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Complement activation links inflammation to dental tissue regeneration

LABORATORY TESTS

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ABSTRACT

In the nineteenth century, researchers identified heat labile proteins circulating in the serum and these proteins were later named the Complement system because it was supposed that they complement the activity of the innate immune system. Complement proteins are primarily secreted by liver hepatocytes and some immune cells and constitute an efficient plasma immune surveillance system. Complement initiates inflammation by inducing vascular modifications and attracting immune cells expressing Complement receptors. Also during bone regeneration several Complement proteins/receptors have been detected and it seems that they can play a major role in this process. Complement C1s was detected during cartilage resorption and contributes to its collagen matrix degradation. This is particularly important for cartilaginous template resorption before ossification of newly regenerated bone. Complement C3 and C5 as well as their respective C3aR and C5aR receptors were detected in mesenchymal stem cells as well as in osteoblasts and osteoclasts. In this article, the authors present a review of literature conducted on Complement local expression and implication in oral tissue regeneration in vivo and in vitro. From the review, it emerges that there is expression of Complement receptors and soluble proteins in dental tissues. In particular, Complement C3b and MAC have been shown to control bacteria growth in the dental pulp while C3a induces pulp stem cell/fibroblast proliferation, and fibroblast recruitment. Complement C5a induces neurite growth, guides stem cell recruitment, and odontoblastic differentiation. Similarly, cultured periodontal ligament cells produce C5a which induces bone marrow mesenchymal stem cell recruitment. In a study reviewed in this article, it has been demonstrated that PDL cells express C5 and produce C5a. The production level of C5a doubled when PDL cells were incubated with extracts from bone filling materials such as OsteoBiol® *Gen-Os*® (Tecnoss®, Giaveno, Italy) of equine and porcine origins. When C5a produced by PDL cells was incubated with human bone marrow mesenchymal stem cells (BMMSCs), C5a bound to BMMSC C5aR and induced its phosphorylation. BMMSC proliferation and recruitment significantly increased when the PDLs were incubated with OsteoBiol® *Gen-Os*®, bone filling materials.

CONCLUSIONS

This review showed Complement implication in two important steps for bone regeneration: bone marrow mesenchymal stem cell proliferation and recruitment to the stimulation/injury site. Moreover, it is evident that PDL cells produce C5a leading to BMMSC proliferation and C5a-dependent recruitment, and these effects can be modulated by bone filling materials, such as OsteoBiol® *Gen-Os*®. Based on the review results, the authors underline that "*dental tissues are prone to infection/traumatic injuries, and severe inflammation may lead to pulp necrosis/periodontal inflammation with subsequent bone resorption. This review highlights that, in addition to its implication in initiating the inflammation, Complement plays a major role in initiating the regeneration process within dental tissues*".

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