REVIEW

DENTIN-PULP COMPLEX IN DEEP CARIES

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Abstract: Deep caries progress highlights the gradual shift from reactionary to reparative tertiary dentine as main feature illustrated by transition between the secondary and tertiary dentin. Three sorts of odontoblasts are described to exhibit their dentinogenic potential in genesis of reparative dentine, the still active primary odontoblasts, the formerly quiescent odontoblasts recently reactivated by molecular signals sent from carious lesion, and the secondary odontoblasts resulting from pulp stem cells. This complex cellular secretor involvement in dentinogenesis presume a range of resulting matrices that explain the miscellaneous mineralized final structures encountered in natural evolution of deep caries and especially as therapeutic outcome in pulp capping. Depending on intensity of cariogenic stimuli the effect may be either reactionary dentin relying on a mild action or reparative dentin, mirroring a strong microbial action. The histological response of dentin-pulp complex comprises any exclusive reactionary or reparative tertiary dentin feature as both conditions usually may cohabitate as mishmash in the same pulp.

Keywords: deep caries, reactionary dentin, reparative dentin, secondary odontoblasts

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1. Introduction

Main histological feature in deep caries relies on the shift from reactionary dentine to reparative tertiary dentine as defensive hard tissue barrier between tooth decay and vital dental pulp [1-3]. A thickness over 0.5 mm is commonly a equivalent cut off line separating microbiologically from formal pulp exposure [4,5].

Unless the reactionary dentine, the reparative dentine is rather a scar-like tissue than a proper dentine, having an amorphous mineralized structure characterized by a small number of irregular dentinal tubules [1,5].

The transition from the secondary to tertiary dentin, characterized by irregular dentinal tubules apparently disconnected with unaffected juxtaposed secondary dentin, is marked in histological classic staining techniques by calciotraumatic line [6].

Simultaneously with caries progress, the dynamic process related to remodeling of dentin-pulp complex is associated with local replacement of dying primary postmitotic odontoblasts with newcomers, namely the odontoblast-like cells that actually are novel recruits stemming from the undifferentiated pulp stem cells. They start to generate reparative dentin not later than 20-40 days after primary odontoblasts passed away [7,8].

As far as the adequate caries treatment is provided these "secondary odontoblasts" are able to generate reparative dentine resembling the former tissue condition due to the more tubular features of new laded down dentine [3,8].

Though in clinical setting is impossible to differentiate the histological structures either of carious or normal dentine, a more realistic approach to achieving a successful treatment outcome is to respect the concept of "minimal intervention dentistry" [9,10].

2. Overall status of dentin-pulp complex in deep caries

Excepting the rampant caries, the long-standing invasive stroke of tooth decay microbiome is mild to moderate. Accordingly, the rate and amount of reparative dentine secretion is directly related to the rather predictable intensity, duration and pulp-ward in situ extension of caries relevant microorganisms [2,5].

During deep caries progress in lading down of reparative dentine actually are involved in concert three sorts of odontoblasts, the still active primary odontoblasts, the formerly quiescent odontoblasts recently reactivated by molecular signals sent from carious lesion, and the aforementioned newborn secondary odontoblasts [11,12]. However, this triad is not kept any longer and finally only the surviving odontoblast-like cells remain in charge with secretion of tertiary reparative dentine [13].

Unless the recently erupted permanent teeth, in adults the secretion of reparative dentine is orchestrated by BMP family (bone morphogenetic proteins), chiefly involved being its members BMP-2, BMP-4, BMP-6, and BMP-7 [14. In deep caries besides the

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new generated odontoblast-like cells that are secreting type I collagen matrix of dentine may occurs similar key secretion reactivated pathways of specific dentine matrix non-collagenous proteins (proteoglycans, glycoproteins, dentin phosphoproteins) which are resolutely involved in matrix biomineralization [15-18].

The BMP signaling network follows three interventional paths, on cell membrane and intra- or extra-cellular by using Smad-interacting proteins for transducing the molecular signals from cellular membrane to cell nucleus [11]. Noteworthy, the severe decrease of p38 transcript, as proved during conversion of primary to secondary dentine secretion, highlights the change of odontoblast transcriptom during natural process of cell maturation [11,12].

The secondary, also termed physiological dentine, exhibits a much longer period to be laded down since the in charge with odontoblasts experience a defense process of autophagy directed to keep up their survival in circumstances of local stress injury or starvation [19,20].

Once misplaced, dentine is a tissue that cannot be restored. In deep caries the diffusion of microorganisms or even their proper invasion keep up the response of tertiary dentine that is located in the closest boundary of external injury [21].

Depending on intensity of microbial stimuli, two kinds of tertiary dentine can be generated, either reactionary dentin (mild action) or reparative dentin (strong action). Unlike the reactionary dentine, in which synthesis are involved still surviving primary odontoblasts, in case of reparative dentine secretion are in charge the odontoblast-like cells since the genuine odontoblasts were eventually killed during dangerous deep caries progress [3,6].

Furthermore, when in reactionary dentinogenesis the genuine odontoblasts cooperate with the growth factors of dentine matrix to obtain a fast synthesis response owing to their abilities to prompt or suppress the gene transcription and even change the stem cells gene expression [6,22,23].

Apparently, the reactionary dentine is not a straightforward response of odontoblasts directly tailored to the intensity of external stimuli since its deposition was observed to be done in various rates [21,24]. A hypothetic explanation might be the difference of gene profile in mature odontoblasts versus the new reactivated ones [25].

Basically, the reparative dentinogenesis presumes initially a complex cascade of occurrences consisting in migration of pulp stem cells from their preexisting niches followed by their multiplication and final differentiation in odontoblast-like cells [26-29]. Somehow on micro-scale the synthesis pattern of reparative dentinognesis reproduces tooth morphogenesis [30-32].

Altogether all sorts of odontoblasts try to provide reparative dentine that predominantly has a focal microscopic appearance as much as similar in its tubular structure to genuine secondary dentine. The main differences reside in faster rate of secretion, mild structural irregularities,

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reduced amount of dentine tubules and, despite the anatomic continuity with preexistent tubules, a frequent angle of deviation angle in their trajectory [2,5].

Particularly in high-rate progress of caries the inadvertent accompanying degenerative and inflammatory pulp lesions result in increased worse quality of dentine. Sometimes connective pulp tissue intrusions occur into the recent laid down layers of dentine as consequence of increased porosity and morphologic defects. Hence the proper dentine condition turned out to be rather fibrodentine than reparative dentine [8].

Presently in carious exposure the common vital pulp therapy by pulp capping with proper biomaterials brings about a mineralized barrier only conventionally resembling dentine since histological actually is either fibrodentin, osteodentin, ectopic calcifications or even dystrophic calcifications of former post-pulp injury reparative scar tissue [5,6,32].

This is not a surprising issue as in progressing deep caries the pulp-dentin complex proved to harbor various types of cells exhibiting dentinogenic potential (primary odontoblasts, reactivated primary quiescent odontoblasts, secondary odontoblasts). Moreover, their secretor involvement in dentinogenesis also presume a range of resulting matrices that explain the miscellaneous mineralized final structures both in deep caries and above all in pulp capping [33].

Though mineralized matrices, both fibrodentin and osteodentin are rather defensive matrices than genuine hard dental tissue as tertiary dentin. Accordingly, due to the demonstrated quite different phenotype of pulp cells participating in configuration of the mineral barrier it is at least reluctant to consider equality between these morphological structures [33].

To identify differentiated odontoblast from pulp stem cells is less important to recognize cell polarization related to tubular matrix deposition, the alignment in palisade or the conventional columnar shape. Functional odontoblasts should express phosphophoryns (non-collagenous proteins), which are specific biochemical markers for these dentinogenetic cells [33].

Following successful pulp capping merely scarce chronic inflammatory cells might remind the former inflammatory damage excepting the amorphous atubular mineralized tissue that occasionally entraps islands of necrotic pulp remnants [6].

Until now no evidence based on dentin phenotypic markers proved that dentin-like calcified bridge is real dentine tissue but rather atubular mineralized tissue [6]. The most wanted tubular dentine generated by pulp capping occurs in humans only after in vivo experiments on previously unaffected teeth [34-36].

It seems that temporary in deep caries is actually present an encouraging status of pre-inflammation, which 8-fold enhances the alkaline phosphatase activity and 2-fold expression of 445 genes in charge with regenerative mechanisms. Furthermore, also some recognized powerful pro-inflammatory

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cytokines, namely TNF-α and IL-1β, shift their deleterious target to beneficial stimulation of tertiary dentin secretion [12].

Hence, definitely the fragile balance between repair of dentin-pulp complex and ongoing initial mild pulp inflammation is maintained by proper inter-action of local innate and adaptive immune responses [13,37,39].

Morphologic base of putative dentin-pulp complex repair in deep caries relies on proved persistence of dental pulp stem cells even in reversible pulpitis, which allows their migration, multiplication and differentiation [12,37,39].

An attractive hypothesis is the capability of pro-inflammatory cytokines TNF-α and IL-1β in mild inflammation to recruit the stem cells and support their differentiation in odontoblast-like cells as long as the immune mechanisms enable the pulp defense against final irreversible inflammation [12].

3. Dentin-pulp complex and the relationship repair-regeneration in deep caries

Despite its tremendous operative progress in dental setting, the contemporary trend of pulp regeneration still failed to elucidate the distinction between regeneration and repair during tertiary dentine formation as outcome of successful pulp capping in deep caries exposure as well as their hard to make out inter-relationship [6,39].

Though the lasting deep caries is associated with chronic pulp inflammation as long as carious microorganism do not invade the dentin barrier a transitory response of reparative dentinogenesis is still preserved. Since normally without operative therapeutic involvement this balance is rapidly overturned, the subsequent irreversible pulpitis definitively stops the secretion of reparative dentine [8].

Nevertheless, in untreated deep caries, despite the one way unwanted evolution facing the pulp survival came up some hopeful issues relying on intricate processes of secondary odontoblasts secretion and pulp regeneration since the healing of dentin-pulp complex benefits from some mechanisms of molecular signals similar to those found in reparative dentine secretion [29,40].

Early pulp responses to caries aggression are interruption of odontoblast layer alignment and the cell volume reduction, followed in underposed connective tissue by vasodilatation and sparse acute and chronic cellular inflammatory infiltrate located in subodontoblastic area [6].

On the other hand, the main histological feature highlighting the specific response of dentin-pulp complex against the cariogenic microbiota, obviously present from the medium depth stadium of carious lesion progress, is tertiary dentine [6].

The tertiary dentine located under still unaffected secondary dentine opposite to the front of microbial attack is a reactionary dentine and is depicted as focal-like deposition. In this stage the primary odontoblasts layer preserved the former position in palisade excepting the original

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columnar shape, which is changing in a more flattened one [6].

Simultaneously with local demineralization the organic acids elaborated by cariogenic microorganisms also set free from nearby primary and secondary dentin both fossilized growth factors and embedded bioactive molecules [6,27,39]. Similar to the use of acid etch [41,42], calcium hydroxide or calcium silicate cements in operative dentistry [43,44], these aforementioned active biomolecules up regulate via p38-MAP pathway the somehow stagnant dentine matrix secretion of primary odontoblasts [6,11].

As the caries progress, in the proximal pulp location the odontoblasts attempt to survive initially responding by autophagy in order to improve their status of metabolic exchanges [6,45-47]. However, since concurrently occurs odontoblasts apoptosis is hard to define if autophagy is an independent, non-apoptotic programmed cell death or a cellular mechanism to avoiding apoptosis [48,49]. Following to autophagy the degenerated odontoblasts, similar to apoptotic ones, eventually disappear subsequent to macrophages implication [50,51].

Despite the lasting concern to elucidating the issues of autophagy versus apoptosis unfortunately were not recorded the expectations since the information was obtained by experiments done in deep cavities preparations on healthy teeth. Therefore, the histological outcome mirrors the response of healthy odontoblasts non-affected by previous carious process, which is definitely dissimilar to pulp odontoblasts behavior in deep caries [52,53].

In essence in rapid advancement of deep caries, as long as is still running the synthesis of reactionary dentine, neither new odontoblasts nor other pulpal cells are involved. Furthermore, the continuous decrease of primary odontoblasts results in morphological alteration of reactionary dentine characterized by fewer dentinal tubules and incomplete mineralization [6].

As the caries progress, in the proximal pulp location the odontoblasts dye and are replaced by fibroblast-like cells, which are in charge to secrete a loose collagen matrix and orchestrate the local repair response toward the gradual replacement of resulting pulp scar with atubular calcified tissue [6].

Actually, in long-standing deep caries with unexposed pulp or in long ago already conservatory treated carious lesions there are not found any exclusive reactionary or reparative tertiary dentin histological features. Both conditions of tertiary dentin are not so discrete in the least and may cohabitate habitually as mishmash in the same pulp [6].

Regenerative healing relies on the signals transmitted by transforming growth factors family (TGF-beta), which are compulsory for differentiation and polarization of secondary odontoblasts originating from pulp stem cells [54,55]. The outcome is the complete removal of damaged tissue and its replacement with original healthy one.

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Practically is achieved a complete tissue restitution [6].

Reparative healing is in fact a fibro-proliferative response since only to some extent substitutes the lost tissue with authentic pulp structure and mainly is characterized by intense collagen synthesis leading to scar-like pattern of restitution. Unlike regeneration, the reparative healing only cancels the adverse effect of carious process and does not enable pulp restitution [6]. Furthermore, it seems that when pulp extracellular matrix undergoes a focal disruption of its integrity the new environmental status shifts the pulpal response from regeneration to repair [56].

Moreover, a still running and more fervent debate was focused on the origin of cells replacing the dead odontoblasts, which are in charge with regeneration of dentin-pulp complex damaged by deep caries [57].

Once the primary odontoblasts are eliminated, the biomolecules of transforming growth factors family, mainly TGF-beta which are also active anti-inflammatory agents, stimulate both the recruitment and proliferation of stem cells harbored in specific pulp niches and chemotaxis of copious pulp fibroblasts [6].

A competition occurs between the recruitment of pulp stem cells and fibroblasts chemotaxis. Proliferating faster, being more numerous and more adapted in human to various chronic inflammatory locations, the winners are fibroblasts. The additional stimulation of transforming growth factor TGF-beta, which has proficient anti-inflammatory effect, also opens the door to enhanced local synthesis of collagen, proteoglycans and fibronectin that eventually results in scar formation [6,58-60].

It seems that the shift between pulp restitution and reparation in deep caries depends on the absence of odontoblasts progenitors just at the site of damage and the faster fibro-proliferative process initiated by fibroblasts since these cells even in the presence of local chronic inflammation are usually involved in connective tissue healing [61-63].

Furthermore, the calcified tissue histological depicted in pulp as consequence of local response to carious process, such as amorphous atubular structures and ectopic pulp stones, are rather dystrophic calcifications and not at all an issue linked to pulp regeneration [64].

In chronic pulp inflammation, which usually accompanies deep caries beside odontoblasts are also involved fibroblasts since their plasticity to change the secretor phenotype according to local environment enable to get mineral dystrophy [65].

The stage-like attempt of dentin-pulp complex to arrest the caries injuries aims a complete restoration of damaged pulp. As lasting pathogenic misbalance hinders a true regeneration and the pulp mechanisms of reactionary or reparative tertiary dentine are exceeded, the local antimicrobial pulp defense shall rely almost exclusively on less efficient scar-like tissues [35,66,67].

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4. Conclusions

In deep caries the main histological response of dentin-pulp complex relies on a gradual shift from reactionary to reparative tertiary dentine. The outcome of defensive mechanisms highlights the wide range of miscellaneous mineralized structures encountered in deep caries progress and in pulp capping. While the reactionary dentin secretion usually mirrors a mild cariogenic stimulus the reparative dentin depends on a strong microbial action. Usually in deep caries progress both conditions, reactionary and reparative dentin, cohabitate as mishmash in the same pulp.

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There are no potential conflicts of interest concerning this study.

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Data availability at request.

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