

Hypothesis

Low Frequency Electromagnetic Fields Might Increase the Effect of Enamel Matrix Derivative on Periodontal Tissues

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Abstract: Periodontal regeneration is a complex goal, which is commonly pursued with a combination of surgical techniques, biomaterials, and bioactive compounds. One such compound is enamel matrix derivative (EMD), a medical substance that is extracted from porcine tooth germs and which contains several protein fractions with BMP- and TGF- β -like action. Activation of TGF- β signaling is required for EMD activity on cells and tissues, and a growing body of evidence indicates that EMD largely relies on this pathway. As low frequency electromagnetic fields (EMFs) have long been investigated as a tool to promote bone formation and osteoblast activity, and because recent studies have reported that the effects of EMFs on cells require primary cilia, by modulating the presence of membrane-bound receptors (e.g., for BMP) or signal mediators, it can be hypothesized that the application of EMFs may increase cell sensitivity to EMD: as TGFBR receptors have also been identified on primary cilia, EMFs could make cells more responsive to EMD by inducing the display of a higher number of receptors on the cellular membrane.

Keywords: tissue regeneration; electromagnetic fields; bone



Citation: Guizzardi, S.; Pedrazzi, G.; Galli, C. Low Frequency Electromagnetic Fields Might Increase the Effect of Enamel Matrix Derivative on Periodontal Tissues. *Appl. Sci.* **2021**, *11*, 10758. <https://doi.org/10.3390/app112210758>

Academic Editors: Giuseppe Perale and Oleh Andrukhov

Received: 10 September 2021
Accepted: 11 November 2021
Published: 15 November 2021

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1. Introduction

The regeneration of compromised periodontal tissues is a complex endeavor, and has been tackled from different angles over the years, including through the use of surgery, membranes, and growth factors [1]. In contrast to bone, the periodontal ligament does not spontaneously regenerate following periodontitis or trauma, and surgery alone has shown inconsistent results. Enamel matrix derivative (EMD), which is an enamel protein matrix obtained from porcine tooth germs, has yielded promising results, promoting the regeneration of both bone and ligament. Considering the still only partially predictable results of periodontal regeneration, solutions that increase its clinical success are sorely needed. The present paper focuses on the adjunctive use of low frequency electromagnetic fields (EMFs), which can act synergically with EMD to improve tissue regeneration.

2. Hypothesis

EMFs have long been explored as a tool to improve bone regeneration, and their ability to promote bone growth in bone wounds and under bone loss conditions has been investigated in many studies. The hypothesis of the present paper, however, focuses on exploring whether EMFs can synergize with EMD, increase cell and tissue sensitivity to EMD, and thus aid it in promoting the regeneration of periodontal tissues (Figure 1), based on the findings of recent research on these treatments.

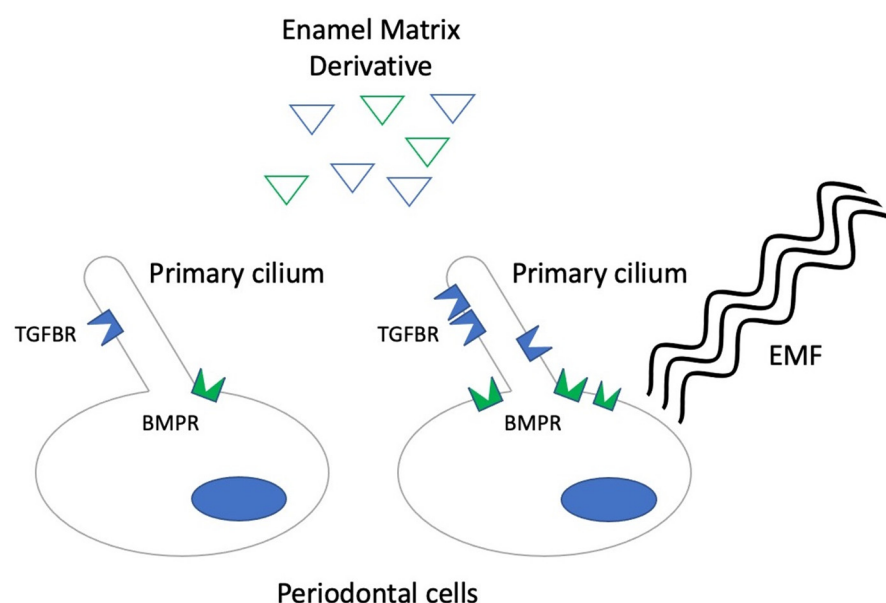


Figure 1. Diagram describing the hypothesized synergistic effect of low frequency electromagnetic fields (EMF) with enamel matrix derivative (EMD). Blue triangles represent the EMD protein fraction with TGF- β -like activity, while the green triangles represent the fraction with BMP-like activity. In the presence of EMFs, higher levels of BMP receptor (BMPR) expression in cells and, possibly, TGF- β receptor (TGFBR) expression on cilia and in the periciliary area is observed, thus making cells more responsive to EMD.

3. Enamel Matrix Derivative

Enamel matrix derivative is a popular therapeutic aid that has been successful in promoting the regeneration of periodontal tissues, including bone, periodontal ligament, and soft tissues [2], while displaying a cytostatic effect toward epithelial cells [3]. Its use is supported by a vast literature [1,4,5]. EMD is obtained from porcine tooth germs and, as such, is a complex compound, containing proteins with different activity [6]. However, it has been repeatedly shown that, besides stimulating BMP-2 and TGF- β 1 expression [7], some protein fractions of EMD actually exert a direct BMP- (fractions 4–6) or TGF- β -like (fractions 8–13) action [8,9], such as promoting Smad2 translocation [10]. A micro-array characterization of gene patterns in gingival and palatal fibroblasts confirmed, strikingly, that EMD was capable of regulating TGF- β target genes [11]. The activation of TGFBR1 receptors—possibly by direct or paracrine action—has actually been shown to be required for EMD activity on palatal fibroblasts [12], periodontal ligament cells [13], and pre-adipocytes [14], for its pro-osteoclastogenic effect on bone marrow [15], and it has been reported that anti-TGF- β antibodies were able to block EMD effects on epithelial cells [16]. Although other components of EMD have been proven to possess distinct biological activities [17,18], it appears that a substantial part of its effectiveness may be due to its capability to stimulate the BMP and TGF- β signaling pathways. Thus, it may find an unexpected ally in low frequency electromagnetic field therapy.

4. Electromagnetic Fields (EMFs) and Cellular Responses

4.1. General Considerations

Electromagnetic fields (EMFs) are a common occurrence, as most man-made electrical appliances generate a fair amount of them. These EMFs compound the EMFs that are intentionally produced and used to transmit signals such radio-waves, Wi-Fi, and cell phones signals, and also natural EMFs [19]. Although ionizing radiations, e.g., X-rays, are prime examples of electromagnetic waves interacting with living matter [20,21], a staggering amount of evidence has consistently shown over the years that non-ionizing radiations, i.e., radiations incapable of ionizing matter, can actually affect cells and tissues [22,23]. After

realizing that the EMFs generated by peculiar electrical wiring or high-power radars could be associated with neoplastic disease [24,25], increasing efforts have been progressively devoted to both reduce the risks associated with the overwhelming EMF pollution that permeates our society [26–41], and use EMFs to benefit patients' health.

4.2. EMFs and Bone

The new application of EMFs in medicine is best characterized by its use in bone healing, as pre-clinical studies have shown that EMFs can increase bone mass in several models of bone loss [42–52], disuse osteoporosis [53–55], diabetes-associated osteoporosis [56], and hyperthyroidism-related bone loss [57]. Its use can also improve bone healing [58–65] in complex clinical situations, such as osteoporotic fractures [66] or arthritis [67]. Numerous clinical investigations have also reported benefits in osteoporosis patients [68–70], and as an adjunctive therapy for non-unions or osteotomies [71–86], although no consensus has thus far been reached on consistent sets of parameters [87]. To further add to the complexity of the issue, EMFs can be generated in a vast range of waveforms, including square, trapezoidal, triangular shape (often known as Pulsed EMFs or PEMFs), and even sinusoidal waves—known as SEMFs [88]—and are often generated as bursts of shorter impulses (PRF EMFs). Their frequencies can range from 0.2 Hz up to 1 kHz [89–92], though in the case of PRF PEMFs, the carrier frequency can be several kHz, and can be applied at different intensities, from a few milli-Tesla up to 1 Tesla and for varying durations.

4.3. EMFs and Cell Signaling

Although EMFs have been shown to induce complex reactions from bone cells, including the activation of several signaling pathways [93], there is a solid body of evidence pointing to the importance of BMP and TGF- β signaling in cell responses to electromagnetic fields. It has long been known that 15 Hz PRF PEMF pulses enhanced TGF- β 1 expression in osteosarcoma cells [94], while a similar stimulation promoted TGF- β 1 secretion in serum-starved MC3T3 cells (Patterson et al. [95]) and in tendon cells [96]. This method also elevated serum TGF- β levels in a rat model of disuse osteoporosis [55]. Complex networks of paracrine feed-forward loops have also been outlined by several works, such as Schwartz et al., who showed that 15 Hz PEMF bursts synergized with BMP to stimulate the expression of TGF- β , both in its latent and active forms [97]. More recently, Selvamurugan et al. have shown that TGF- β signaling is required to gain the effects of 15 Hz, 67 ms-long PRF PEMFs in human bone marrow cells, supporting the activity of miRNA21, a microRNA that suppresses the TGF- β signaling inhibitor Smad-7 [98]. Recent studies, however, have reported exciting new findings on the mechanisms of cell responses to EMFs, including the involvement of primary cilia, which sheds new light on the biological action of electromagnetic fields and may also provide a rationale as to why EMFs could enhance EMD action.

4.4. EMFs and Primary Cilia

Primary cilia are solitary organelles composed of a peculiar inner microtubular structure [99] that can be found on a vast range of cell types, at least in certain differentiation stages [100]. Primary cilia appear as long cytoplasmic extroflexions, which, unlike flagelles, are non-motile and possess an axoneme that is supported by a basal body, which forms when the mother centriole is docked at the cytoplasmic membrane [101]. The periciliary area may therefore act as a microtubule organizing center, and the role of primary cilia in cells is often, maybe unsurprisingly so, to act as a sensor for stimuli of different nature, including mechanical stress, e.g., fluid shear stress in kidney epithelial cells or in osteocytes [102].

The first evidence that cilia are required for EMF stimulation dates back to the report by Yan et al. [103], who showed that 0.6 mT, 50 Hz pulsed EMFs increased the proliferation, mineralization, and expression of differentiation markers in primary rat calvaria cells, but these effects were not observed when primary cilia were disrupted by siRNA inhibition of

the intraflagellar transport protein 88 (IFT88), a molecule that controls the movement of cargo along the axoneme [104]. These findings were then confirmed by Wang et al. [105], who were able to inhibit the response of osteocyte-like MLO-Y4 cells and the expression of Rankl and Opg—two key controllers of bone turnover—to 0.5 mT, 15 Hz PRF PEMFs by silencing the Polaris protein, which is required for cilia formation [106].

Several signaling pathways have thus far been associated with these primary cilia-mediated cell responses to electromagnetic fields: PI3K/AKT has been shown to be activated by 50 Hz, 0.6 mT PEMFs in rat calvaria osteoblasts, which require the presence of primary cilia [107]. There is also evidence indicating that the cAMP/PKA/CREB signaling pathway is activated by PEMF in the same cell model [108] and that Wnt10b/ β -catenin is also required for osteoblast responses to sinusoidal EMFs [109]. What is most interesting is that, in this latter study, Wnt10b appeared to co-localize at the base of the cilia, only to be recruited and disappear upon EMF stimulation. This is also consistent with an important study by Xie et al., which demonstrates that BMP receptor II (BMPRII) was required for the increased BMP-Smad1/5/8 signaling in primary rat calvaria cells after PEMF stimulation, and that PEMFs up-regulated the expression of BMPRII at the base of the cilia, which in turn were required for BMPRII signaling [110].

4.5. Primary Cilia and Membrane Trafficking

Primary cilia have also been singled out as key structures for controlling vesicle trafficking and membrane receptor expression. The base of the cilia in many cell types, including fibroblasts, are normally surrounded by a special membrane domain known as the cilium pocket region (CiPo), which has a peculiar biomolecular composition and is a hotspot for both exo- and endocytosis [111], while the tip of the cilia is a source of extracellular vesicles [101]. Cilia and the surrounding membrane area thus appear to be rich in clathrin-coated pits, clathrin-coated vesicles [112], endosomes [100,113–115], and possibly caveolae [116], which are controlled by the complex cytoskeletal network that underlies and surrounds cilia [101]. Vesicle endocytosis is a power tool that cells use to control the array of membrane-bound receptors exhibited on their surface. Cells can actually tune their signaling capabilities by removing available receptors from the membrane or by providing more free receptors for ligand binding [115]. Somewhat unsurprisingly, then, cilia and the periciliary area are rich with several kinds of receptors, including the BMP receptor, but also PDGFR and TGFBR [113,117]. TGF- β receptors, in particular, have been shown to be localized at the tip of the primary cilia in fibroblasts, and their signaling has been proven to be regulated by vesicle trafficking, as clathrin-mediated endocytosis promotes their activation [116], whereas caveolin-mediated endocytosis downregulates TGF- β signaling [118].

Although no published evidence has addressed the effect of electromagnetic fields on the turnover of TGF- β receptors in the ciliary and periciliary area yet, there is evidence supporting the hypothesis that EMFs can actually control clathrin-mediated endocytosis in murine B16F10 melanoma cells [119–121], autophagy in human neuroblastoma SH-SY5Y cells [122], phagocytosis in mouse macrophages [123], and endocytosis at synapses [124]. There is also solid evidence that 75 Hz, 2.5 mT PEMFs upregulate the expression and membrane density of adenosine receptors in osteoblastic cells [125], as well as in other cell models [126], and this could provide a clue as to one way that EMFs could also control TGF- β signaling.

5. Hypothesis Testing

Although the pre-clinical in vitro and in vivo testing of this hypothesis may appear straightforward, when it comes to the chosen model, the most challenging factor is possibly the choice of the optimal parameters for EMF stimulation, most noticeably EMF frequency, waveform, and intensity, but also the duration of treatment. The plethora of experimental conditions proposed in the literature has often relied more on technological availability, convenience, or the need to use distinctive instruments and protocols for commercial

reasons than purely scientific rationales, but recent attempts to apply machine learning algorithms to pinpoint the most promising experimental parameters [127] may prove a first step in the right direction. The most common stimulation regimes supported by the literature are 75 Hz EMFs with trapezoidal waves, with treatment intensities in the range of 1.5–2.5 mT and 15 Hz PRF PEMF bursts with intensities of 0.3–1.8 mT. In the case of sinusoidal waves, however, 50 or 60 Hz waves with intensities between 0.6 and 1.8 mT are possibly the most common parameters in the literature.

6. Conclusions

Electromagnetic fields may prove to be a relatively inexpensive support treatment to enhance the effectiveness of EMD in restoring periodontal tissues, such as periodontal ligament, as they have been shown to act on several signaling pathways, and because there is mounting evidence that they can regulate the membrane receptor availability on and around primary cilia. Their action is known to affect BMP receptors, and we hypothesize that it might also affect TGF- β receptors, by controlling membrane trafficking. This, in turn, would make cells more sensitive to the action of BMP and TGF- β growth factors (Figure 1), which are pivotal to the action of EMD, either through paracrine stimulation or through the direct action of some of the protein fractions contained in EMD.

Author Contributions: Conceptualization, C.G., G.P. and S.G.; writing—original draft preparation, C.G.; writing—review and editing, G.P.; supervision, S.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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