline for 140 mM Na^+ (right panel) in the external solution (originally appeared in Allard et al., 2006).

Voltage-gated sodium channels

The view that odontoblasts could have a sensory receptor function raises the question of excitable properties of the cells and the expression of voltage-gated sodium channels. In this respect, we recently identified the expression and localization of voltage-gated Na^+ channels and demonstrated that they are functional in odontoblast cell membrane (Allard et al., 2006). Physical charac-

teristics of sodium currents and expression of the transcripts of four genes (*SCN1A*, *SCN2A*, *SCN3A* and *SCN2B*) encoding, respectively, the pore-forming α subunit isoforms $Na_v1.1$, $Na_v1.2$ and $Na_v1.3$ and β2 subunits reveal the neural phenotype of odontoblasts. More importantly, we demonstrated that these cells are excitable and produce all or no spike in response to depolarizing currents (Fig. 6). This finding lets us believe that odontoblasts might be able to transduce and integrate diverse somato-sensory signals known to elicit nociceptive responses and initiate bursts typical of nerve cells. Finally, the excitable properties of odontoblasts, the concentration of mechano-sensitive, thermo-sensitive (TRPV1) ion channels (Okumura et al., 2005) preferentially in the terminal web and the clustering of key molecules (α, β subunits, ankyrin G) at the site of odontoblast–nerve close contact bring a new role for odontoblasts as sensor cells. The latter operate as molecular transducers of dentine fluid flow to trigeminal ganglion. How the firing of odontoblasts is transmitted to neighboring nerve cells remains the main open question.

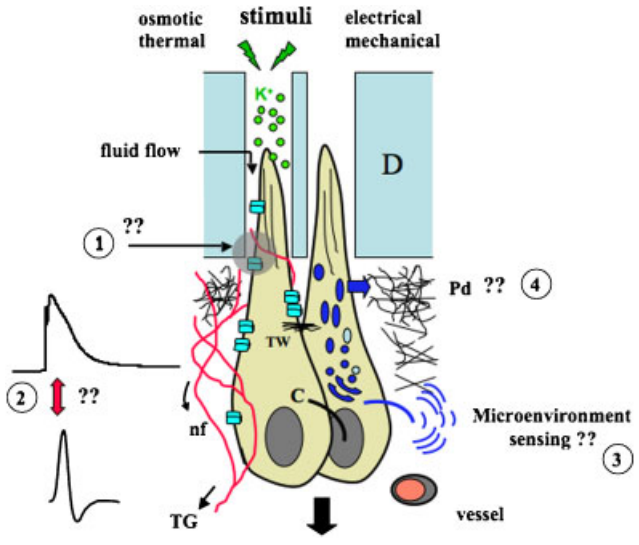

Fig. 7. Schematic representation of hypothetical mechanisms underlining the role of mechano-sensitive ion channels ( ) and cilium structure (C) to odontoblast response under stimuli. Odontoblasts may operate as excitable sensor cells whose excitation is transmitted to nerve fibers (nf) and conducted to the trigeminal ganglion (TG). The question marks (1, 2) refer to the remaining open question of the type of transmission of excitation from odontoblasts to nerve endings (intercellular communication? chemical synapses?). Identically, the question marks (3, 4) concern the putative role of primary cilia in the regulation of the architecture of primary or secondary dentine formation as odontoblasts move centripetally toward the pulp core (black arrow) throughout the life of the tooth. Pd, predentine; TW, terminal web.

CONCLUSION

In conclusion, odontoblast could be considered as a unique cell. At the functional level it is both a highly specialized cell for the synthesis and secretion of dentine under the strict control of external stimuli via at least cilia sensing, and a mechano-sensor cell by initiating, via movements of dentinal fluid within tubules, tooth pain transmission (Fig. 7). This point of view is enhanced by the recent investigation on changes in sensitivity of dentine to cold produced by acid etching and by oxalate treatment (desensitizing agent) suggesting that a transduction mechanism could involve specific cold receptors (Chidchuangchai et al., 2007). The latter might correspond to thermo-sensitive ion channels (TREK-1, TRPV1) previously detected on odontoblast cell membrane. Thus, the sensory function of odontoblasts highlighted by their excitable properties should be taken as a serious support to the hydrodynamic theory. These cells should be given a pivotal role in the dynamic of the pulp/dentine complex.

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