

## To heal or not to heal? Chemokines as determinants of constructive or destructive inflammatory microenvironments

Dear Readers,

Dental pulp stem cells gained attention as a subpopulation of postnatal stem cells with the ability of multipotential differentiation. Therefore, these cells, specifically SHED (stem cells from human exfoliated deciduous teeth), have been extensively investigated as a potential cellular source to clinical regenerative intervention<sup>12</sup>.

Despite the buzz generated by the potential 'external' tissue engineering (and tooth-engineering) application of dental pulp stem cells, its 'intrinsic' role in dental pulp and periapical tissues repair also have been investigated<sup>6</sup>.

In this context, dental pulp stem cells are supposed to be recruited and activated upon pulp hypoxia, injury and infection, and initially would participate in reparative host response<sup>3</sup>. The initial pulp response to injury is characterized by the classic inflammatory vascular and cellular events, being Gram-negative bacteria and their products (such as LPS) described to be a major trigger of host response in pulp environment.

Interestingly, endodontic infections associated with Gram-negative *Enterococcus faecalis* induce pulp cells to produce the chemokine CXCL12 (also called SDF-1, stromal cell-derived factor-1)<sup>10</sup>. CXCL12 is considered the major chemoattractant factor for the stem cells, whose effect is mediated by its binding to the receptor CXCR4, characteristically expressed by and a marker of stem cells populations<sup>5</sup>. The role of CXCL12-CXCR4 axis in stem cells mobilization was demonstrated in different experimental models, and its modulation was proposed to be a useful therapeutic strategy aiming tissue repair and regeneration. It is important to consider that stem cells mobilization (similarly to inflammatory cell migration) is dependent on inflammation-induced adhesion molecules and chemokines, which characterize a 'constructive' inflammation setting, or, in other words, reinforce the involvement of certain inflammatory mediators in repair process<sup>1</sup>.

However, considering that CXCL12 is observed in both inflamed pulpal and periapical tissues<sup>9</sup>, why noxious stimuli of such tissues leading to a subsequent inflammation not always evolve to a successful tissue repair outcome?

In this issue of the JAOS, Sipert, et al.<sup>11</sup> (2013) describes that while both permanent and deciduous teeth derived dental pulp fibroblasts produce CXCL12 upon LPS stimulation, a simultaneous production of the chemokine CCL3 was also observed. However, while a minor impact in CXCL12 production is described, a clear increase in CCL3 production was observed.

Conversely to CXCL12, CCL3 (also called MIP-1 $\alpha$  - macrophage inflammatory protein-1 alpha) is a prominent inflammatory chemokine<sup>7</sup>. CCL3 is a ligand for the chemokine receptors CCR1 and CCR5, being associated with the recruitment of monocytes/macrophages via CCR1 and lymphocytes polarized into Th1 phenotype by CCR5. Therefore, considering the evident role of such leukocyte subsets in the upregulation of the inflammatory response, usually associated with the production of cytokines such as TNF- $\alpha$  and IFN- $\gamma$ <sup>4</sup>, a predominant expression of CCL3 rather than CXCL12 suggest a trend towards a chronic inflammation instead to inflammation resolution. Accordingly, inflamed dental pulp is characteristically described as a pro-inflammatory environment<sup>2,8</sup>.

Therefore, while CXCL12 can be active even in a chronic inflammation setting, the ultimate cytokine milieu under a stronger influence of CCL3 would not favor healing properties of MSCs. Indeed, pro-inflammatory cytokines have a negative impact in MSCs-mediated healing, being associated with decreased proliferation and differentiation potential. However, while a classic healing scenario is not generally observed in chronically inflamed pulpal and periapical tissues, it is still possible to consider that MSCs play an active role in determining lesions activity or stability, in the view of the potent immunosuppressive properties presented by these cells<sup>6</sup>.

Therefore, the study presented by Sipert, et al.<sup>11</sup> (2013) not only describes the production of the chemokines CXCL12 and CCL3 by pulp cells, but also reinforce the importance of the simultaneous analysis of factors that can lead to constructive and destructive inflammation. Individual analysis of isolated factors may drive biased conclusions, and a broad and simultaneous analysis of distinct classes of mediators seems to be a rational way to elucidate the global immunoregulatory network that determines pulpal and periapical inflammation outcome.

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