

# Indirect versus direct pulp capping: reactionary versus reparative dentin

## Editorial

Pulp therapies aiming to keep alive the dental pulp use either indirect or direct procedures. It depends of the stage and depth of the carious lesion, of the exposure time, and the degree of bacterial invasion, associated or not with the pulp degradation. Our aim was to clarify the formation of reactionary or reparative dentin.

### Indirect pulp capping and the formation of reactionary dentin

Facing a limited carious dentin, a certain number of layers are found. In this context, the most external part of the dentin constitutes a disorganized layer including a high number of bacteria tightly packed. They colonize and enlarge the dentino-enamel junction, widening the gap between the carious enamel and the soft carious dentin. Debris such as cell walls remnants remaining after by vegetal chewing, and fibers issued from muscle-like 'meat' may also be present. The soft carious dentin located beneath this zone of food debris is a mixture of bacteria and demineralized dentin that may be removed without drilling, using only manually sharp excavators. At the surface of this layer, the carious dentin is fully demineralized. The soft carious dentin displays enlarged tubules, containing bacteria acting within these reservoirs. This layer is totally deprived of peritubular dentin. From the surface to the depth of the lesion, the dentin progressively is less demineralized. Apatitic crystals provide some consistency to this layer. Gradually peritubular dentin reappears. The next carious layer includes a mixture of infected tubules filled by cariogenic bacteria and bacteria-free tubules. A continuous ring of peritubular dentin surrounds the lumens of the canaliculi. Intertubular dentin gradually reach the original structure. Demineralization and reprecipitation occurs at the surface of apatitic crystals, increasing their size in three directions. In the sound dentin, crystals display the following main dimensions: 34Å thick, 139Å wide and 250Å long. In the carious dentin, the crystals increase in thickness, and enlarge. Measurements indicate a 90Å (65-70Å) thickness x 300Å in width, and a length of x 500Å. Crystals reach a final diameter of 120-135Å according to Takuma et al.<sup>1</sup>

In the sclerotic zone, the tubules are filled by intratubular precipitations. The needle-like crystals are thicker and longer than the crystals located within the sound intertubular dentin. In addition to hydroxyapatite crystals, whitlockite, octacalcium phosphate, and amorphous calcium phosphate (ACP) have been also identified.<sup>2,3</sup> A calico-traumatic line separates the dentin already formed during the secondary dentinogenesis from the reactionary dentin. The newly formed dentin is either tubular, or formed by calcospheritic globules that have not merged. The reactionary dentin is in continuity with 'normal' tubular dentin. The dentin may be formed in reaction to the carious decay, or this material is structured as a bone-like tissue, including cells into osteoplasts displaying a bone-like appearance to this structures. Different types of dentin result from the speed of formation of the tertiary dentin. All these structures are elaborated by odontoblasts and eventually they may be replaced by the differentiating cells of the Höhl layer acting as substitute. Bjørndal & Kidd<sup>4</sup> have suggested that it is not necessary and even dangerous to eliminate

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the deepest zone of the soft carious dentin. There is a risk of pulp exposure. This layer should be removed either by hand excavators or by drilling up to the affected dentin. The deepest carious region, near the sclerotic zone should be kept in order to avoid a pulp exposure, and "re-mineralization" occurs within a few months. Then the carious tissue may be eliminated without taking any risk.

Calcium hydroxide or other bioactive agents contribute efficiently to the formation of reactionary dentin, a structure close to secondary dentin. These indirect capping through transdentinal stimulation of the odontoblasts and Höhl cell layers stimulate reactionary dentinogenesis. Demonstration was done by Sognaes and Wislocki<sup>5</sup> that these layers containing acid mucopolysaccharides, alkaline phosphatase, glycogen and carbohydrate groups are stained. Anti-osteopontin, antibodies against the dentin phosphophoryn was present except in the mantle dentin, predentin and inner non-calcified layer of dentin. BSP<sup>6</sup> reduced antigenicity for type I collagen and proteoglycans was detected in the sclerotic dentin (Septier et al., 1998). In dentin, DMP1 is normally cleaved, releasing N-terminal (N-ter) (37kDa) and a C-terminal (C-ter) (57kDa) fragments.<sup>7</sup> Labeling was enhanced with the anti-DSPP. In the sclerotic dentin layer, DMP1 was intensely labeled in both the peritubular and intratubular dentin. This focus on some specificities of the carious dentin.

### Direct pulp capping and the formation of reparative dentin

The treatment of a pulp exposure involves direct capping. Pulp exposed after a deep carious lesion may be treated by bioactive molecules or by differentiated pulp cells. Since the discovery by Herman<sup>8</sup> of the calcium hydroxide [Ca(OH)<sub>2</sub>] method, we get a better understanding of the mechanisms of reparative dentin formation which are involved. The benefits of direct capping of the dental pulp results from the specific effects of each agent. A Zinc Oxide Eugenol (ZnO), coverage seems to be favorable and not cytotoxic. Glass Ionomer (GI), the resin-modified glass ionomer (RMGI), adhesive system, calcium-silicate based materials, have also been used, but all were displaying some cytotoxicity. The capping agents include Mineral Trioxide Aggregate (MTA), TheraCal a light-curable MTA-like material, Proroot MTA and other bioactive molecules of the SIBLING family. Their efficiency varies according to the inflammatory degree, and depending on the pulp degradation by bacteria releasing exogenous

proteases, in close association with endogenous metalloproteinases. Many effects of these molecules acting as capping agents have been already reported. Bone sialoproteins,<sup>9</sup> BMP7, Dentonin (a fragment of the MEPE protein),<sup>11</sup> amelogenin gene-splice products,<sup>12,13</sup> pulp stem cells<sup>14</sup> and Dentin Extracellular Matrix Molecules<sup>15</sup> were evaluated for their efficiency as capping agents.

Accidental pulp exposure is followed by a series of events. Apical pulp cells (SCAP) slide along the pulp root, beneath the odontoblasts and Höhl cell layer. They are issued from the apical part of permanent or exfoliated deciduous teeth (SHED). These stem cells may be in reduced number or totally absent. Stem cells may survive and arise within the inflamed pulp. They migrate, proliferate, and undergo differentiation into terminal cell lines. The lack of progenitors may be counterbalanced by the Induced Pluripotent Stem Cells (iPS). The targeted addition of Growth Factor or Transcription Factors may provoke the dedifferentiation of adult cells and influence their commitment into cells displaying self-renewal and multipotency. Retroviral introduction of *Oct3/4*, *Sox2*, *c-Myc* and *Klf4* induced the differentiation of pluripotent stem cells (iPSC). Positive markers contribute to the terminal differentiation. The positive markers include STRO-1, CD13, CD44, CD24, CD29, CD73, CD90, CD105, CD106, CD146, Oct4, Nanog and  $\beta 2$  integrin, whereas there are also negative markers such as CD14, CD34, CD45 and HLA-DR.

Once pulp cells are differentiated into odontoblasts/osteoblasts, they contribute to cell proliferation and differentiation. Beneath a scars layer due to the elevated pH of the alkaline capping agent, pulp cells accumulate, trans-differentiate and form a layer expressing positive markers of dentin. The cells accumulate in front of the pulp exposure. They become odontoblast-like, and contribute to the formation of a dentin-like bridge (osteodentin). They mineralize and despite the presence of tunnels (tunnel-like structures) the dentinal bridge isolates the dental pulp from the oral cavity. Exposure to saliva contributes to the re-mineralization of this layer. This osteodentin bridge displays barrier properties. The presence of reparative dentin occludes more or less the pulp exposure, and keeps the tooth alive. Reparative dentin displays high type I labeling. Bundles of type III collagen are in close vicinity with fibronectin.<sup>16</sup> Transforming Growth Factor isoform is expressed in carious tissue, both in odontoblasts and this factor increases in tertiary dentin.<sup>17</sup>

Reactionary and reparative dentins are related to indirect or direct pulp capping used as therapeutic methods

1. Reactionary dentin results from the activation and stimulation of synthetic activities of odontoblasts and Höhl cells. Beneath the calico-traumatic line, the newly formed dentin is constituted a reaction toward the carious lesion or restorative materials.
2. Reparative dentin is produced by the recruitment, proliferation and differentiation of pulp stem cells becoming later odontoblast and/or osteoblast-like cells. They will further contribute to the formation of a bone-like structure.
3. Altogether the two structures are implicated in the tooth healing and/or to pulp regeneration and mineralization. These reactions constitute a therapeutic aspect, whereas the other is related to pulp regeneration by using pulp stem cells.

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## Conflicts of interest

The authors declare that there are no conflicts of interest.

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