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Biological activity of mesenchymal stem cells in the surface of implants

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Abstract
The biocompatible materials applied to the implant surfaces are the target of recent literature studies. Modification of implant surfaces in different ways such as: application of additional ions, surface microstructure change, surface or laser ultrasound alteration or application of various substances such as recombinant proteins are among the most affected by articles published in literature. The mesenchymal cell reaction to these materials is according to the literature, in the same percentage positive to the osteointegration process. It is emphasized in the literature that implant success as a key evaluation key has more to implement implant treatment protocol ranging from dental health amenity and subsequent of the choice of implant type depending on the alveolar shape of the ridge level. Osteointegration is a procedure that should initially be physiologically independent of the type of implant pile material. With this physiological process, it can-not "boast" for implant success or implantation depending on the brand of the selected implant, as the breadth of synthetic or natural materials that promote osteointegration is relatively large.

Keywords: mesenchymal cells, implants

Introduction

Entry

Implant success assessed according to predetermined criteria emphasizes whether to invest in modifying the implant surface in order of increasing osteointegration capacity. There are enough techniques for modifying the implant surface; ranging from increasing the severity of the game with the addition of negative invasive loads on the surface affecting the faster migration of the mesenchymal cells to reach intervention [1, 2, 3, 4, 5]. Still more in depth painting of the implant surface with hydroxyapatite or cobalt or magnesium, which again stimulate the differentiation of mesenchymal cells into active osteoblast cells. This topic summarizes the most recent data published in the literature on recent modification of the implant surface with the aim of integration as a key element in implant success [5, 6, 7, 8]. The biological response of the cells near implant surfaces is significantly influenced by the type of material from which the implant is made, the structural plan of the implant surface and the properties of the implant surface material [7-12]. At the time when implant replacement of the missing teeth, it is a functional and aesthetic demand, growing by patients, it is worth emphasizing the importance of evaluating the elements mentioned above. This importance then directs specific implantation technology and protocols according to specific clinical cases [12-21]. While most of the constituent elements of the implant surface are important for the mechanical stability of the implant, the type and properties of the implant material the surface eventually contributes to implant osteointegration. The study examines the surface parameters of dental implant materials that contribute to improving cell response and implant osteointegration [1, 22, 23, 24]. The focus of the article is on facts published in the literature, in the way the surface plan affects in mesenchymal cell response and in osteoblast-oriented differentiation. Mesenchymal cells regardless of the source from where they are taken, have high regeneration and differentiation capabilities depending on local markers that guide them depending on local tissue needs. These cells have been turned into inspiration for further research into many articles and literature reviews, as their adaptation to differentiation in osteoblasts has been used largely for the osteointegration process [24-30]. Dental implants are successful for as long as they are fixed to the bone where they are located. Among them, there is a need to create a stable, timely connection of osteointegration type. Implant success assessed according to predetermined criteria emphasizes whether to invest in modifying the implant surface in order of increasing osteointegration capacity. There are enough techniques for modifying the implant surface; starting with the increase in the severity of the game with the increase of the negative invasive loads on the surface that affect the faster migration of the mezenchymal cells to reach intervention.(30-34) Even more deeply the implant surface with hydroxyapatite or with cobalt or magnesium, which repeatedly stimulate the differentiation of mesenchymal cells into active osteoblasts. This topic summarizes the most recent data published in the literature on recent modification of the implant surface with the aim of nonintegration as a key element in implant success. Almost most studies have experimented with rats on these implant surface modifications and subsequently histologic analyzes have been performed to evaluate the activity of alkaline phosphatase or any display of a certain protein responsible for osteoblastic inductance originating from mesenchymal cells [35. 3, 5, 36, 37, 38]

Induction-induced mutation is induced by any protein on the implant surface, pro- or anti-inflammatory markers, surface modification with laser, or change of titanium material to tantalum, application of cobalt-fluoride strontium over the implant surface. All these efforts are only in implants and applied in vitro, in rare cases in vivo to rats. The patient element, where implant placement is applied, is also forgotten with the idea that the patient plays the individual role by expressing individual characteristics as his health status (we are different because we have different immune levels and are suffering from different combinations of diseases, or have passed [39-44]. The other element is the surgeon's doctor who applies the implant placement, by switching to the implantable dose or not to certain implant protocols for human reasons, neglect, etc. The type of suture used at the end of the implant procedure is another element that affects implant success, supported by one of the latest literature studies [22, 34, 45, 44, 45].

The application of short and thin implants in cases of bone loss or in the case of bone marrow atrophy is noticed, resulting in implant failure and outputting the use of this implant category. But from the point of view of all of factors mentioned above, the literature provides information on the potential for impact on all stages of the osteointegration procedure. This was also the main orientation of the study.

Materials and methods

The study is of a review type, in order of finding out how the implant surface affects the activity of the mesenchymal cells. Electronic search is conducted to find articles by using MEDLINE, PubMed, in the period from 2011 to 2018.

First step

Includes finding the main terms, extracted from articles that talked about mezenchymal cells and implant surfaces. These terms, in the MESH database at "PubMed" site, were:

1. Mesenchymal cells (91099)
2. Implant Surface (5799)
3. Implants, mesenchymal cells (259).

Second step

When attempting to specifically talk about the activity of the mesenchymal cell related to the implant surface in contact, it was noted that there were about 73 items, specifically divided as follows:

1. Biocompatibility and osteoinduction
2. Mesenchymal cells and modification of the implant surface
3. About the oral mesenchymal cells
4. Intercourse implants - mesenchymal cells.

Third step: the second step specific terms were further applied to extract articles specifically referring to the interconnection of the mesenchymal cell activity and the implant surfaces.

1. Activity of mesenchymal cells stimulated by implant surfaces (6)
2. Mesenchymal cells stimulated by titanium (38)
3. Mezencimal oral cells stimulated by titanium implants (8)
4. Biological activity of mesenchymal cells stimulated by implant surfaces (3).

Fourth step: After analyzing abstracts and articles collected up to this stage, criteria for inclusion and non-inclusion was analyzed. 36 articles were selected at this stage. The criterion of inclusion in the analysis was all the articles that directly evaluate the impact of implant surfaces on the incubation of mesenchymal cells.

The non-inclusion criteria were:

1. Studies that did not directly assess the relationship between the effect of the implant surface and the activity of the mesenchymal cells.
2. Studies in the form of case-report.
3. Studies that examine less than 10 cases.

Fifth step: Analyzing 36 articles for obtaining valuable study information.

To categorize the data, the studies involved were rank irozuan on the basis of the analysis and evaluation model and on the basis of the size of the patient sample, using the following data:

Valuable and scientifically and clinically based:

- Review of randomized clinical specimens
- Two or more randomized samples
- A randomized sample and 2 or more prospective studies
- Clinically well-documented: a randomized patient sample and 2 or 3 prospective studies [45].

Results

The processing results of the collected data are presented in the tables below.

Table 1 summarizes the data on the separation of items depending on the type of selected mesenimal cells (in vivo, in vitro), the year of publication of the article and the number of authors-authors.

Table 1: This table presents the selected articles organized on basis of the year of publication, the type of article and the number of co-authors included in the article.

Type of article/No. of authors	Year of publication 2011- 2013		Year of publication 2014-2016		Year of publication 2017-2019	
	≤5	>5	≤5	>5	≤5	>5
In vitro at rats	-	2	-	2	-	2
In vivo at rats	-	-	2	-	1	3
In vitro at patients	-	2	1	6	5	6
In vivo at patients	-	-	-	2	-	2
Total	0	4	3	10	6	13

The effect assessment of changes in the implant surfaces is presented with data obtained from the selected items in Table No.2. It is known that the most popular modifications proposed by the literature on the implant surface are: the application of recombinant proteins, lasers, theirs, nanotubules of titanium, various substances and ultrasound.

Table 2: Separation of the items collected depending on the type of article based on the modification of the implant surface.

Type of study/ No. of patients	Recombinant protein	Laser	Ions: Zn, Co, Sr, Mg, Li	Titanium nanotubules	Various substances	Ultra sounds
In vitro at rats	1	-	2	1	2	-
In vivo at rats	1	-	2	-	2	1
In vitro at patients	4	2	3	4	7	-
In vivo at patients	2	-	-	-	2	-
Total	8	2	7	5	13	1

Below are the 36 selected items

Articles evaluating the effect of modulation of the in vitro implant surface into a sample of cells from rats, totaled **6** articles:

1. Yusa K *et al*. in 2011 evaluated in vitro bone mineral regeneration induced by Zn ions on modified zinc implants surfaces [46].
2. In 2013, Galli C *et al*. evaluated the effect of lithium chloride on stimulating the activity of mesenchymal cells on the hydrophilic titanium surfaces [47].
3. Manfredi *et al*. studied the role of PGE2 in modulating the signaling of mesenchymal cells in titanium microstructures on implant surfaces. This study was conducted in 2016 [48].
4. Herranz - Diez C *et al*. in 2016, analyzed the effect on mezenimal cells versus titanium niobium-hafnium excreted by recombinant fibronectin [49].
5. Zhou F, *et al*. In 2017, the effect of gastrinin on osteoclastogenesis was evaluated, adjusting signaling by NFATc1 to stimulation of osteointegration [50].
6. Tsuchiya S *et al*. in 2018 they evaluated the effects of titrated kaepferol fixed on the titanium surface and how this affected the differentiation of the mesenchymal cells [51].

Articles where the effect of modulation of the implant surface in vivo is evaluated in the sample of cells obtained from rats, in total are 6 articles

1. Hao WX *et al*. in 2016 published the article on the effect of hydrocholesterol on implant surfaces with coated hydroxyapatite [52].
2. By 2016 Zhou J *et al*. published the article on the effect of cobalt-fluorite, strontium on potential differentiation of mesenchymal cells [53].
3. Yu Y *et al*. in 2017, with the aim of improving osteintegration, data on the modification of the implant surface of Zn / Mg ions were published [54].
4. Ping Z *et al*. in 2017 published the article on the effect of melatonin on the potential differentiation of mesenchymal cells on the implant surfaces [55].
5. In 2018, An Y *et al*. They published the article on the modification of the application of ultrasound to differentiation of mesenchymal cells [56].
6. In 2018, Shao D *et al*., Evaluated in vitro the effect of oral implants with modified miR-122 cells, expressed in implant osteointegration [57].

The articles evaluating the effect of modulation of the implant in vitro surface to the sample of cells taken by the patients, are in total 20 articles:

1. Calzado-Martin A *et al*., In 2011 evaluated the effect of mechanical surface abrasion of implants on differentiation of mesenchymal cells [58].
2. Omar OM *et al*. but in 2011 they published an article on the effect of recombinant proteins in the osteogenic reaction of the classical pathway of monocytic activation [59].
3. In 2014, Wang G *et al*. evaluated the effect of magnesium ions on possible differentiation of mesenchymal cells on implant surfaces [60].
4. Yang HW *et al*. in 2015, published an article about bone marrow osteogenic bone marrow origin, to implants with hydroxyapatite coatings [61].
5. The effect of retinoid acid on the stimulation of lipopolysaccharides from the mesenchymal cells taken from the bone marrow on the implant surfaces was analyzed by Yan Q *et al*. By 2015 [62].
6. In 2015, Burghardt J *et al*., Evaluated the data collected by the interaction of copper in the regenerative capacity of the mesenchymal cells from the cyst of the patients [63].
7. Sisti KE *et al*. In 2016 evaluated the modification of the laser implant surface and the ability of the mesenchymal cell interaction on this modification [64].
8. Yusa K *et al*., In 2016, emphasized the role of zinc ions in the differentiation of osteoblasts and the mineralization of mesenchymal cells taken from dental chicken [65].
9. In 2016, He J *et al*., Emphasized the role of hydroxyapatite on the implant surface, differentiation and bone marrow biopsy [66].
10. Li G *et al*, in 2017, published data on the enamel matrix derivatives in the differentiation of periodontal ligand cells and how they can be used for differentiation of mesenchymal cells [67].
11. In 2017, Bressel TAB *et al*., Published data on the in vitro application of a group of human cells of the modified laser implant surface [68].
12. By 2017, Hyzy SL *et al*, published data on the effects of morphogenic bone marrow proteins applied to the implant surfaces [69].
13. D'Alimonte I *et al*., Published in 2017 data on osteogenic differentiation of mesenchymal cells, a comparative analysis between the mesenchymal cell reaction obtained from adipose tissues and dental pulp [70].
14. Zheng D *et al*., In 2017, analyzed the activation of alendronate in order of increasing osteogenic effect on implant surfaces [71].
15. Lauria I *et al*. in 2018 published the article on modification on the implant surface, in order of differentiating the mezenchymal cells with the topographic signals, into the mesenchymal cells taken from the umbilical cord of the patients [72].
16. Kwon YS *et al*., In 2018, published data on the osteogenic differentiation of mezenchymal cells on superhydrophilic implant surfaces [73].

17. Chao Deng *et al*., In 2018, differentiation of mesenchymal cells originated from periodontal ligament, but in diabetic patients with high blood glucose levels [74].
18. In 2018, Chen J *et al*., Published data on the effect of the double-layer system on the implants, the release of Il-4 and gamma interferon [75].
19. In 2019 Singhatanadgit W *et al*. published an article on the long-term clinical impacts of implant success, expressed with osteointegration level in relation to T lymphocyte interaction and nanotubes of titanium oxide [76].
20. By 2019, Wei F *et al*., Published an article on the modification of titanium nanotubules with exosomes derived from proteins produced by macrophages [77].

Articles where the effect of modifying the implant surface in vivo is evaluated in patients, in total there are 4 articles

1. Maleki-Ghaleh H *et al*., Published data on the effect of magnesium silicate trikalcium over implants on differentiation of mesenchymal cells in 2015 [78].
2. Yu-Chi Chang *et al*. in 2016 published data on the in vivo study of the success of fibronectin dental implants [79].
3. Guillem-Marti J *et al*., In 2019, evaluated the effect of mesenchymal cells on modified implant surfaces using the heparin-binding fragment of fibronectin [80].
4. In 2019, Smaranda Dana Buduru *et al*., Showed the advantages and disadvantages of the three categories of mesenchymal embryonic stem cells in the context of bone regeneration [81].

Discussions

installing bioactivity on metallic biomaterials by imitating the extracellular matrix is crucial to stimulating specific cellular responses in stimulating indenter regeneration. Fibronectin as extracellular matrix protein is commonly used for biomaterial functionality [80].

It is known that human bone cells have ability to fasten on surfaces that are wet with fibronectin, including osteoblast-like cells. Particles of fibronectin, especially heparin-related areas, are also distinguished as the initial affluent [82].

Titanium implant surfaces are modified in various methods with the sole purpose of increasing the potential for osteointegration. Laser treatment (Yb-YAG) is a modest and flexible modification of the implant's surface. By creating micro and macroscopic changes usable for implantation orointegration, the oxidized surface layer improves osteointegration by increasing utilization as implant bone [68].

Various implantation modifications have been made to improve tissue-involved interactions involved in bone fixation, implant failure, and osteogenesis of the contact. Influence can be performed in vivo in potential and in vitro reactions to cellular bio-susceptibility. The advantageous effect of the macroscopic structure is on osteogenic differentiation supported by the ostopontin gene expression. (83) Osteopontin is an extracellular protein structure and an organic bone component. Synonyms for this protein include sialoprotein I and 44K BPP (bone phosphoprotein) [83].

With the aim of improving osteointegration and longterm implant success, it is urgent to create a multifusion implanted titanium surface with spontaneous osteogenic, angiogenic and antibacterial properties. Implant bone implantation as a basic process requires the activation of osteoprogenic cells to adhere to the implant surface, to proliferate, to differentiate into osteoblasts and to produce the mineralized matrix [76]. The long-term success of the implant placed depends not only on osteointegration between the implant and the bone, but also on the response of the patient's immune system level. Implant placement, even biocompatible materials, promotes the response of T lymphocyte cells, stimulated by the interaction between implant and cells. It is widely known about T cell lymphocyte responses to titanium oxide nanotubules [76].

To avoid ectopic bone formation and to reduce side effects, it is necessary to stimulate the functioning of the process via exosomes from macrophages stimulated with bone morphogenetic proteins 2. Exosomes are extracellula nano vasculars that play a key role in cellular communication. The exosomes are naturally secreted in the form of nano-sized vesicles, produced by cells, playing a role in intercellular communication [77].

Installing bioactivity to metallic biomaterials by imitating the extracellular matrix is important for stimulating specific cell responses until stimulation of induration regeneration. Fibronectin is an extracellular matrix protein, commonly used to promote biomaterial functionality. (61) Modifying the titanium surface promotes bone formation and shortens the osteopathic period. Kaempferol is a flavonoid that has the capability to promote osteogenic differentiation of bone marrow cells [51].

The use of reduced intensity ultrasounds (LIPUS) is a promising technique in promoting osteogenesis. Several studies have reported the influence of this technique on osteointegration to endocrine implants, especially in different implant topographies. Initial interaction between cells and the implant surface increases by applying LIPUS and potential regulatory mechanisms [56]. The inflammatory reaction that occurs between tissues and implants after implantation has attracted increased attention due to local necrosis leading to implant failure. Since macrophages play a role in all phases of inflammation, proinflammatory macrophages and anti-inflammatory macrophages affect both phenotypes and may pass from one type to another at specific moments that are important in wound healing and induration regeneration. In this way, thinking that implant biomaterials can be used to facilitate the passage of macrophages from one phenotype to another, we can stimulate or reduce the inflammation or healing process. The anti-inflammatory prophylaxis macrophage phenotype modulating system can be used to achieve immune response control to the implants [75]. In order to improve the stimulation of osteintegration, implant surfaces can be modulated with lasers. The Yb-YAG laser is a controllable and flexible treatment in surface modification, creating a superficial surface area of mirko and nanometer and an oxide layer that enhances the integration of implants by increasing the applicability as a bone implant material [63]. The periodontal ligament has cells that resemble the characteristics of the mesenchymal cells and are considered as candidates for potential application in therapeutic periodontal regeneration. The enamel matrix derivatives are widely used in stimulating periodontal regeneration, but the effects of these derivatives on osteogenic differentiation of the periodontal ligament on implant surfaces are not yet clear [67]. Surface processing of titanium implants induces the differentiation of

osteoblasts from the mesenchymal cells even in the absence of exogenous bone factors. Addition of morphogenic bone protein is clinically used to improve bone formation and osteointegration but may cause inflammation and bone-related complications [69]. White sebaceous India is the best source of mesenchymal cells that have been subjected to many studies on the possibility of therapeutic use in bone repair / remodeling. In order of better evaluating the osteogenic potential of these cells, the characteristics of these cells positioned on the sebaceous tissue in the skin and on the pulp of the third affected molars as well as well-defined sources for the mesenchymal cells are evaluated. From both sources, mesenchymal cells showed the same morphology with fibroblast and expression of the mesenimal markers [70].

The bone is the most direct dynamic organ and its dynamism consists in the delicate balance between osteoclastic and osteoblastic formation. Significant osteoclastic activation is associated with many diseases such as osteoporosis, Paget, osteoclastic bone metastases. Agents that may inhibit osteoclastic formation or function are promising alternatives to treating these diseases with osteoclastic activity-based. Traditional Chinese medicine has attracted attention to possible interventions in osteoclastic activity. Gastrodine is one of these agents, although the direct action of this agent does not know the way it is performed [50].

The peri-prosthetic osteolysis starts from the process of obstruction of bone regeneration, caused by the initial phase post-detachment. This is thought to be the beginning of implant failure and the reason for the reopening of the surgical procedure. Melatonin is thought to be an agent that promotes bone regeneration and reduces bone resorption in the osteolytic areas caused by titanium.

These implant effects may have been initiated by the activation of Wnt / beta-catenin, which stimulates osteogenic differentiation. The ability of melatonin to model the balance between beta cellinase and osteoprotegerin receptor activator, suppressing osteoclastogenesis may implicate the protective effects of melatonin on resorption on the implant surfaces [55].

Implantation of alendronate over the implants offers the possibility of promoting osteogenesis without potential side effects with systemic administration of this medication. Alendronate is immobilized on titanium by two methods: phosphorylation and aminizomy, pathways by which osteoblasts and mesenchymal cells on controlled surfaces are reacted [71]. To evaluate the effect of composite layers loaded with 20 alpha hydroxyl cholesterol and collagen on the surfaces of titanium-coated substrate, to the osteogenesis of the mesenchymal cells. [52] Zinc is an essential element for proliferation, differentiation and survival in different human cells. Isolated zinc ions on titanium surfaces stimulate the ability to express osteoblastic genes and to deposit calcium in the mesenchymal cells [65]. Clinics require antibacterial, angiogenic and osteogenic capabilities of the implant surface by placing inorganic bioactive elements [53]. Surface topography topography enhances the activation and differentiation of osteoblasts. The effects of E2 prostaglandin in different surface topographies can be modeled by signaling the differentiation of osteoblast on titanium surfaces into endocentric implants with different topographies. Application of indomethacin as a cyclooxygenase inhibitor over the surface of the implants [48].

The physical environment as an integral part of the mesenchymal cells is critical in regulating the function and differentiating cells in the specific lines of the process. Most studies have focused on modeling polymer matrices, including the extracellular matrix. The presence of inorganic substrates of hydroxyapatite plays an important role in the cytoskeletal organism in the migration and differentiation of mesenchymal cells. (66) While metal materials used for bone replacement have reduced bioactivity, the use of adhesive cells is a common strategy to improve cellular response to these surfaces. In recent years, the use of recombinant proteins has been presented as an alternative to native proteins and shortened peptides due to fact that they have the biological potential of native proteins while improving stability. Fibronectin with two different recombinant fragments are the proteins analyzed in the study [49]. To improve the antimicrobial and regenerative properties of titanium implants, it is very much the case that implants are placed on the implant surfaces. Copper with different concentrations is thought to be one of these elements that inhibits bacterial growth and stimulates the biological reactions of mesenchymal cells [63]. Evaluation of the effect of retinoid acid on suppression of inflammatory reaction and stimulation of osteoblastic differentiation of mesenchymal cells from bone marrow to titanium surfaces in the lipid-induced microambient [62].

As one of the most important ions associated with ostreointegration, magnesium involved in micro and macro structures, applying plunging into rich plasma of magnesium, is another approach to increasing osteointegration. Surface morphology, chemical properties and the amount of free magnesium ions are evaluated by scanning electromicroscopy, spectrometer [60]. The promotion of bone formation on implant surfaces is an important step to ensure implant success. There are studies on the effect of lithium in the mesenchymal cell response to cellular osteoblastic differentiation on implanted surfaces with different typologies and humidity [47].

The monocyte / macrophage system plays an important role in host protection, healing of wounds and immune system regulation on biomaterial surfaces. Monocytes can be activated in classical or alternative pathways as result of the reaction from biomaterials [59].

Conclusions

The activity of mesenchymal cells in the implant surfaces is an important element of the research center in the field of scientific research regarding implant success or impertinence. This fact is based on the large number of articles published over the years, an increasing number.

The marketing of various dental materials firms has visibly increased the need to conclude which material applied to the implant surfaces is more successful in promoting osteointegration.

Implant success is influenced by several factors, one of the most important being the selection of the implant depending on the alveolar ridge, the patient's health status, and subsequently the biocompatible material applied on the implant surface, as the literature data are numerous in number.

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