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THESE POUR LE DIPLOME D'ETAT DE
DOCTEUR EN CHIRURGIE DENTAIRE

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Isaac Asimov

L'esprit intuitif est un cadeau sacré et l'esprit rationnel une fidèle servante.
Albert Einstein

A mes grands-parents,

A mon père et ma mère,

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TABLE DES MATIERES

Liste des abréviations

β-TCP : β-tricalcium phosphate

BMSC : Cellules souches issues de la moelle osseuse

CSA : Cellules souches issues du tissu adipeux

CSM : Cellules souches mésenchymateuses

GMSC : Cellules souches issues de la gencive marginale

HA : Hydroxyapatite

IL-1 : Interleukine 1

PDLSC : Cellules souches issues du ligament parodontal

PGA : Acide polyglycolique

PRP : Plasma riche en plaquette

RTG : Régénération tissulaire guidée

INTRODUCTION

Contexte et objectif de l'étude

Le parodonte est le tissu de soutien de la dent. Il est un tissu hautement spécialisé et en perpétuelle renouvellement[1]. Ce système d'attache se compose de tissus mous, gencive et ligament parodontal, ainsi que de tissus durs, cément et os alvéolaire. Le parodonte est divisé en deux parties : superficielle et profonde. La gencive appartient au compartiment superficiel et est responsable des échanges *via* le sulcus de fluides entre la cavité buccale et le parodonte. Elle est le siège de manifestations parodontales comme la gingivite et le témoin d'atteintes sous-jacentes chroniques. Quant à lui, le parodonte profond est composé du ligament parodontal, du cément et de l'os alvéolaire. Il a un rôle d'encrage, de stabilisation et d'amortissement de la dent. L'infection parodontale la plus commune est la parodontite[2,3]. Cette pathologie multifactorielle est due à une contamination de bactéries opportunistes associée à un ou plusieurs facteurs de risque (i) locaux tels que le tartre, les caries (ii) généraux tels que le diabète, le VIH (iii) ou encore liés aux conditions de vie tels que l'addiction tabagique, le niveau socio-économique. En réponse à cette agression bactérienne, le processus inflammatoire mis en place va progressivement détruire le parodonte, aboutissant à une perte prématurée de l'organe dentaire[4].

Les traitements conventionnels ont pour objectif de réduire la charge bactérienne par une élimination non-chirurgicale ou chirurgicale de la plaque et du tartre associés à une hygiène rigoureuse par le patient. Malheureusement, ces traitements aboutissent à la formation d'un tissu cicatriciel (long épithélium de jonction) entraînant des séquelles esthétiques et fonctionnelles. Face à ces limites, plusieurs thérapeutiques ont été développées pour tenter de restaurer la perte de tissu[5] : (i) la greffe d'os autogène, (ii) l'implantation de biomatériaux osseux tels que des dérivés ou substituts osseux, (iii) la régénération tissulaire guidée (RTG) basée sur l'exclusion tissulaire par la mise en place d'une barrière de porosité variable[6] et (iv) l'implantation de facteurs de croissance, tel que l'EMDOGAIN®[7,8]. Cependant, les résultats

cliniques manquent de prédictibilité due aux capacités de régénération intrinsèque du patient, au type de défaut (nombre de parois, par exemple) ou encore à l'approche chirurgicale[9,10]. Ces nombreuses limites ont finalement conduit au développement de nouvelles stratégies thérapeutiques comme la médecine régénératrice.

La médecine régénératrice, discipline associant des cellules souches mésenchymateuses (CSM) à un biomatériau, est une alternative prometteuse aux techniques chirurgicales actuelles[11]. Bien qu'attrayantes, ces stratégies restent controversées quant au choix de la combinaison CSM/biomatériau ainsi qu'à leur efficacité et utilisation chez l'homme[12,13]. En effet, de nombreuses études scientifiques, fondamentales, précliniques et cliniques ont été publiées dans ce domaine[14].

L'analyse systématique de la littérature permet d'augmenter la valeur individuelle d'études scientifiques. Basée sur une stratégie standardisée, cette analyse est un outil essentiel pour élaborer les preuves de concept de manière fiable et précise, et fournit un point de départ pour la pratique clinique[15]. Dans le cas de la médecine régénératrice parodontale, une revue systématique de la littérature peut fournir des informations précieuses pour une pratique clinique appropriée.

L'objectif de ce travail est d'effectuer une revue systématique de la littérature pour clarifier l'efficacité de l'utilisation de CSM associées à un biomatériau en médecine régénératrice parodontale, sur des modèles animaux précliniques et chez l'homme.

ARTICLE

“Periodontal regenerative medicine using mesenchymal stem cells and biomaterials: a systematic review of pre-clinical studies”

Sophie PORTRON, Assem SOUEIDAN, Anne-Claire MARSDEN, Mia RAKIC, Christian VERNER, Pierre WEISS, Zahi BADRAN, Xavier STRUILLOU

-Soumis : Dental Materials Journal -

1. Résumé

Contexte : La maladie parodontale est une pathologie inflammatoire répandue aboutissant à la destruction des tissus de soutien de la dent. A ce jour, aucun traitement conventionnel ne permet de régénérer *ad integrum* le parodonte.

Objectif : Cette revue systématique de la littérature a pour objectif d'analyser l'utilisation de CSM associées à un biomatériau pour la régénération parodontale sur des modèles animaux précliniques et chez l'homme.

Méthodes : L'analyse des bases de données ainsi qu'une recherche manuelle dans les principaux journaux de la discipline a été réalisée jusqu'en juillet 2018. Ces recherches suivent le protocole PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines). Les critères d'inclusion sont : l'utilisation de CSM associées à un biomatériau, le nombre de spécimen précisément indiqué, une mise en place *in vivo*, une évaluation histologique et radiologique, une publication en anglais. Pour chaque étude, les résultats ont été analysés et le risque de biais évalué.

Résultats : Cinquante articles ont répondu aux critères de sélection et ont fait l'objet d'une analyse systématique standardisée. Trente-neuf études utilisent un modèle animal préclinique (cochon, mouton ou chien) et 11 articles ont été publiés chez l'homme. L'analyse du risque de biais des articles sélectionnés met en évidence la faible puissance statistique de ces études, principalement due à un protocole opératoire dépourvu d'expérimentation randomisée et en double aveugle. Nos résultats montrent que l'association de CSM avec un biomatériau adapté entraine un effet bénéfique sur le tissu parodontal nouvellement formé, chez des modèles animaux précliniques et chez l'homme.

Conclusion : La revue systématique de la littérature menée nous a permis de montrer l'intérêt thérapeutique de la médecine régénératrice en parodontologie.

Des études cliniques sont nécessaires afin de déterminer l'association optimale CSM/biomatériau pour régénérer le parodonte. Une importance devra également être portée sur le tissu nouvellement synthétisé avec la caractérisation du type de cément formé ainsi que l'organisation et l'orientation des fibres ligamentaires régénérées.

2. Article

PERIODONTAL REGENERATIVE MEDICINE USING MESENCHYMAL STEM CELLS AND BIOMATERIALS: A SYSTEMATIC REVIEW OF PRE-CLINICAL STUDIES

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Key words: mesenchymal stem cells, periodontal diseases, periodontal regeneration, review, systematic, pre-clinical study.

Declarations of interest: none

ABSTRACT

Context: Periodontitis is a common inflammatory disease resulting in soft and hard tissue destruction around the teeth. Conventional treatment strategies fail to restore *ad integrum* periodontal tissue.

Objective: This systematic review aimed to analyse the use of mesenchymal stem cells (MSC) and biomaterial for periodontal regeneration from preclinical animal models and human.

Methods: To July 2018, electronic databases were searched and additional hand-search in leading journals was performed. The research strategy was achieved according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The including criteria were as follows: studies using MSC, biomaterial, with the precise number of

specimens, and *in vivo* studies, with histologic and radiologic analysis, written in English. The data was extracted from each article and the risk of bias was assessed for individual studies.

Results: A total of 50 articles met the criteria of inclusions and were investigated in the systematic review.

Conclusions: These results indicate that the association of MSC with suitable scaffold may provide beneficial effects on periodontal regeneration in preclinical animal models and humans, with no adverse effects of such interventions. Future studies need to identify the suitable association of MSC and biomaterial for periodontal regeneration and to characterize the type of new cementum and the organization of the periodontal ligament fiber regeneration.

INTRODUCTION

The periodontium is a highly specialized and dynamic tissue. It consists in a tooth-anchoring device made of two soft tissues, the gingiva and the periodontal ligament, and of two hard tissues, the cement and the alveolar bone. The gingiva, part of the superficial periodontium, is composed of an epithelium and a connective tissue, forming a periodontal attachment system that allows fluid exchange and assures a complete crimp around the tooth[1]. As for the deep periodontium, made of the periodontal ligament, the cement and the alveolar bone, it acts like an alveolar anchorage system, enabling both stability and damping of the tooth. In the oral environment, the periodontium is confronted with more than 1000 bacteria species[2]. Thus, the space between the tooth and the surrounding gingiva, called sulcus, can become a gateway to potential inflammatory diseases. The most common cause of periodontal destruction is periodontitis[3, 4]. This multifactorial disease is due to an opportunistic bacteria contamination on a specific site, paired with local risk factors (e.g., insufficient oral hygiene, decay) and

general risk factors (e.g., HIV, diabetes). In response to this bacterial aggression, an inflammatory process in the gingival sulcus will slowly destroy the periodontal structures and attachment, leading to tooth mobility and premature tooth loss[5].

Conventional treatment strategies are based on a sustained decrease in the microbial load through a non-surgical or a surgical elimination of the dental plaque associated with assiduous plaque control from the patient. In spite of great progress in the understanding of the pathogenesis of periodontitis, the tools to treat it seem to only postpone the unavoidable tooth loss linked to periodontal disease, and fail to restore *ad integrum* periodontal tissue, proving it unsatisfactory both for patients and for dental surgeons. Since the 1970s, several procedures have been attempted to restore such lost tissues, including autogenous bone grafting, implantation of biomaterials including bone derivatives and bone substitutes, guided-tissue regeneration (GTR) procedures[6], and implantation of biologic factors, including enamel matrix proteins[7, 8]. Still, these strategies fail to regenerate the complete periodontium damage since the quality of repaired tissue remain variable and limited[9, 10]. To date, complete periodontal regeneration is not achievable in a highly reproducible and easy way. Therefore, functional and aesthetic sequelae are commonly found in treated patients with a history of periodontitis.

That is why, re-establishing the original structure, proprieties and functions of the diseased periodontium remains a significant clinical challenge. To address this issue, regenerative medicine using an effective combination of mesenchymal stem cells (MSC) and biomaterial have become subjects of particular interest[11]. Thus, a wide variety of the studies focus on MSC and try to combine their potential with suitable biomaterials in order to obtain a periodontal regeneration[12]. Despite numerous publications in pre-clinical animal models and

humans, the efficacy of the association of MSC and biomaterial for periodontal regeneration remain controversial[13, 14].

To increase the value of individual preclinical studies as proof of concept for randomized clinical trials, systematic reviews have been proposed as the standard method for analysing experimental work involving animals[15]. Systematic review is an essential tool for summarizing evidence reliably and accurately. It provides a starting point for guideline developers for clinical practice. In the case of regenerative medicine for the enhancement of periodontal regeneration, a systematic review may provide valuable information for a suitable clinical practice.

In this context, the purpose of the present systematic review was to assess the scientific literature to obtain more clarity on the efficacy of periodontal regeneration strategies using the association of MSC and biomaterials in pre-clinical animal and human studies.

MATERIAL AND METHODS

The different studies concerning periodontal regeneration with the help of MSC and biomaterials on human or animal models have been collected and analysed.

Information sources and search strategy. The research strategy was achieved according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[15] as much as possible. Original articles were searched using electronic and manual databases until March 2018. Furthermore, relevant articles were screened by hand to potentially add relevant new articles.

This search was applied to Medline, Cochrane Library, Lilacs and Report Evidence-based Practice Centers (EPC). Electronic searches were completed by additional hand-search

performed for the International Journal of Periodontics and Restorative Dentistry, the Journal of Clinical Periodontology, the Journal of Dental Research, the Journal of Periodontal Research and the Journal of Periodontology.

The following Medical Subject Heading (MeSH) terms and keywords were used: “stem cell”, “periodontal”, “regeneration”, “biomaterial”, and “*in vivo*”. Only English articles were included, and no publication dates or publication status restrictions were imposed.

Study selection and inclusion/exclusion criteria. For the selection of studies, two investigators (SP, XS) screened the titles and the abstracts of the publications in an unblended, standardized manner. Selection was based on the inclusion and exclusion criteria defined so as to include only the most valuable articles (**Table. 1**). Studies deemed to meet the inclusion criteria and those with insufficient information to make a clear decision were selected. The second phase consisted of assessing the whole articles by the same investigators to determine the eligibility of the study. The selection process was recorded in detail to a PRISMA flow diagram (**Figure. 1**). Any disagreements between the two investigators regarding inclusion of a study were resolved by discussion.

Data collection process and data items. The characteristics of the study were extracted independently by the same investigators and recorded. The data were compared for accuracy and any discrepancies were discussed and resolved by consensus.

Both reviewers extracted from the included studies the following data: (1) Cell type, passage number, differentiation, number per defect; (2) Biomaterial (+/- membrane); (3) Animal models: species, strain, sex, age, weight; (4) Number of defects per group; (5) Defect type, size, induced inflammation; (6) Treatment groups; (7) Observation period; (8) Qualification

of newly formed tissues; (9) Results (**Table 2**). If one of these data is not reported in the table, it means that the information is not mentioned by the authors.

Risk of bias in individual studies. To ascertain the risk of bias in eligible articles, the same investigators in a blind manner evaluated their methodology either by SYRCLE's Risk of Bias tool for animal intervention studies[16], or by Risk Of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool[17] modified for human non-randomized trials; or by the Cochrane Collaboration's tool for human randomized trials[18]. The case reports were excluded from the risk of bias analysis because of the absence of adapted methodology.

Regarding SYRCLE's Risk of Bias tool, the unit of analysis errors is assessed as a "high risk of bias" if the interventions to parts of the body within one participant (i.e., splits mouth: control and experimental side) was reported. In addition, many items remain as "unclear" due to the poor description of methodology. In order to complete the investigation, two items were added mentioned as follows: "mention of randomization" and "mention of binding".

Concerning the Cochrane Collaboration's and SYRCLE's Risk of Bias tool, we considered that there was no exclusion of animals when the number of animals reported in the method section equaled to the number mentioned in the results section. Disagreements between the investigators were resolved by consensus.

Data synthesis. A meta-analysis could not be performed because of the studies' heterogeneity. Consequently, we conducted a descriptive and systematic analysis of the studies.

RESULTS

Study selection. Taking into account the previously defined criteria, 1423 studies were initially identified (**Figure. 1)**. The electronic search of Medline, Cochrane library, Lilacs, EPC databases provided 1300 articles. Additionally, 123 studies were selected by hand-searching the International Journal of Periodontics and Restorative Dentistry, the Journal of Clinical Periodontology, the Journal of Dental Research, the Journal of Periodontal Research and the Journal of Periodontology. After adjusting for duplicates and reading the title and/or the abstract, 96 studies remained. Out of these, 96 were discarded because after reviewing the whole article, it appeared that these papers clearly did not meet the inclusion criteria. A total of 50 articles were included in the systematic review.

Study characteristics. The studies were then ranked in a comparative table (**Table 2 and 3**) according to the alphabetical order. These tables show a wide variety of combinations of MSC and biomaterials. The review began with an analysis of the type of population, mainly of preclinical animal species. Indeed, experimental models in majority are found in dogs, employed in 25 studies. Twelve studies were performed with miniature pigs and two with sheeps. Only 11 studies have been performed with humans. A variety of periodontal defects were used in the selected studies, including class III furcation defects (7 studies), fenestration defects (3 studies), intrabony with class II furcation defects (1 study), class II furcation defects (6 studies), dehiscence defects (2 studies), a root-shaped implant sockets (2 studies), alveolar sockets (2 studies), combined periodontal-endodontic lesions (1 study) but most of the articles used intrabony defects (26 studies). It seemed relevant to underline that although periodontitis is an inflammatory disease, the defects models employed in preclinical studies were largely not inflammatory (in 26/39 studies, defects were surgically created). Then, the

studies were categorized according to the type of MSC or biomaterial used. The periodontal ligament stem cells (PDLSC) were by far the most studied with 16 publications, whereas bone marrow stem cells (BMSC) were used in only 12 studies. As for scaffolds, collagen is used in most of the studies (10 studies). The general analysis of clinical studies has shown that studies mostly based on animals mainly used a combination of PDLSC and collagen.

Risk of bias within studies. Figure 2 shows the overall results of the risk of bias assessment. Subgroup analyses was performed to assess the quality of preclinical studies (**Figure. 2a**), non-randomized human trials (**Figure. 2b**) and randomized human trials (**Figure. 2c**), using an adapted methodology. Firstly, the risk of bias assessment for preclinical animal studies was investigated. Establishing that only 44% and 72% of the studies do not mention randomization or blinding respectively, our data show a high score of unclear risk of bias for the selection, performance and detection items (47%, 95% and 95% respectively). Interestingly, the data outcomes were adequately addressed for 87% of the studies. Furthermore, the majority of the studies were free from selective outcome reporting (67%). Thereafter, non-randomized human trials were investigated for the quality of the methodology. Results revealed that 75% and 50% of the studies were marked for unclear risk of bias for pre-intervention and at-intervention items respectively. On the opposite, post-intervention items display a low risk of bias (88%). As expected for randomized human trials, our results did not show a high risk of bias. However, regarding selection bias, 33% of the included studies were marked for an unclear risk of bias. In addition, only 33% of the articles were considered to have a low risk of bias for its performance and detection. Finally, all studies were considered to have a low risk of bias for their attrition and reporting.

Synthesis of results. For each study, the relevant results are summarized for studies of preclinical animal models (**Table. 2**) and for Human studies (**Table. 3**). Overall analysis showed the association of MSC and biomaterial enhancement of periodontal regeneration for the majority of the studies.

DISCUSSION

The significant impact of periodontal disease on general health and the quality of life necessitates the need to regenerate the damaged tissue more effectively[19]. Consequently, the regeneration of bone, cementum and an effective periodontal ligament remains a major challenge. Periodontal regenerative medicine is considered as a promising treatment modality for future therapy. Along this line, the present systematic review intended to investigate the controversial results raised from the scientific literature on the efficacy of the periodontal regeneration strategies, using the association of MSC and biomaterials in pre-clinical animal models and humans.

Literature searches retrieved 50 studies. After a careful analysis, our results revealed that it was not possible to perform direct head-to-head comparisons of these studies as a result of variations between studies, in terms of the healing time after cell transplantation, the biomaterials applied, the defect type and size, the used cell types and passage number, and the number of cells per defect. Not surprisingly, no meta-analysis of the data could be carried out.

Indeed, the study of the risk of bias has revealed that poor reporting of animal studies in scientific publications is of serious concern. Preclinical animal studies and case reports are, in

general, analysed with less methodological rigour than trials. Key measures to avoid bias such as, randomization and blinding, were infrequently reported. This may lead to an overestimation of the effects of cells on periodontal regeneration compared to the group control system. This seriously hampers drawing reliable conclusions from animal studies. Despite these limitations, the combined analysis of the included studies still generated extra and valuable information that could not be derived from the individual analysis of studies.

Periodontal regenerative medicine is a multidisciplinary field combining biology and engineering. In this context, the present discussion focuses first on MSC and second on biomaterials used for periodontal regeneration.

Stem cell biology has become an important field in regenerative medicine and tissue engineering therapy since the discovery and characterization of MSC. In particular, stem cells have great versatility at the level of tissue regeneration for many different characteristics and can modulate chronic inflammation, a central feature in periodontitis. Given the characteristics of these cells, they are considered a potentially useful tool for the efficient regeneration of periodontal tissues[20]. Thus, one of the most important issues for clinical application of regenerative medicine approaches is the type of cell used.

Bone marrow has been the main source of MSC used for regenerative medicine. For several years now, BMSC has been the object of a lot of periodontal regeneration research, more often on animal models. To date, there exists only one case reported on a human suffering from chronic periodontitis. The authors concluded that the combination of BMSC and Platelet-rich Plasm (PRP) should entail a radiological and clinical improvement in terms of pocket depth, attachment gain, loss of bleeding on probing, and tooth mobility[21]. In addition, a randomized trial, focusing on the safety and the efficacy of regenerative treatment of

infrabony defects using autologous BMSC, combined with collagen scaffolds enriched with fibrin glue is ongoing (NIH clinical trial registration number: NCT02449005). The combination of BMSC and PRP has also been a success on animal models in 3 different studies, each independently conducted by Simsek *et al*, Hasegawa *et al* and Kawaguchi *et al*[22–24]. Even though the periodontal regeneration was nearly complete in the study by Simsek *et al*, both Hasegawa and Kawaguchi unfortunately concluded with incomplete tissue regeneration and particularly, that of the alveolar bone. With average positive results, the BMSC seems to enable an improvement in bone, periodontal ligament and cement regeneration[25, 26]. However, bone marrow suffers certain limitations that are related to its painful harvest and to the limited number of collectable cells. In light of these limitations, authors investigate other sources of adult tissues in order to collect stem cells. Within the orofacial area, several sources of MSC have attracted scientific interest, given their similarity to BMSC, their immunoregulatory capacity, and their minimally invasive harvest procedure[27].

Periodontal (PDL) derived cells. Thirty years ago, the concept that stem cells may reside in the periodontal tissues was put forward by Melcher[28]. Not until 2004, periodontal ligament stem cells were first isolated and characterized as stem cells[29]. Over the past several years, the number of animal studies on PDL-derived cells have been increasing. Not surprisingly, in the present systematic review, the majority, i.e., 40% of the 50 studies were dedicated to periodontal ligament-derived cells. Feng *et al.,* were the first to transplant progenitor cells of the periodontal ligament combined with calcium carbonate, into periodontal defects of 3 patients suffering from chronic periodontitis. The results concluded in a gain of clinical attachment with a decrease in pocket depth, a bone tissue regeneration and finally, a recession improvement over 72 months[30]. Menicanin *et al.,* have combined autologous PDLSC to a gelatin scaffold on sheep models. The results in the test groups were very encouraging due to

a superior regeneration with the development of cement, bone and ligament structures[31]. In addition, Liu *et al.* and Ding *et al.*, independently obtained the same types of results, with a near complete regeneration of the periodontal tissues after implanting a combination of autologous PDLSC to HA/βTCP in intrabony defects on porcine models over a period of 12 weeks[32, 33]. Moreover, in order to simplify the clinical protocol set for the dental surgeon in his everyday practice, some studies use periodontal ligament cells without isolating the stem cells beforehand. Combined with either a collagen scaffold, calcium carbonate, PGA, HA, β-TCP or hyaluronic acid, different authors agree that their cells shown a significant improvement in terms of the height and thickness of the bone, of cement and the periodontal ligament regeneration[30, 34–39]. A systematic review by Bright *et al.*, on PDL-derived cells for periodontal regeneration reported that 12 out of the 17 included studies relate a statistically significant positive effect in periodontal regeneration[14]. A recent randomized clinical trial on 20 patients suffering from chronic periodontitis revealed that the implantation of PDLSC associated with Bio-Oss® over a period of 1 year significantly improved the alveolar bone height and the clinical parameters over time, but no significant differences between the implantation of PDLSC/Bio-Oss® and the implantation of only Bio-Oss® were found[40]. In conclusion, even if the results are contradictory, the majority of the studies reveal a positive and promising effect on the regenerative potential of PDL-derived cells.

The use of dental pulp stem cells (DPSC) has shown some potential towards regenerating the periodontium. Interestingly, 3 independent case reports described an improvement of the clinical parameters of periodontitis by the implantation of DPSC with collagen scaffold[41, 42] or β-TCP[43]. Although the results of several pre-clinical animal studies and case reports were promising, human randomized trials are required to evaluate the efficacy of those procedures in regenerating true periodontal defects.

The others stem cells used. The efficiency of cellular therapy using autologous gingival fibroblasts has been evaluated by Fawzy *et al.*, when they were combined with gingival margin stem cells (GMSC) to Bio-Oss® or IL-1ra-releasing HA-ECM scaffold on a miniature pig subject. Whatever the biomaterial used, the team of researchers concluded with a reduction of pocket depth, a gain of clinical attachment and of bone density[44, 45]. In 2008, Yamamiya *et al.,* conducted a study on 30 patients suffering from chronic periodontitis, where they combined periosteal cells with PRP and HA over a period of 1 year[46]. The results were positive from a clinical and a radiological point of view. Okuda *et al.,* also studied the same combination in a dog model and reached the same conclusion[47]. Adipose stem cells (ASC) has always seemed very appealing to researchers in periodontal regeneration. Tobita *et al.,* and Ozasa *et al.,* implanted ACS into periodontal defects on canine models with PRP[48] or fibrin gel[49], respectively. The morphometric, histologic, immuno-histologic and radiological analysis confirmed a superior bone, cement and ligament formation in the cell group.

Interestingly, a previous systematic review and meta-analysis, which included a large number of studies using only animal models (sheep, dog, minipigs, rats, mice), provided evidence for the enhancement of periodontal regeneration by the implantation of either PDL-derived cells or BMSC[50, 51].

To have a chance of achieving periodontal regeneration, the cells need to be delivered and stabilized on the defect by a biomaterial. The concept of a scaffold is based on a biomimetic strategy, capable of incorporating and releasing molecules, and permitting cell to cell and cell to matrix interactions. The choice of the releasing method will depend on the type of cell population released and on the type of defect; specifically, the number of alveolar bone walls involved. When defects are larger, outcomes may improve when cells are associated with bone substitute or cell sheets attached with PGA are transplanted onto the tooth root surface,

after which the bone defects are filled with bone substitute[36, 38, 39, 52, 53]. On the opposite, gel scaffold might be used when lesions are retentive. As shown in this systematic review, clinical studies mainly use a scaffold made of collagen. Collagen materials may be particularly useful due to their biocompatibility, resorbability, cell occlusiveness and their capability of promoting wound healing. Collagen offer a safe scaffold material because of occurring naturally and being involved in numerous physiological processes. Although collagen can be constituted into various forms such as fibers, sheets, hydrogels, and sponges[11]. Most biomaterials have some drawbacks such as follows: unpredictable cell-biomaterial interactions, non-homogeneous biodegradation, immune reaction, and low efficiency cell seeding. Injectable scaffolds, easily applied without invasive surgery, can improve cell retention, distribution and more importantly activate in situ cell proliferation and differentiation. Hydrogels are not only biocompatible with a high resorption level but they show a better cell retention than other injectable biomaterials, as confirmed by a number of studies[54]. They can be prepared from alginate, chitosan, collagen or cellulose, seeded with cells and then gelation can be initiated by changing the temperature, pH, cross-linking or radical polymerization. The goal is to obtain a high cell retention followed by a good integration capacity and a high level of surviving cells with reduced side effects and minimal stress for the patient[12].

The present systematic review achieves, for the first time, a comprehensive analysis of the scientific literature concerning the periodontal regenerative medicine. To date, current data indicate that MSC associated with suitable scaffolds may provide beneficial effects on periodontal regeneration in preclinical animal models and humans. In particular interest, the human studies suggest that there are no adverse effects of such interventions[40, 42].

Although clinical trials are promising, future animal studies are still needed to determine the suitable association of MSC and biomaterial for periodontal regeneration and to characterize the type of cementum, and the organization of the periodontal ligament fiber that is regenerated. Furthermore, these studies should also compare periodontal regenerative medicine with the gold standard therapies used to repair periodontium.

CONCLUSION

Several approaches using MSC for regenerating damaged periodontium are under study with varying degrees of clinical applications. Given the heterogeneity of the studies concerning the periodontal regenerative medicine, narrative reviews are insufficient. A systematic approach appears essential to provide guidance to support future studies and should provide information that can be generalized. Our results indicate that MSC may provide beneficial effects on periodontal regeneration. The present systematic review supports crucial information for the implementation of regenerative medicine strategies in clinical practice in the future.

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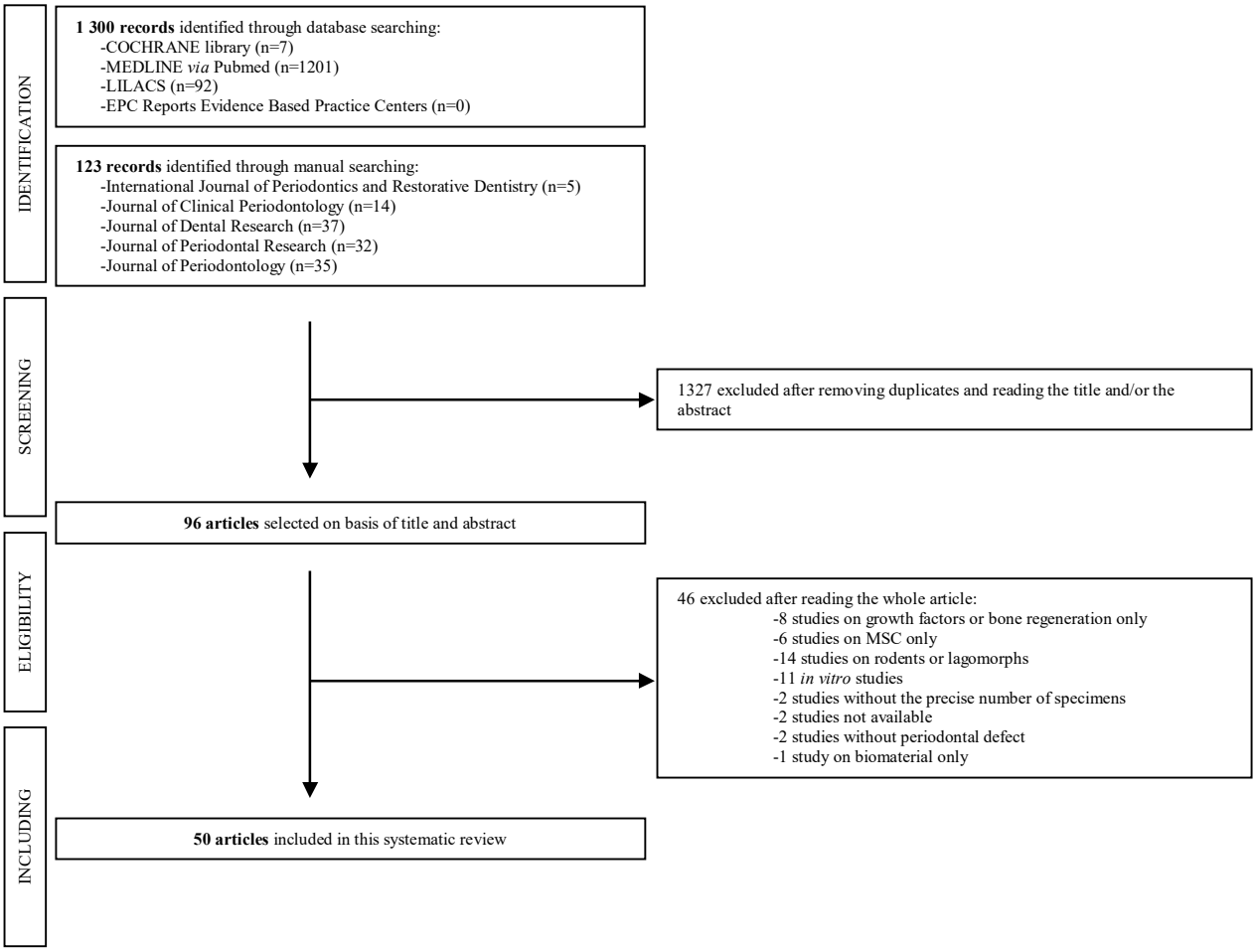

Figure. 1: PRISMA flowchart for identifying eligible studies.

Inclusion criteria:	Exclusion criteria:
✓ Studies using MSC ✓ Studies using biomaterial ✓ Studies with the precise number of specimens ✓ *in vivo* studies ✓ Studies with histologic and radiologic analysis ✓ Studies written in English	- Studies using only MSC - Studies using growth factors only - *in vitro* studies - *in vivo* studies on rodents and lagomorphs - Studies on implant or bone regeneration only - Studies with $p > 0.05$ - Review - Studies without control groups

Table. 1: Inclusion and exclusion criteria.

Reference	Cell type / passage number / differentiation / number per defect	Biomaterial +/- membrane	Animal model / species / sex / age / weight	Number of defects per group	Defect type / size / induced inflammation	Treatment groups	Observation period	Qualification of newly formed tissues	Results
Akizuki J. *et al* 2005[34]	-PDLC -P4-6 -vit C stimulation -1 x 10^5 /sheet	Hyaluronic acid sheet	DOG Beagle, female, 3 years-old, 9.8 and 11.2 kg	5 (a,b)	-dehiscence defects -5 x 5mm² -no inflammation	(a) PDLC + hyaluronic acid sheet (b) hyaluronic acid sheet	2 months	-Histological: HES, Masson trichrome staining -Histomorphometric	No sign of inflammation or recession in the 2 groups. **Formation of cement, bone, and ligament** more significant in the group (a) than in the group (b)
Chen G. *et al* 2015[55]	-DFSC -undifferentiated	Gelatin electrospun sheet (APES) + treated dentin matrix (TDM) + native dental pulp extracellular matrix (DPEM)	MINIATURE PIG 1 year old	3 (a,b)	-root-shaped implant socket -no inflammation	(a) DFSC + DPEM + APES + TDM (b) TDM	3 months	-Histological -Radiological: micro-CT -Immunohistochemical: Col-1, Col-3, periostin, DMP-1 sialophosphoprotein, GFP	The sandwich composites APES/ TDM/DPEM and DFSC **generated peridontal ligament - like tissues**
Ding G. *et al* 2010[33]	-PDLSC -P0 -undifferentiated -2 cell sheets	HA / β-TCP + gelatin membrane	MINIATURE PIG female Wuzhishan, male Guizhou, 6-8 months old, 30-40 kg	6 (a,b,c,d,e)	-intrabony defects -3 x 7 x 5mm³ -inflammation	(a) PDLSC autologous +HA-β-TCP (b) PDLSC allogenic +HA-β-TCP (c) PDLC autologous and allogenic + HA-β-TCP (d) HA+β-TCP (e) empty defect	3 months	-Clinical: CAL, PD, GR, blood and biochemical tests -Histological: HES -Histomorphometric -Radiological: CT	Allogenic and autogenous PDLSC have **improved** periodontal regeneration in the same way compared to other groups; with a **nearly complete recovery of bone cement** and **ligament**
Dogan A. *et al* 2002[56]	-regenerated periodontal ligament derived cells -P4 -undifferentiated -2 x 10^5	Autologous blood coagulum	Dog	2 (a,b)	-class II furcation defects -5 x 2mm² -no inflammation	(a) regenerated periodontal ligament derived cells + autologous blood coagulum (b) empty	1,5 months	-Histological: HES -Histomorphometric	Seeding of cells into periodontal defects **promote the bone regeneration and adaptation of connective tissue fibers** on exposed dentin surface **with limited cementum formation**
Dogan A. *et al* 2003[57]	-regenerated periodontal ligament derived cells -P4 -undifferentiated -2 x 10^5	Autologous blood coagulum	Dog	2 (a,b)	-fenestration defects -5 x 5mm² -no inflammation	(a) regenerated periodontal ligament derived cells + autologous blood coagulum (b) empty	1,5 months	-Histological: HES -Histomorphometric	In the cell-seeding group, the **main periodontal healing pattern was connective tissue adaptation**, characterized by parallel bundles of collagen fibrils resting on root dentin

Fawzy El-Sayed KM. *et al* 2012[44]	-GMSC -P3 -undifferentiated -2 x 10^7	Bio oss® + Bio-Gide®	MINIATURE PIG 1 female and 7 males, 18 ± 1 months old, 46.9 ± 4.6 kg	8 (a,b,c,d,e,f)	-intrabony defects -3 x 7 x 5mm^3 -inflammation	(a) GMSC + Bio oss® (b) GMSC + collagen scaffold (c) bio oss® (d) collagen scaffold (e) mucoperiosteal flap and root planning only (f) without intervention	3 months	-Clinical: CAL, PD, GR, BOP, PI -Histological: HES -Histomorphometric -Radiological: CT	The treatments with GMSC compared with scaffolds alone or control groups have **entailed better results**
Fawzy El-Sayed KM. *et al* 2015[45]	-GMSC -P3 -undifferentiated -2 x 10^7	IL-1ra-releasing HA-ECM + Bio-Gide®	MINIATURE PIG 2 females and 6 males, 5-6 years old, 50.8±7.2kg	8 (a,b,c,d)	-intrabony defects -3 x 7 x 5mm^3 -inflammation	(a) GMSC + IL-1ra-HA-ECM (b) GMSC + HA-ECM (c) mucoperiosteal flap and root planning only (d) without intervention	4 months	-Clinical: CAL, PD, GR, BOP, PI -Histological: HES -Histomorphometric -Radiological: CT	Outcomes were significantly better in experimental groups (a, b) as compared to control groups (c, d). The results **support the concept of cell-based therapy in conjunction with suitable scaffolds** for future periodontal regeneration
Fu X. *et al* 2014[58]	-PDLSC or SHED -P3 -vit C stimulation -2 cell sheets	HA / β-TCP	MINIATURE PIG female, 9-12 months old, 40-45 kg	6 (a,b,c)	-intrabony defects -5 x 7 x 7mm^3 -inflammation	(a) PDLSC + HA-β-TCP (b) SHED + HA-β-TCP (c) HA-β-TCP	3 months	-Clinical: CAL, PD, GR -Histological: HES -Radiological: CT	No significant difference between the 2 groups PDLSC and SHED, both have **significantly improved periodontal regeneration** with a very **small inflammatory area**
Gao ZH. *et al* 2016[59]	PDLSC: -P3 -vit C stimulation -2 cell sheets DPSC: -P2-P3 -undifferentiated -2 x 10^6	HA / TCP	MINIATURE PIG 18 months old, 50-60 kg	46 (a) 9 (b)	-root-shaped implant socket -4.1 x 10mm^2 -no inflammation	(a) HA + TCP + DPSC + PDLSC (b) dental implants	6, 12 months	-Clinical: PD, GR, gingivitis, peri-implantitis -Histological: HES, toluidine blue staining -Radiological: CT, micro-CT -Biochemical: compressive strength, modulus of elasticity, torsional force -SEM	These data showed that the group (a) could function as well as the group (b). Histological staining showed that **PDL like and bone tissue** had been generated, similar to the natural sample in both groups. Neither the group (a) nor the group (b) showed gingivitis or peri-implantitis. However, the restoration success rate was significantly lower in with the group (a) than with the group (b)
Hasegawa N. *et al* 2006[22]	-BMSC -undifferentiated -2 x 10^7	Atelocollagen	DOG Beagle, female, 12-20 months old, 10-14 kg	6 (unclear)	-class III furcation defects -4mm in depth -no inflammation	(a) BMSC + atelocollagen (b) no treatment	1 month	-Histological: HES -Immunohistochemical: GFP, Proliferating Cell Nuclear Antigen (PCNA)	Outcome showed that the defects were almost **regenerated with cementum, periodontal ligament, and alveolar bone** after MSC transplantation
Inukai T. *et al* 2013[35]	-PDLC -undifferentiated	Atelocollagen	DOG 18-36 months old, 15-25 kg	5 (unclear)	-intrabony defects -4 x 5mm^2 -no inflammation	(a) PDLC + atelocollagen (b) atelocollagen + PBS (c) no treatment	1 month	-Histological: HES -Histomorphometric -Radiological: dental X-ray	Both **cement and bone heights as well as bone surface were more significant** in the group with PDLC

Iwata T. *et al* 2009[36]	-PDLC -P3 -osteoinductive medium -9 x 10^4	PGA / β-TCP	DOG Beagle male, 10 kg	4 (a,b)	-intrabony defects -5 x 5 x 4mm^3 -no inflammation	(a) PDLC + PGA + β-TCP (b) PGA + β-TCP	1,5 months	-Histological: HES, Azan staining -Histomorphometric -Radiological: micro-CT	PDLC permitted **bone and cement regeneration** with correctly **orientated collagen** while a limited formation bone was noted in the control group
Jiang J. *et al* 2010[60]	-Periosteal cells -P3 -undifferentiated -5 x 10^6	β-TCP + ePTFE membranes	DOG Beagle, 9.5 and 10.5 kg	4 (a,b,c)	-class III furcation defects -3 x 4mm^2 -inflammation	(a) PDLSC + atecollagen (b) atecollagen (c) empty	3 months	-Histological: HES, Mallory's trichrome stain -Histomorphometric -Radiological	PDLSC associated with atecollagen **significantly improve periodontal and bone formations** compared to control groups (b,c)
Kawaguchi H J. *et al* 2004[23]	-BMSC -P3 -undifferentiated -2 x 10^6, 5 x 10^6, 1 x 10^7, 2 x 10^7	Atelocollagen	DOG Beagle female, 10-14 kg, 12-20 months old	Unclear	-class III furcation defects -4mm in depth -no inflammation	(a) BMSC + atelocollagen (b) atelocollagen	1 month	-Histological: HES, Azan staining -Histomorphometric	In the BMSC group, neocement covered nearly all denuded dentin surface, added to bone and ligament formation (Sharpey's fibers like). But no *ad-integrum* bone recovery. No root system ankylosis or root resorption
Khorsand A J.*et al* 2013[61]	-DPSC -P3 -undifferentiated -2 x 10^7 /default	3-4 Bio-Oss® granules	DOG Mongrel male 1-2 years old, 14-22 kg	10 (a,b)	-intrabony defects -3 x 5 x 8mm^3 -inflammation	(a) DPSC + Bio-Oss® (b) Bio-Oss ®	2 months	-Histologic: HES -Histomorphometric	The **cement** generated in the presence of DPSC **was thicker and covered a bigger surface** compared with the control group. Likewise the formation of **ligament was more significant** in the test group. However, **no noticeable difference in bone formation** between the 2 groups
Lang H. *et al* 1998[62]	-Primary cell cultures from alveolar bone and periodontal ligament -vit C stimulation -2 x 10^7 /ml	Gelita® + ePTFE membranes	MINIATURE PIG Trol types, 4-8 years old	8 (a,b,c,d,e)	-intrabony and class II furcation defects -inflammation	(a) cells + Gelita® (b) Gelita ® (c) empty with membrane (d) empty without membrane (e) no treatment	10, 30, 90 days	-Clinical: PI, PD, GR, Sulcus Bling Index -Histological: polyfluorochrome labeling, toluidine blue staining	The study shows that the primary cell cultures from alveolar bone and periodontal ligament leads to formation of **new cementum and bone**
Li H. *et al* 2009[63]	-Cryopreserved or No-cryopreserved BMSC -P4 -undifferentiated -5 x 10^6 /ml	Collagen membrane + ePTFE membranes	DOG Beagle, female, 12-18 kg	9 (a,b) 8 (c)	-fenestration defects -5 x 5mm^2 -no inflammation	(a) BMSC cryopreserved + collagen (b) BMSC no cryopreserved + collagen (c) collagen	2 months	-Histological: HES, Masson's staining -Histomorphometric	**BMSC** whether cryopreserved or not **showed a better periodontal regeneration** with bone, cement and ligament neoformation compared with the group with collagen only

Liu Y. *et al* 2008[32]	-PDLSC -P3 -undifferentiated -2 x 10^7	HA / β-TCP + gelatin membranes	MINIATURE PIG 12 months old, 30-40 kg	24 (a) 12 (b,c)	-intrabony defects -7 x 3 x 5 m^3 -inflammation	(a) PDLSC + HA-β-TCP (b) HA-β-TCP (c) no treatment	3 months	-Clinical: CAL, PI, PD, GR, BOP -Histological: HES, GFP -Radiological: CT	The treatment with PDLSC **entailed bone, ligament and cement regeneration** with a **good anchoring of Sharpey's fibers** compared with the other groups
Liu Z. *et al* 2016[64]	-BMSC -undifferentiated	collagen-hydroxyapatite scaffold	DOG Beagles, male, 12 months old 10.5-1.2 kg	6 (a,b,c,d)	-intrabony defects -3 x 5mm^2 -no inflammation	(a) BMSC + HA + collagen (b) BMSC + HA + collagen-cross linked (c) empty (d) no treatment	3 dogs : 3 months 3 dogs : 6 months	-Histological: HES, Masson's staining -Radiological: Micro-CT	In group (a,b), **newly formed alveolar bone, periodontal ligament and cementum** were regenerated without aberrant events. **BMSC provided no added value** to healing
Menicanin D. *et al* 2014[31]	-PDLSC -P3 -undifferentiated -2 x 10^6	Gelfoam® + Gore-Tex®	SHEEP female	7 (a,b)	-intrabony defects -5mm in depth -no inflammation	(a) PDLSC + Gelfoam® (b) Gelfoam®	2 months	-Histological: HES, modified tetrachrome -Histomorphometric -Immunohistochemical: OPN, BSP, COL-I, αSMA, BrdU	PDLSC group shows a **superior regeneration in bone** and **collagen fibers** (similar to Sharpey's fibers) inserted in neocement
Mrozik MK. *et al* 2013[37]	-PDLC -P3 -undifferentiated -1 x 10^7	Gelfoam® + resorbable barrier membrane	SHEEP Merino ewes, 3-5 years old, 63.5-72.0 kg	7 (a,b) 6 (c)	-dehiscence -10mm in depth -no inflammation	(a) PDLC + Gelfoam® (b) Gelfoam® (c) empty	1 month	-Histological: HES, tetrachrome staining -Histomorphometric	**Enhanced cementum regeneration** following allogeneic PDLSC implantation
Nagahara T. *et al* 2015[26]	-BMSC -P3 -undifferentiated -2 x 10^7	β-TCP / atelocollagen	DOG Beagle, female, 10-14 kg	20 (a,b) 16 (c) 10 (d)	-class III furcation defects -4mm in depth -inflammation	(a) BMSC + β-TCP + atelocollagen (b) BMSC + atelocollagen (c) β-TCP + atelocollagen (d) atelocollagen	1 and 2 months	-Histological: HES, Azan and TRAP Staining -Immunohistochemical: OPN	The new cementum length in the groups (a,b) was higher at 4 and 8 weeks compared to control groups. And **new connective tissue fibers** were inserted into the cementum in both groups (a,b). The new bone volume was improve in group (a) but no in group (b)
Nakahara T. *et al* 2004[65]	-PDLSC -undifferentiated -3 x 10^5	type I (70–80%) and type III (20–30%) atelocollagen + ePTFE membranes	DOG Beagle, female, 10-12 kg	6 (a,b)	-fenestration defects -6 x 4mm^2 -no inflammation	(a) PDLSC + atecollagen (b) empty	1 month	-Histological: HES, Masson's trichrome staining -Histomorphometric	**Cement formation was a lot more significant** with PDLSC But **no difference in bone formation** between the groups
Nakajima R. *et al* 2014[52]	-dental socket-derived stem cells -osteoinductive medium	PGA + β-TCP	DOG Beagle	6 (a,b)	-intrabony defects -5 x 5mm^2 -no inflammation	(a) DSC / PGA + β-TCP (b) PGA + β-TCP	2 months	-Histological: HES, Azan staining	A histologic analysis showed **newly formed bone** in both groups, whereas newly formed **cementum-like tissue and Sharpey's fiber-like** tissue were observed in the group (a) only.

Nunez J. *et al* 2012[66]	-CDC or PDLSC -P5-6 -undifferentiated - CDC >75 x 10^4; PDLDC >75 x 10^4	collagen	DOG Beagle, male, 1 year old, 10 kg	8 (a,b,c)	-intrabony defects -3 x 4mm² -inflammation	(a) CDC + collagen (b) PDLSC + collagen (c) collagen	3 months	-Histological: Toluidine blue staining -Histomorphometric	**Higher rates of cement found** in test groups as well as a more significant **gain in attachment** and in **conjunctive tissue**. PDLSC or CDC **failed to stimulate** further the **bone regeneration**
Ozasa M. *et al* 2014[49]	-ASC -P4	fibrin gel	DOG Beagle, female, 50-56 months old 9-11 kg	unknown	-class II furcation defects -4mm in depth -inflammation	(a) ASC + fibrin gel ® (b) fibrin gel	1,5 months	-Histological: AZAN -Histomorphometric -Radiological: micro-CT	ASC transplanted sites have shown **periodontal regeneration**, including **new alveolar bone**, **periodontal ligament** and **cementum formation** with **vertically inserted fibers**
Paknejad M. *et al* 2015[67]	-BMSC -P3 -undifferentiated -2 x 10^7 /default	Bio oss®	DOG Mongrel, male, 1-2 years old, 14-22 kg	9 (a,b)	-intrabony defects -4 x 4mm² -inflammation	(a) BMSC + Bio oss® (b) Bio oss®	2 months	-Histological: HES -Histomorphometric	Formation of **new cementum** and **periodontal ligament** were **significantly higher** in the test group. Whereas bone formation in the test and control groups were no statistically different
Simsek SB. *et al* 2012[24]	-BMSC or Autologous cortical bone -undifferentiated -1 × 10^7 /ml	PRP autologues	DOG Mongrel, 15 kg	6 (a,b,c,d,e)	-class II furcation defects -5mm x 2mm² -no inflammation	(a) BMSC + PRP (b) autogenous cortical bone + PRP (c) PRP (d) autogenous cortical bone (e) no treatment	2 months	-Histological: HES -Histomorphometric	The regeneration of cement and alveolar bone was more significant in the groups (a,b,d), even if, in these 3 groups, **BMSC** showed the **highest potential** for **periodontal regeneration**.
Sonoyama W. *et al* 2006[38]	-PDLC + SCAP -P1-3 -4 x 10^6	Gelfoam® + HA + β-TCP	MINIATURE PIG male, 4-8 months old, 20-40 kg	6 (a,b)	-alveolar socket -no inflammation	(a) [PDLC + SCAP / Gelfoam®] + HA + β-TCP (b) HA + β-TCP	1 month	-Histological: HES -Immunohistochemical: human mitochondria antibody -Radiological: CT	**Periodontal regeneration observed** in test groups: formation of a bio-root with a good compressive force
Suaid J. *et al* 2011[68]	-PDLSC -P2-3 -undifferentiated -3 x 10^5	collagen sponge + absorbable membrane Goretex	DOG Beagle, 10–20 kg, 1.46 ± 0.18 years old	7 (a,b)	-intrabony with class II furcation defects -5 x2mm² -no inflammation	(a) PDLSC + collagen (b) collagen	3 months	-Histological: HES -Histomorphometric	The results presented **a better periodontal regeneration** in the group with LAD cells
Suaid J. *et al* 2012[69]	-PDLSC -P2-3 -undifferentiated -3 x 10^5	collagen + 2 absorbable membranes (GTR)	DOG Beagle, 10-20 kg, 1.46 ± 0.18 years old	7 (a,b,c,d)	-intrabony with class II furcation defects -5 x2mm² -no inflammation	(a) PDLSC + collagen (b) collagen + GTR (c) GTR (d) empty	3 months	-Histological: HES -Histomorphometric	The group with LAD cells showed **a better periodontal regeneration with a more significant bone and cement** width

Tobita M. *et al* 2013[48]	-ASC -P2 -undifferentiated -1.5 x 10^7 /ml	PRP gel	DOG Beagle, 9 or 10 months old, 8-10 kg	8 (a,b,c)	-intrabony with with class III furcation defects -5mm in depth -no inflammation	(a) ASC + PRP gel (b) PRP gel (c) empty	2 months	-Histological: HES, Azan or elastic van Gieson staining -Histomorphometric -Immunohistochemical: Osteocalcin -Radiological: X-ray	**Better bone, cement and ligament-like regeneration** in test group. the group without treatment showed gingival invasion
Tsumanuma Y. *et al* 2011[53]	-PDLC or BMSC or Periosteal cells -P3 -osteoinductive medium -cell sheet	PGA / β-TCP / type I collagen	DOG Beagle, male, 10 kg	4 (a,b,c,d)	-intrabony defects -5 x 5mm² -no inflammation	(a) PDLC / PGA + β-TCP / type I collagen (b) BMSC / PGA + β-TCP / type I collagen (c) Periosteal cells / PGA + β-TCP / type I collagen (d) PGA + β-TCP / type I collagen	1 month	-Histological: HES, Azan staining -Histomorphometric -Immunohistochemical: neurofilament protein	**PDL cells** group shows a more **significant cement thickness.** Moreover, presence of correctly **orientated collagen fibers**, while they are slanted in the group (b) and parallel in the group (c). However, **no difference in bone formation or in long junctional epithelium**
Tsumanuma Y. *et al* 2016[39]	-PDLSC -P5 -osteoinductive medium -cell sheet	PGA / β-TCP / collagen + absorbable membrane (GTR)	DOG Beagle	8 (a,b,c)	-intrabony defects -5 x 5mm² -no inflammation	(a) PDLSC autologous / PGA + β-TCP + collagen (b) PDLSC allogenic / PGA + β-TCP + collagen (c) β-TCP + collagen	2 months	-Histological: Azan staining -Enzyme-linked immunosorbent assay: CRP, IL-10, IFN-c, CD30 -Histomorphometric -Radiological: micro-CT	In the group (b), **dense collagen fibers** were observed, which attached **perpendicularly** to the cementum-like tissue. In the groups (a,c), collagen fibers were oriented **obliquely or parallel** to the root surface. There were **no differences** between the **autologous or allogenic groups** in the histomorphometric analyses
Wei N. *et al* 2010[70]	-BMSC -P3 -2 x 10^7 / defect	Alginate hydrogel	DOG Beagle male, 6-10 months old, 5-10 kg	4 (a,b)	-class III furcation defects -5mm in depth -no inflammation	(a) BMSC + hydrogel (b) empty	1,5 months	-Histomorphometric: HES or Masson trichrome -Immunohistochemical: BrdU, α –SMA, osteocalcin	The transplanted BMSC **migrated** into the periodontal ligament, alveolar bone, cementum and blood vessels. BMSC transplantation has the potential to **regenerate periodontal tissue**.
Yang J. *et al* 2013[71]	-Embryonic stem cells -P43-45 -GFP-label -1 x 10^6 / defects	collagen	MINIATURE PIG female 5 months old 25-30kg	6 (a,b)	-classe II furcation defects -4 x 5 x 3 mm^3 -inflammation	(a) embryonic stem cells MSC + collagen (b) collagen	3 months	-Clinical: PD, CAL -Histological: HES -Immunohistochemical: GFP, periostin; aspirin, cementum attachment protein, osteopontin; osteocalcin, RUNX2	Embryonic cells to **improve the regeneration of periodontal furcation defects** is feasible

Yang KC. *et al* 2016[72]	-DPSC: P3-P5 -epithelial cells: P2-P3 / 1.76-3.1 x 10^6 -odontoblastic-induced DPSC: 20.3-33.2 x 10^6 -osteoblastic-induced DPSC: 19.2-27.8 x 10^6	gelatin chondroitin-hyaluronan	MINIATURE PIG 7 males, 10 females, 5-7 weeks old	8 (a) 3 (b,c,d)	-alveolar sockets -no inflammation	(a) cells layers + scaffold (b) scaffold (c) empty (d) without intervention	13.5 months	-Histological: HES -Immunohistochemical: DMP-1, OPN, COL-1, CK14, VEGF -Radiological: X-ray	This study demonstrated that a **bioengineered cell / scaffold** could achieve **tooth regeneration**. The regenerated tooth had **crown**, **root**, and **pulp structures** with enamel-like tissues, dentin, cementum, odontoblast-like cells, and periodontal tissues.
Zang S. *et al* 2016[73]	-BMSC -P3-5 -undifferentiated	-chitosan -anorganic bovine bone	DOG Beagles, 15 months old, 10-15 kg	6 (a,b,c,d,e,f)	-intrabony defects -4 x 7mm² -no inflammation	(a) BMSC + chitosan (b) BMSC + chitosan + anorganic bovine bone (c) chitosan + anorganic bovine bone (d) chitosan (e) anorganic bovine bone (f) empty	2 months	-Histological: HES, Masson's trichrome staining -Histomorphometric -Immunohistochemical: osteocalcin -Radiological: micro-CT	BMSC associated with chitosan / anorganic bovine bone scaffolds **could promote periodontal re**pair. The quantity of the newly formed bone and cementum in the groups (b,e) was significantly higher compared with the other groups.
Zhu B. *et al* 2017[25]	-PDLSC or BMSC (iliac- or jaw-derived) -P2-4 -osteoinductive medium	treated dentine matrix (TDM) + ceramic bone (CA)	MINIATURE PIG 2 years old	10 (a) 8 (b)	-intrabony defects -5.2 x 5mm² -no inflammation	(a) jBMSC + PDLSC + TDM + CA (b) iBMSC + PDLSC + TDM + CA	3 months	-Histological: HES, Masson's trichrome -Immunohistochemical: Col 1	Both construct implantation, JBMSC or IBMSC showed **PDL-like tissue regeneration**. However, the implantation of **JBMSC** seems to **be more appropriate to form parallel collagen fibers** and bone tissue

Table 2: Comparative table of pre-clinical animal studies in periodontal regeneration combining MSC and biomaterials.
Abbreviations: HA, Hydroxyapatite; TCP, Tricalcium Phosphate; PGA, Polyglycolic Acid; ePTFE, e-Polytetrafluoroethylene; PRP, Platelet-Rich Plasma; DPSC, Dental Pulp Stem Cells; PDLSC, Periodontal Ligament Stem Cells; PDLC, Periodontal Ligament Cells; DFSC Dental Follicle Stem Cells; CDC, cementum derived cells; GMSC, Gingival Margin Stem Cells; SHED, Stem cells from Human Exfoliated Deciduous teeth; BMSC, Bone Marrow Stem Cells; ASC, Adipose Stem Cells; MSC, Mesenchymal Stem Cells; SCAP, Stem Cells from Apical Papilla; CAL, clinical attachment level; PI, plaque index; PD, probing depth; GR, gingival recession; BOP, bleeding on probing; HES, hematoxylin eosin stain; ECM, Extracellular Matrix; OPN, Osteopontin; BSP, Bone Sialoprotein; Col, collagen; αSMA, alpha smooth muscle actin; GFP; Green Fluorescent Protein; TRAP, Tartrate-Resistant Acid Phosphatase; CRP, Serum C-reactive protein; IL-10, Interleukin-10; INF-c, Interferon-c; CD, Cluster of Differentiation; VEGF, Vascular Endothelial Growth Factor; DMP-1, Dentin Matrix Protein-1; CT, computed tomography; SEM, scanning electron microscopy.

Reference	Cell type / passage number / differentiation / number per defect	Biomaterial +/- membrane	Animal model / species / sex / age / weight	Number of defects per group	Defect type / size / induced inflammation	Treatment groups	Observation period	Qualification of newly formed tissues	Results
Aimetti M. *et al* 2014[41]	-DPSC -P0 -undifferentiated	Collagen sponge (type III)	HUMAN male 56 years old	1	-intrabony defects -inflammation	DPSC + collagen sponge scaffold	6 and 12 months	-Clinical: CAL, PI, PD, GR -Radiological: dental X-ray	At the 12 months examination, the CAL gain amounted to 6 mm with a residual probing pocket depth of 3 mm. No apical displacement of the gingival margin was observed
Chen FM, e*t al* 2016[40]	-PDLSC -undifferentiated -cells sheets	Bio oss® + Bio-Gide®	HUMAN Male, female 26.05±4.44 - 30.04±7.90 years old	20 (a) 21 (b)	-intrabony defects ≥ 3mm in depth -inflammation	(a) PDLSC + Bio-oss® (b) Bio-oss®	3, 6 and 12 months	-Clinical: CAL, PD, GR -Radiological: dental X-ray	**Significant difference** between the experimental and the control groups **was not observed**
Dhote R. *et al* 2015[74]	-allogenic human umbilical cord -P0 - rh-PDGF-BB stimulation -1 x 10^6 / default	β-TCP	HUMAN 8 males and 6 females, 20 - 43 years old	12	-intrabony defects ≥ 5mm in depth -inflammation	(a) allogenic human umbilical cord + β-TCP (b) open flap debridement	6 months	-Clinical: CAL, PI, PD, GR, BOP -Radiological: dental X-ray	Stimulated cells implantation resulted in a **significant added benefit** in terms of **CAL** gains, **PD** reductions greater **radiographic defect fill** and improvement in linear bone growth
Feng F. *et al* 2010[30]	-PDLC -P1 -undifferentiated	calcium carbonate	HUMAN male 25 and 42 years old	Patient n°1 12 teeth Patient n°2 3 teeth Patient n°3 1 tooth	-intrabony defects - ≥ 6mm in depth -inflammation	PDLC + calcium carbonate	3-72 months	-Clinical: CAL, PD, GR, BOP, PI -Radiological: dental X-ray	PDLP implantation **improve periodontal tissue regain**, specifically marked by a significant decreased in gingival recession and increased attachment gain
Hermandez-Monjaraz B *et al* 2018[42]	-allogenic DPSC -P3 -undifferentiated -5 x 10^6/ default	Collagen sponge +Teflon-coated titanium membrane	HUMAN male 61 years old	1	-intrabony defects -inflammation	Allogenic DPSC + collagen sponge	3, 6 months	-Clinical: PD, mobility -Radiological: Cone beam volumetric tomography; bone mineral density	The gingiva showed **no signs of inflammation**, and **depth** of the periodontal pocket and dental **mobility** both **decreased.** Densitometry assays revealed an **increase in bone mineral density** in the walls of the defect
Ki V. *et al* 2017[75]	-PDLSC -P0 -undifferentiated	Abgel®©™ : gelatin sponge	HUMAN male 27 years old	1	-intrabony defects -9mm in depth -inflammation	PDLSC + Abgel®©™	24 months	-Clinical: CAL, PD, GR, relative attachment -Radiological: dental X-ray	PDLSC implantation has resulted in successful clinical and radiographic parameters : CAL decreased PD and satisfactory defect fill of intrabony defects

Li Y. *et al* 2016[43]	-DPSC -P3 -undifferentiated	β-TCP	HUMAN female 30 and 38 years old	Patient n°1 1 tooth Patient n°2 1 tooth	-combined periodontal-endodontic lesions -5-6mm in depth -inflammation	DPSC+β-TCP	1, 3, and 9 months	-Clinical: CAL, PI, PD, GR, BOP, furcation lesion, mobility -Radiological: dental X-ray	DPSC graft **dramatically improved** the clinical symptoms of periodontitis.
Okuda J. *et al* 2009[47]	-Periosteal cells -P0 -undifferentiated	HA+PRP	HUMAN female 53, 63 and 71 years old	3	-Intrabony defects -inflammation	Periosteal cells+ HA+PRP	6 months	-Clinical: PD, CAL -Radiological: dental X-ray	On average , results show a reduction of pockets of 6mm, a gain in attachment of 4.3mm at 6 months
Rosen PS. *Et al* 2015[76]	-MSCs allografts (Osteocel, NuVasive) -undifferentiated	demineralized freeze-dried and freeze-dried bone allografts + BioXclude®	HUMAN Male and female 39-70 years old	6	-class III and IV furcation defects -inflammation	MSC + BioXclude®	6, 9, 24 or 30 months	-Clinical: furcation lesion -Radiological: dental X-ray	4 furcations treated were completely closed 1 furcation was reduced to Class I on their facial aspect while the lingual aspect was completely closed 1 remained as a Class III furcation
Yamada Y. *et al* 2005[21]	-BMSC -osteoinductive medium -1 x 10^7 /mL	PRP gel	HUMAN female, 54 years old	1	-intrabony defects -inflammation	BMSC + PRP gel	12 months	-Clinical: CAL, PD -Radiological: dental X-ray	A **reduction of 4mm** when probing, a clinical **attachment gain of 4mm** with **no** more **bleeding** or tooth **mobility**
Yamamiya K. *et al* 2008[46]	-periosteal cells / -P0 -undifferentiated	HA + PRP	HUMAN 14 females and 1 males, 55.8 - 9.1 years old	15 (a,b)	-intrabony defects -6mm in depth -inflammation	(a) periosteal cells + PRP + HA (b) HA + PRP	12 months	-Clinical: CAL, PD, GR, BOP, gingival inflammation -Radiological: dental X-ray	the test group presented better results with **enhancement in CAL gain** and **bone density** even if the **control group obtained satisfying** results

Table 3: Comparative table of human studies in periodontal regeneration combining MSC and biomaterials.
Abbreviations: TCP, Tricalcium Phosphate; PRP, Platelet-Rich Plasma; DPSC, Dental Pulp Stem Cells; PDLSC, Periodontal Ligament Stem Cells; PDLC, Periodontal Ligament Cells; BMSC, Bone Marrow Stem Cells; MSC, Mesenchymal Stem Cells; CAL, clinical attachment level; PI, plaque index; PD, probing depth; GR, gingival recession; BOP, bleeding on probing.

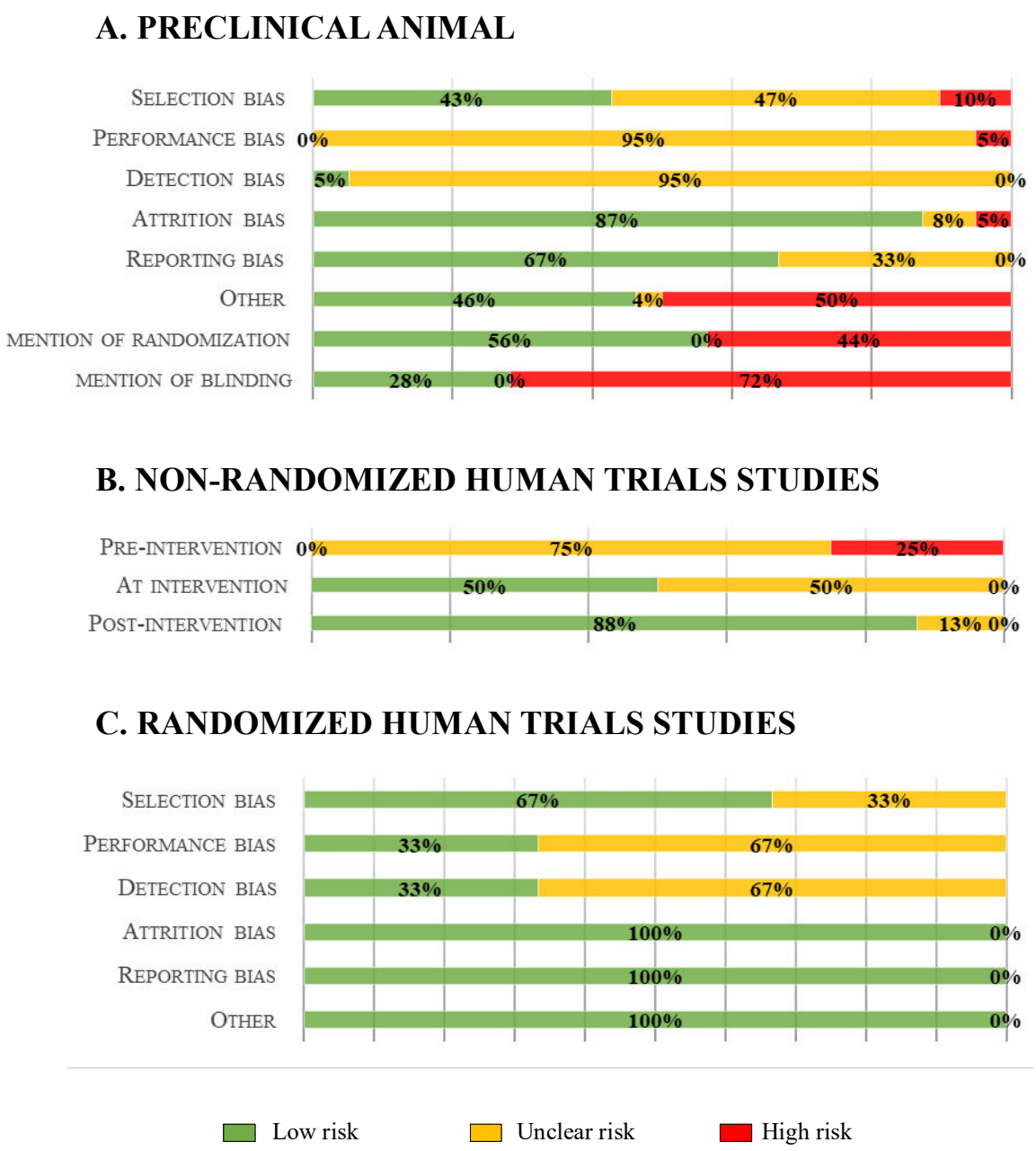

Figure 2: Risk of bias assessment of included studies.
A. Risk of bias graph for animal studies, using the SYRCLE's tool, averaged per item.
B. Risk of bias graph for non-randomized human trials, using the ROBINS-I tool, averaged per item.
C. Risk of bias graph for randomized human trials, using the Cochrane Collaboration's tool, averaged per item.
The green, yellow and red colors depict the percentages of studies with low, unclear or high risk of bias of the total number of assessed studies.

DISCUSSION ET CONCLUSION

L'impact des maladies parodontales sur la santé publique et sur la qualité de vie des patients justifie les nombreuses recherches actuelles pour obtenir un retour *ad integrum* du tissu parodontal[16]. Pour atteindre cet objectif, les défis majeurs sont la régénération de l'os alvéolaire, du cément et d'un ligament parodontal fonctionnel. La médecine régénératrice apparait très prometteuse pour relever ces défis. Dans ce contexte, notre étude systématique a pour objectif d'analyser les résultats controversés issus des articles scientifiques portant sur l'association de CSM et de biomatériau en médecine régénératrice parodontale.

Suivant le protocole standardisé PRISMA, notre analyse de la littérature a permis de sélectionner 50 articles. L'analyse rigoureuse de ces études scientifiques montre que leur comparaison directe n'est pas permise. D'une étude à l'autre, les disparités sont trop élevées en termes de types cellulaires, de biomatériaux, de défauts parodontaux, de modèles précliniques ou encore du temps d'implantation. Par conséquent, une méta-analyse ne peut être réalisée entre les articles sélectionnés.

Dans le but d'évaluer la fiabilité de chaque article sélectionné, l'utilisation de 3 tests adaptés au type d'étude (préclinique chez animal, préclinique chez l'homme non-randomisée ou randomisée) a permis une analyse du risque de biais pertinente. Pour limiter les risques de biais, les paramètres clés d'un protocole clinique sont la randomisation des échantillons et la réalisation de l'étude en double aveugle. Ces paramètres sont trop fréquemment absents dans les études précliniques chez l'animal et dans les rapports de cas chez l'homme. Ceci peut entrainer une surestimation des effets de l'association cellules souches et biomatériau sur la régénération parodontale comparé au groupe contrôle. Cette conclusion concerne la majorité des résultats des études sélectionnées dans cette analyse systémique. Malgré ces limites,

l'analyse combinée de ces études permet d'aboutir à des informations fiables qui n'auraient pas pu être obtenues par une analyse individuelle.

Cellules souches issues de la moelle osseuse (BMSC)

Depuis plusieurs années, les BMSC font l'objet de nombreuses recherches en régénération parodontale. À ce jour, il n'existe qu'une seule étude chez l'humain atteint de parodontite chronique. Les auteurs ont conclu que l'association de BMSC et du plasma riche en plaquettes (PRP) entraîne une amélioration radiologique et clinique en termes de profondeur de poches, du gain d'attache, du saignement lors du sondage et de la mobilité dentaire[17]. Actuellement, un essai randomisé axé sur la sécurité et l'efficacité du traitement régénératif de l'association BMSC autologue et collagène enrichi en colle de fibrine, est en cours (numéro d'enregistrement NIH: NCT02449005). La combinaison de BMSC et du PRP a également été un succès sur des modèles animaux dans 3 études différentes, chacune menée indépendamment par Simsek *et al*, Hasegawa *et al* et Kawaguchi *et al*[18–20]. Même si la régénération parodontale était presque complète dans l'étude de Simsek *et al*, Hasegawa *et al* et Kawaguchi *et al* ont malheureusement conclu à une régénération incomplète des tissus et en particulier de l'os alvéolaire. Ces résultats encourageants suggèrent que les BMSC contribuent à la régénération osseuse, du ligament parodontal et du ciment[21,22]. Cependant, la moelle osseuse souffre de certaines limites liées à son prélèvement douloureux et au nombre limité de cellules prélevées. Face à ces limites, d'autres sources tissulaires ont fait l'objet de recherche. Au sein de la zone oro-faciale, plusieurs sources de CSM ont suscité un intérêt scientifique, par leur similarité avec les BMSC, leur capacité d'immunorégulation et leur procédure de prélèvement mini-invasive[23].

Cellules dérivées du ligament parodontal (PDL)

Il y a trente ans, Melcher[24] avait émis l'hypothèse que des cellules souches pouvaient résider dans les tissus parodontaux. Ce n'est qu'en 2004 que les cellules ont été isolées du ligament parodontal et caractérisées comme des cellules souches (PDLSC)[25]. Au cours des dernières années, le nombre d'études animales sur PDLSC a considérablement augmenté. Sans surprise, notre étude montre que la majorité des articles (40%) est consacrée aux cellules dérivées du ligament parodontal. Feng *et al* ont été les premiers à transplanter des cellules progénitrices du ligament parodontal combinées à du carbonate de calcium chez 3 patients atteints de parodontite chronique. Les résultats montrent un gain d'attache clinique, une diminution de la profondeur de la poche, une régénération du tissu osseux ainsi qu'une amélioration de la récession sur 72 mois[26]. Menicanin *et al* ont implanté dans un modèle de défaut parodontal induit chez le mouton, des PDLSC autologues associées à un biomatériau composé de gélatine. Les résultats encourageants des groupes tests montrent une régénération supérieure du cément, de l'os alvéolaire et du ligament[27]. De même, Liu *et al* et Ding *et al*, ont indépendamment obtenu le même type de résultats, avec une régénération quasi complète des tissus parodontaux après implantation d'une combinaison de PDLSC autologue et HA/βTCP dans des défauts intra-osseux sur des modèles porcins pendant 12 semaines[28,29].

Afin de simplifier le protocole clinique pour le chirurgien-dentiste dans sa pratique quotidienne, certaines études utilisent des cellules ligamentaires parodontales sans isoler préalablement les cellules souches. Combinés à un biomatériau composé soit de collagène, de carbonate de calcium, de PGA, de HA, de β-TCP ou de l'acide hyaluronique, les différents auteurs s'accordent à dire que la présence de cellules dérivées du PDL améliore significativement la hauteur et l'épaisseur de l'os alvéolaire, la formation de cément et du

ligament parodontal[26,30–35]. De même, la revue systématique de Bright *et al* renforce ces conclusions. Ils rapportent que 12 des 17 études incluses concluent à un effet positif et statistiquement significatif de l'implantation de cellules dérivées du PDL sur la régénération du parodonte[12]. Par ailleurs, un essai clinique randomisé récent portant sur 20 patients atteints de parodontite chronique a révélé que l'implantation de Bio-Oss®, associée ou non aux PDLSC sur une période de 1 an, améliore significativement la hauteur de l'os alvéolaire et des paramètres cliniques[36]. En conclusion, même si les résultats semblent contradictoires, la majorité des études révèlent un effet positif et prometteur sur le potentiel régénératif des cellules dérivées de PDL.

Cellules souches issues de la pulpe dentaire (DPSC)

L'utilisation des DPSC a montré un certain potentiel de régénération du parodonte. En effet, chez l'homme 3 rapports de cas menés indépendamment ont décrit une amélioration des paramètres cliniques de la parodontite par l'implantation de DPSC combiné à un biomatériau à base de collagène[37,38] ou β-TCP[39]. Bien que les résultats de plusieurs études précliniques chez l'animal et de rapports de cas soient prometteurs, des essais cliniques randomisés chez l'homme sont nécessaires pour évaluer l'efficacité de ces procédures en régénération parodontale.

Autres types cellulaires utilisés en médecine régénératrice parodontale

Fawzy *et al* ont étudié l'implantation des cellules souches issues de la gencive marginale (GMSC) associées à un biomatériau de HA-ECM libérant IL-1ra ou Bio-Oss® chez le cochon. Quel que soit le biomatériau utilisé, l'équipe de chercheurs conclut à une réduction de la profondeur de poche, un gain d'attachement clinique et une augmentation de la densité osseuse[40,41].

En 2008, Yamamiya *et al* ont mené une étude sur 30 patients atteints de parodontite chronique. Des cellules périostées combinées à du PRP et de l'HA ont été implantées sur une période de 1 an[42]. Les résultats montrent une amélioration des paramètres clinique et radiologique. Okuda *et al* ont également étudié la même combinaison dans un modèle de chien et ont obtenu des conclusions similaires[43].

Les cellules souches issues du tissu adipeux (CSA) ont toujours été une source cellulaire très attrayante pour les chercheurs en médecine régénératrice. Tobita *et al*, et Ozasa *et al*, ont implanté des CSA dans des défauts parodontaux sur des modèles canins avec PRP[44] ou du gel de fibrine[45], respectivement. Quel que soit le type de biomatériau, les analyses morphométriques, histologiques, immuno-histologiques et radiologiques ont montré la formation d'os alvéolaire, de cément et de fibres ligamentaires après implantation des CSA, comparé aux groupes contrôles.

Nos résultats concernant les CSM sont en accord avec les conclusions de revues systématiques et méta-analyses précédemment publiées[46,47]. A ce jour, la communauté scientifique s'accorde pour affirmer que les CSM ont un effet bénéfique sur la régénération du complexe parodontal. Gaubys *et al* ont récemment montré par une méta-analyse de 10 articles, que le type de cellule implanté influence la régénération du cément et du ligament parodontal, alors que le choix du biomatériau impact d'avantage la régénération de l'os alvéolaire[48].

Pour optimiser la régénération parodontale, les cellules doivent être délivrées et stabilisées au niveau du défaut par un biomatériau. Ce dernier répond à un certain nombre de critères définis par le concept de biomimétisme. Il doit être capable d'incorporer et de libérer des molécules et de permettre les interactions cellule - cellule et cellule - matrice. Le choix du biomatériau

dépendra du type de cellules et du type de défaut, tel que le nombre de parois osseuses alvéolaires impliquées. Pour des défauts de grandes tailles, les résultats peuvent être améliorés par l'implantation des cellules associées à un substitut osseux et/ou à des membranes de PGA[32,34,35,49,50], par exemple. En revanche, un biomatériau de type hydrogel sans substitut osseux peut être utilisé lorsque les lésions sont étroites avec quatre parois[51]. Notre analyse systématique montre que les études inclues utilisent majoritairement des biomatériaux composés de collagène. Ces matériaux à base de collagène présentent de nombreux avantages tels que leur biocompatibilité, leur résorbabilité et leur capacité à favoriser la cicatrisation[11]. Un biomatériau permet d'obtenir une rétention cellulaire élevée suivie d'une bonne capacité d'intégration, une biodégradation homogène et d'un niveau élevé de cellules viables avec des effets secondaires réduits et un stress minimal pour le patient[14].

Notre revue systématique réalise une analyse complète de la littérature scientifique dans le domaine de la médecine régénératrice parodontale. À ce jour, nos données confirment que les CSM associées à des biomatériaux appropriés ont des effets bénéfiques sur la régénération parodontale sur des modèles animaux précliniques et chez l'homme. Les études sur l'homme montrent qu'il n'y a pas d'effets indésirables suite à telles interventions[36,37].

Cependant, avant que cette thérapeutique soit utilisée en routine, il convient de répondre à un certain nombre de question : (i) définir le biomatériau idéal pour amener les cellules au niveau du défaut, (ii) comprendre l'impact des propriétés immunologique et immunorégulatrice des CSM dans ce contexte de maladie inflammatoire, (iii) définir quel type cellulaire est le plus efficace pour régénérer l'ensemble du complexe parodontal. La maladie parodontale n'étant

pas une pathologie de stade terminale, il conviendra également de prendre en considération le ratio bénéfice/coût.

Bien que les essais cliniques soient prometteurs, des études précliniques sont encore nécessaires pour caractériser le type de cément ainsi que l'organisation des fibres parodontales nouvellement formées. De plus, de nouvelles études devraient être menées pour comparer la médecine régénératrice parodontale avec les thérapies de référence couramment utilisées.

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RESUME

La maladie parodontale se caractérise par une destruction progressive et irréversible du système d'attache de l'organe dentaire pouvant aboutir à la perte de celui-ci. Cette maladie inflammatoire est d'origine infectieuse et multifactorielle.

A l'heure actuelle, le contrôle de l'infection et la suppression de l'inflammation peuvent être obtenus par des techniques (i) non chirurgicales, basées sur une hygiène irréprochable et un nettoyage des surfaces radiculaires en profondeur (ii) et/ou chirurgicales, assistées ou non par l'utilisation de membrane ou de biomatériau. Ces thérapeutiques ne permettent qu'une cicatrisation des tissus sans retour *ad integrum*, aboutissant à des séquelles à la fois fonctionnelles et esthétiques.

Dans ce contexte, de nouvelles stratégies utilisant des cellules souches associées à un biomatériau ont été développées pour régénérer les tissus lésés. Bien que ces stratégies apparaissent très prometteuses, leur efficacité reste controversée.

Face à cette problématique, une analyse systémique de 50 articles sélectionnés portant sur la régénération parodontale, les cellules souches et les biomatériaux chez les modèles animaux précliniques et chez l'homme a été réalisée.

Ces données nous ont permis de conclure que l'association de cellules souches à un biomatériau permet de régénérer le complexe parodontal. A ce jour, le principal défi réside dans l'identification d'une combinaison idéale cellule / biomatériau en vue d'application clinique sécurisée et reproductible en régénération parodontale.

RUBRIQUE DE CLASSEMENT : Parodontologie

MOTS CLEFS MESH

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Stem cells, biocompatible materials, tissue engineering, periodontium, periodontitis

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