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Differential Expression of Polarization in Odontoblasts and Epithelial cells

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ABSTRACT

Cell polarity identifies the asymmetry of a cell. Various types of cells, including odontoblasts and epithelial cells, polarize to fulfill their destined functions. Odontoblast polarization is a prerequisite and fundamental step for tooth development and tubular dentin formation. Current knowledge of odontoblasts polarization, however, is very limited, which greatly impedes the development of novel approaches for regenerative endodontics. Compared to odontoblasts, epithelial cell polarization has been extensively studied over the last several decades. The knowledge obtained from epithelia polarization has been found applicable to other cell types, which is particularly useful considering the remarkable similarities of the morphological and compositional features between polarized odontoblasts and epithelia. In this review, we first discuss the characteristics, the key regulatory factors, and the process of epithelial polarity. Next, we compare the known facts of odontoblast polarization with epithelial cells. Lastly, we clarify knowledge gaps in odontoblast polarization and propose the directions for future research to fill the gaps, leading to the advancement of regenerative endodontics.

Keywords: cells, odontoblasts, epithelial, polarization,

1. Introduction

In a broad sense, cell polarity can be defined by either the structural or the functional asymmetry of a cell. Basically, all types of mammalian cells experience polarization process during their lifecycles either transiently or permanently. Cells undergo transient polarization process when they respond to exterior stimuli. However, some cells undergo permanent polarization process to achieve destined cellular fates, including epithelia, neurons, and odontoblasts. Odontoblasts are a layer of dental cells that orderly align along the dental pulp. Odontoblast polarization marks the morphological change from a symmetrical mesenchymal cell to an asymmetrical odontoblast, with a columnar cell body aligned in a single layer and a cytoplasmic process extending from the cell body to the predentin. During primary odontogenesis, the polarized arrangement and morphological change of odontoblasts is a fundamental step for tubular dentin formation. It ensures the formation of tubular dentin and subsequently enables the existence of dentinal fluid and neural fibers within the dentinal tubules. In dentin regeneration, a similar transition of odontoblasts is eagerly desired, since the reconstruction of the tubular microstructure is now a major challenge in developing novel dentin regeneration strategies. Using current strategies, the regenerated dentin is morphologically more similar to bone, rather than dentin since the organized tubular structure is usually missing. This “osteodentin” explicitly impairs the biological properties of regenerated dentin, including its sensation transduction and mechanical properties. Therefore, understanding the mechanism of odontoblast polarization is pivotal for functional dentin regeneration. However, apart from the descriptions of cell morphology, there are few publications on odontoblast polarity (João, and Arana-Chavez, 2004).

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The polarization process of epithelial cells has been extensively studied and major characteristics have been described in detail. First, their plasma membranes are divided into apical, lateral, and basal domains that exhibit different features; for example, the different distribution of membrane lipids between apical and basal membranes and the existence of intracellular junctions between adjacent cells. Within the cells, the asymmetric cytoskeleton distribution and the repositioning of organelles mark the intracellular polarity of a cell, together with the dispersion of epithelial polarity protein complexes. Each of these components is controlled by multiple factors, including Rho GTPases that are the predominant ones. All these components form a delicate molecular network, and contribute to the establishment of epithelial cell polarity. Moreover, these critical factors, especially the regulatory molecules, are also applicable in other types of cell polarity, such as neurons or migrating cells.

Multiple similarities have been found between epithelial cells and odontoblasts, including the features of cell morphology, development, function, and composition (McGuire *et al.,* 2014). .Therefore, in this paper we use epithelial cell polarity as a template to analyze the "knowns" and "unknowns" of odontoblast polarity. After introducing the features of epithelial cell polarity, regulatory factor Rho GTPases and the polarization process, we summarize the current understanding of odontoblast polarization and compare the differences between the two cell types. We hope that this review will shine a light on the "unknowns" of odontoblast polarization for further dental studies.

Characterizations of epithelial cell polarization

Epithelial cells exhibit apicobasal polarity defined by three plasma membrane domains, including apical, lateral, and basal domains (Rodriguez-Boulan, and Macara, 2014) .The apical domains face the lumen and enable material exchange. The lateral domains connect adjacent cells via specialized intercellular junctional structures. The basal domains adhere to the underlying basement membrane or extracellular matrix (ECM). The basal and lateral domains have similar components and are thereby named as basolateral domains (Román-Fernández, and Bryant, 2016). The characteristic components in epithelial polarization include the formation of intercellular junctions, the asymmetric cytoskeleton distribution, the reposition of organelles, and the distinct distribution of polarity complexes and membrane lipids. Each of these components is precisely regulated by multiple signaling pathways, among which the Rho GTPases are the predominant ones throughout the whole process (Mack, and Georgiou, 2014). Moreover, these components themselves also act as intermediate scaffolds in constructing a polarized epithelial cell. A precise coordination of all components is required to guarantee an accurate polarization process (Fig. 1).

Intercellular junctions

There are several types of junctions around a polarized epithelial cell. Tight junctions (TJ), adherens junctions (AJ), desmosomes, and gap junctions are located at the intercellular space from apical to basal regions sequentially, while hemidesmosomes and focal adhesions are located between basal cell domains and underlying ECM. Despite the strict structural demarcation among the junctions, they are closely related during junction formation and epithelial polarity development (Giepmans, and van IJzendoorn, 2009).TJs are the most featured intercellular junctions during epithelial polarization. They function as a "gate" to occlude intercellular gaps for selective para-cellular permeability, and as a "fence" to mechanically segregate protein or lipid dispersion within the lipid bilayer, thereby defining the boundary of apical and basolateral domains (Zihni *et al*., 2016). TJs are composed of transmembrane structural proteins that constitute diffusion barriers and cytosolic adaptor proteins that connect the surface membrane to the cytoskeleton network. The structural proteins include tetraspans of the claudin family and MARVEL-domain proteins like occluding (Van Itallie, and Anderson, 2013).Cytosolic adaptor plaque is a network of proteins containing complicated proteinprotein interacting motifs, including zonula occludens (ZOs), cingulin, and JACOP. In short, occludins maintain the stability and barrier function of a TJ, claudins regulate the permeability (Günzel, and Alan, 2013) and ZOs function in TJ assembly. ZO-1, the most important regulator of TJ formation, functions in various ways, including assembling occludins and claudins as scaffolding proteins, binding to and regulating actin cortex components, and promoting cadherin-mediated intercellular adhesion via regulating the spatial organization of tension (Balda, and Matter, 2016).

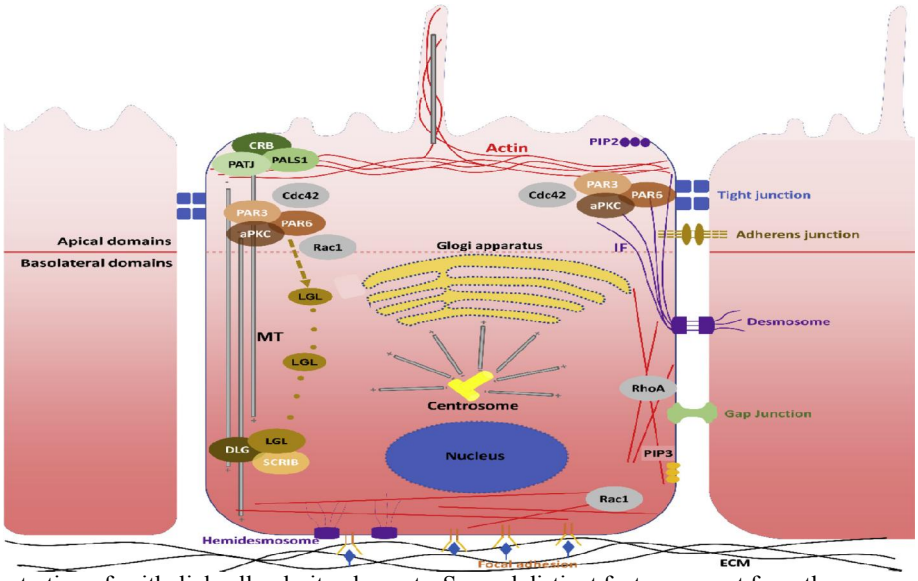

Fig. 1: Illustration of epithelial cell polarity elements. Several distinct features, apart from the apparent difference in cell morphology, could be seen, including polarity complexes, intracellular junctions, reorganized cytoskeletons, repositioned organelles and regulating molecules. **1**. Polarity complexes include apical PAR6/ PAR3/aPKC complex, apical CRB/PALS1/PATJ complex, and basolateral SCRIB/LGL/DLG complex**. 2.** Intracellular junctions related to epithelial polarity include adherens junctions and tight junctions. Tight junctions mark the boundary of apical surface domains and basolateral surface domains. **3.** Actin filaments and microtubules are reorganized. Actin majorly form the cortical belt encircling the most apical end of the lateral membrane domain and support apical junctions. Microtubules are majorly non-centrosomal and polarized with their plus ends stabilized at the basal cell cortex and minus ends anchored to cell-cell junctions or at the apical pole. Besides, a part of microtubules also orientates apically from the centrosome. Moreover, microtubules also form the primary cilium, where MTs originate from the centrosome toward the tip of the cilium. **4.** Specific organelles are repositioned, including the nucleus, the centrosome and Golgi apparatus. The nucleus is located near the basal pole of a cell, and the centrosome is localized near the apical surface above the nucleus, and Golgi apparatus accompanies the movement of centrosome and remains adjacent to the centrosome. **5.** Regulatory factors mainly include Rho GTPase members Rac1, Cdc42 and RhoA. The three molecules coordinate in regulating cytoskeleton reorganization to generate epithelial cell polarity. Furthermore, they can also directly interact with polarity complexes and even co localize with specific organelles and regulate their activities. Other features, like the distribution of lipids PIP3 and PIP2 are also shown.

Cytoskeleton distribution

Cytoskeleton network includes three components: actin filaments, microtubules, and intermediate filaments. In polarized epithelia, actin filaments form a belt-like cortex that encircles the most apical domains of the lateral membrane to support the apical junction complex, and form stress fibers at the basal domains to support focal adhesions (Miyoshi, and Takai, 2008) .Microtubule rearrangement is also dramatic from a radial centrosomal array, to a highly asymmetric distribution with distinct orientations. The majority of microtubules are not centrosome orientated and instead apicobasal polarized. Their plus ends are rooted at the basal cell cortex and their minus ends are anchored to the intercellular junctions or to the apical domains. The release and rearrangement of microtubules may associate with γ-tubulin ring complex (Oakley *et al.,* 2015) .E-cadherin mediated AJs formation (Li, and Gundersen, 2008). Another two minor populations include microtubules orientating from the centrosome to the apical membranes, which are related to apical protein trafficking, and microtubules forming the primary cilium, where microtubules originate from the centrosome toward the tip of the cilium (Sugioka, and Sawa, 2012). A thick layer of intermediate filaments lie within the terminal web and below at the rootlets of the cellular processes. A few isolated intermediate filament bundles extend along the apical half of the lateral membrane, where they bind to desmosomes (Oriolo *et al.,* 2007) .Moreover, a faint but distinct intermediate filament network has also been observed at the basal pole where it attaches to hemidesmosomes.

Odontoblast cell polarization

Odontoblasts are another type of polarized cells (Figure 2) which possess a number of distinct features when compared to epithelial cells. In contrast to epithelial cells, much less is known about odontoblast polarization. Therefore, we compare both the similarities and differences between odontoblast and epithelial cells to underline the knowledge gap in odontoblast polarization.

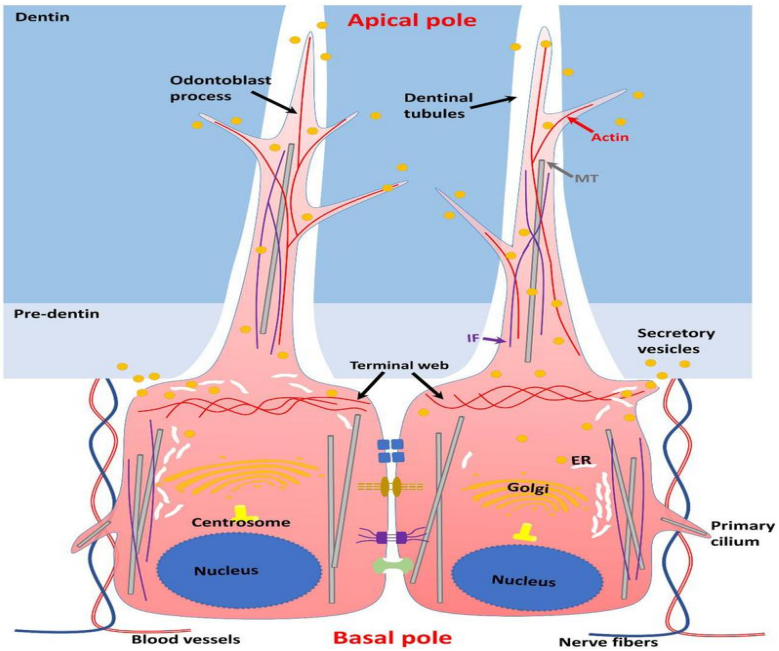

Fig.2: Illustration of polarized odontoblasts. Unique features of odontoblasts are shown, including the polarized cell morphology, cellular processes (including odontoblast process and primary cilium), organelles distribution (including the nucleus, Golgi apparatus, ER, centrosome and secretory vesicles), cytoskeleton arrangement, and cell-cell junctions.

Cell morphology

Epithelial cells can be divided into squamous, cuboidal and columnar epithelial cells based on cell morphology. In contrast, the morphology of odontoblasts is more consistent. Generally, odontoblasts exhibit a large columnar cell body aligning at the pulp periphery and a long process inside the dentinal tubule.

Cellular process

Epithelial cellular processes are seen at the apical pole of epithelial cells and can be divided into primary cilia (immotile cilia), motile cilia, and microvilli. Primary cilia are short processes that exist on all mammalian cells and only one primary cilia can be seen within one epithelial cell. The main function of primary cilia is sensory receptors. Contrary to the "9+0 axoneme" microtubule structure of primary cilia, motile cilia contain "9+2 axoneme" and usually exist in respiratory tract to help remove mucus and dirt. Microvilli only enclose microfilaments and cytoplasm and usually exist in the small intestine to enhance absorption efficiency. In terms of odontoblast, only one long process is seen in an odontoblast and multiple branches can be observed from the trunk of the process. The cytoskeletal constitutes of odontoblast process include actin filaments, microtubules and intermediate filaments. Actin filaments and microtubules concentrated on the apical pole of odontoblasts with the onset of tooth development (Diekwisch, 1989). Vimentin, a type III intermediate filament protein, exhibits a change in the distribution during odontoblast polarization, that it was uniformly localized within the cytoplasm of pre-odontoblasts while it accumulated in the apical pole of polarized odontoblasts (Lesot *et al.,* 1982). Apart from cytoskeletons, the odontoblast process also contains vesicles related to exocytosis and endocytosis (Linde, and Goldberg, 1993). which differs from epithelial processes. The function of odontoblast processes mainly involve collagen secretion and mineralization during dentin formation,primary cilia have also been detected in the supranuclear region at the basal pole of

odontoblasts (Thivichon-Prince *et al.,* 2009).and function in both microenvironment sensation and dentin modeling via Shh and Wnt signaling pathways (Couve *et al.,* 2013).

Apical-basolateral polarity

The apical pole of epithelial cells lines on the outside (skin) or inside cavities and lumina of bodies, while the basal pole opposites the apical pole and faces connective tissues. The apical pole of odontoblasts is usually defined as the pole of odontoblast process which faces the predentin/dentin, while the basal pole faces the dental pulp (Ruch *et al.,* 1995). Although an opposite polarity has been announced based on an inverted expression of virus-carrying proteins and an inverted distribution pattern of aquaporin 4/5, a pair of epithelial polarity proteins (Tjäderhane *et al.,* 2013).

The basement membrane

Epithelial cells interact with underlying connective tissues via the basement membrane, a network formed by fibrous proteins and glycosaminoglycans. Reconstruction of ECM occurs during epithelial polarization, which is mainly mediated by integrin via an "outside-in" and "inside-out" pathway (Lee, and Streuli, 2014). Instead of basement membrane, the interaction between odontoblasts and inner dental pulp fibroblasts is intermediated by a sub-odontoblastic cell layer called Hohl's cells (Tziafas, 2003), which may differentiate into functional odontoblasts in reparative dentinogenesis. Moreover, a basement membrane-like tissue initially formed between pre-ameloblasts and pre-odontoblasts during primary odontogenesis, while it was reconstructed and finally degraded with the onset of predentin mineralization (Kjoelby *et al.,* 2002).

Blood vessels and nerve fibers

Epithelial layers contain no blood vessels or nerve fibers, therefore nourishment is acquired via diffusion from underlying connective tissues through the basement membrane. On the contrary, both capillaries and neural fibers (Heymann 2002 & Magloire *et al.,* 2009) are found within the odontoblast layer, in which the capillaries provide nutrition support for odontoblasts and the neural fibers sense and respond to stimuli.

Cell-cell junctions

Cell-cell junctions of epithelial cells have been described in detail above. All four intercellular junctions including AJs (Heymann *et al.,* 2002) .TJs, gap junctions and desmosomes have been found between adjacent odontoblasts. Although TJs are demonstrated as a critical factor in inducing epithelial polarization, their structure (macular or continuous) and function (barrier only or also a polarization inducer) in odontoblasts remain controversial (Xu *et al.,* 2016) Moreover, as the key factor in AJs, the expression of cadherins in odontoblasts is also worth noticing ((Heymann, 2002). E-cadherin expression is absent in differentiating odontoblasts and weak in mature odontoblasts, while N-cadherin can be found in differentiated odontoblasts and Hohl's cells. Both proteins are down-regulated in adult teeth, but N-cadherin can be re-expressed in the dental pulp of carious and injured teeth (Heymann *et al.,* 2002). However, contradictory results were also reported from in vitro studies that E-cadherin was up-regulated by Nfic with the differentiation of odontoblast while N-cadherin was down-regulated (Lee *et al.,* 2014) .

Polarity complexes

The dynamic expression and function of polarity complexes in epithelial cells have been described throughly above. In odontoblasts, however, relevant studies are scarce and fail to provide a theoretical support in explaining odontoblast polarization. Up until now, none of the PAR complexes have been described in odontoblasts, although PAR3 has been detected at the proximal TJs in ameloblasts and is proposed to mediate in the formation and maintenance of the proximal TJs (Lehembre *et al.,* 2008). Similarly, no reports discussing the expression of CRB/PALS1/PATJ and SCRIB/LGL/DLG complexes in odontoblasts have been found.

Cytoskeleton distribution

In odontoblasts, the distribution of actin filaments, microtubules, and intermediate filaments varies with that in epithelial cells. Actin filaments form a terminal web apically where the process

originates from the cell body, and meanwhile stretch into the odontoblast process and its branches (Magloire *et al.,* 2009) .Microtubules align parallel with the long axis of the odontoblast cell body and form the odontoblast process in the core and the primary cilia (Diekwisch, 1989). Intermediate filaments similarly align parallel along the axis of the cell body and form the odontoblast process in the core (Magloire *et al.,* 2009).

Organelles

In odontoblasts, the positions of organelles also change with the maturation of odontoblasts (Ruch *et al.,* 1995). During odontoblast polarization, the nucleus moves to the basal pole, the Golgi apparatus moves to the supranulear region, and the centrosome locates between these two organelles. ER is distributed at two regions within the cytosol, that a well-developed and flattened ER is found laterally and parallel to the long axis of the cell, and a secretory vesicle-rich RER-filled area where the RER is abruptly interrupted is simultaneously found proximal to the process (Ruch *et al.,* 1995).

Membrane lipids

In contrast to epithelial cells, the distribution of PIP3 and PIP2 have not been reported in odontoblasts. While changes in odontoblast plasma membrane components, including increased adenylate cyclase activity, and redistribution of concanavalin binding sites have been correlated with odontoblast terminal differentiation (Ruch *et al.,* 1995). It was widely accepted that epithelio-mesenchymal interactions are necessary for odontogenesis (Ruch *et al.,* 1995). There are 3 major components involved in the interactions, including the inner dental epithelium, the dental basement membrane and the growth factors. It was initially reported that dental epithelium was indispensable to initiate odontoblast polarization, while later non-dental epithelium was also found to possess such functions. For non-dental epithelium, the dental mesenchymal tissues would first promote the transformation of those non-dental epithelium into an inner dental epithelium, which then induced odontoblast differentiation. Second, the epithelio-mesenchymal basement membrane was believed necessary that its removal impedes the odontoblast polarization process. Moreover, when co-cultured with epithelium, the removed basement membrane would be reconstructed before the initiation of dental mesenchyme differentiation (Karcher-Djuricic, *et al.,* 1978). The epithelio-mesenchymal basement membrane is dynamic and its components change accompanying odontoblast polarization (Lee *et al.,* 2014 & Ruch *et al.,* 1995), including the disappearance of collagen type III, the modification and turnover of glycosaminoglycans, and the restricted distribution of fibronectin at the apical pole of polarized odontoblasts which surrounded dividing pre-odontoblasts (Lesot *et al.,* 1982). The basement membrane is gradually degraded with the onset of predentin mineralization (Kjoelby *et al.,* 2002) the recent development of biological engineering approaches have succeeded in inducing odontoblast polarization *in vitro* independent of epithelium signals. For example, by culturing dental pulp cell pellet on microfilters, odontoblast-like cells, identified by their polarized morphology and long cell processes, could be observed adjacent to the filter pores (Lü *et al.,* 2011b). Moreover, dental stem cells cultured on an artificial microtubular scaffold could polarize, differentiate and even form organized tubular dentin (Ma *et al.,* 2017). Furthermore, single odontoblast also managed to polarize in vitro on a similar microtubular platform, further refuting the necessity of epithelial signals in inducing odontoblast polarization (Ma *et al.,* 2018).

Conclusion

Cell polarity represents the asymmetric status of a cell, either in morphology or in function. Odontoblast polarization is a critical step in both the primary tubular dentin formation and dentinal tissue regeneration. Currently, there are limited data on odontoblast polarization, and the gap of knowledge in odontoblast polarization impedes the development of novel strategies for regenerative endodontics. Considering the similarities between epithelial cells and odontoblasts, we use epithelial cell polarity as a template to narrate the known and unknown facts in odontoblast polarity in this review. By summarizing the characteristic components and the network during epithelial cell polarization, we extract critical factors in epithelial polarization that might also be involved in odontoblast polarization and compare these factors between these two cell types. It is clear that despite the similarities in morphology, many characteristics of epithelial polarity at the molecular level are missing in odontoblasts, such as the distribution of inositol lipids, the existence of polarity complexes, and the

effect of small GTPases. Therefore, by comparing the polarity between epithelial cells and odontoblasts, we underline the gap in odontoblast polarization and propose an orientation for future odontoblast studies, which will guide the development of new strategies in regenerative dentistry.

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