

Biomaterials Applied to Bone Regeneration

Subjects: **Pathology**

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Bone loss raises great concern in numerous situations, such as ageing and many diseases and in both orthopedic and dentistry fields of application, with an extensive impact on health care. Therefore, it is crucial to understand the mechanisms and the determinants that can regulate osteogenesis and ensure bone balance. In particular, new strategies for the improvement of the ability of biomaterials to trigger and sustain osteogenesis need to be developed. Autophagy is a well conserved lysosomal degradation pathway, which is known to be highly active during differentiation and development. An extensive revision of the literature on biomaterials, both for orthopedic and dentistry applications, enhancing osteogenesis by modulation of the autophagic process is here presented. Already investigated conditions regulating bone regeneration via autophagy need to be better understood for designing novel biomaterials with improved bioactivity.

Osteogenesis

autophagy

biomaterials

bone regeneration

osteoblasts

ceramics

polymers

stem cells

alumina

silver

1. Introduction

A biomaterial is any material (e.g., polymer, ceramic, metal, or composite) that has been engineered to interact with biological systems for a medical purpose, either a therapeutic (treat, augment, repair, or replace a tissue function of the body) or a diagnostic one. Biomaterials are used every day in dental and orthopedic applications, surgery, and drug delivery. They can be derived either from nature or synthesized in the laboratory using a variety of chemical approaches and materials. Biomaterials can be broadly categorized in metals, polymers, ceramics, and composite materials. This classification is followed in this section to discuss biomaterials promoting bone regeneration by modulating the autophagic process. The research in the field of biomaterials applied to bone regeneration is actually focused on the modifications of their surfaces in order to improve their bioactivity. In this perspective two strategies can be used: the functionalization of the biomaterial/cell interface by linking to its surface osteoinductive/osteocductive molecules; and the modification of surface topography to make them more suitable for cell growth and differentiation. In the following paragraphs many examples of these strategies are given, relating them to the biomaterial used.

Table 1 provides an overview of the biomaterials discussed in this section along with the experimental model they were tested and the signaling pathway involved (where applicable).

Table 1: Biomaterials, experimental models, and signaling pathways.

Biomaterial	Model	Pathway	Reference(s)
Silicon, Orthosilic acid	Murine preosteoblast MC3T3-E1	BMP2/RUNX2 Col1	[1][2][3][4]
Silica NPs	Murine preosteoblast MC3T3-E1	ERK1/2, LC3, p62	[5][6][7][8]
Chitosan	Primary hMSCs	mTOR/S6K/S6/4E-BP1	[9][10][11]
TiAl6V4 particles	Osteocytic cell line MLO-Y4	IFN- β	[12][13][14]
Titanium	hBMSCs		[15][16]
Titanium	Human osteoblasts	PI3K/Akt	[17]
Titanium	Murine preosteoblast MC3T3-E1		[18]
Titanium	Murine preosteoblast MC3T3-E1	β -catenin/YAP	[19]
Alumina	rBMSCs	Wnt BMP	[20][21][22]
Silver NPs			[23][24][25][26][27][28]
Silver NPs	Mouse		[29]
Silver NPs	hMSCs		[30][31]
Hydroxyapatite	DPSCs		[32]
Hydroxyapatite	DPSCs	IL-6	[33]

Hydroxyapatite	Murine preosteoblast MC3T3-E1	mTOR	[34]
Hydroxyapatite	PDLSCs	AMPK mTOR	[35][36]
Fluorapatite	hASCs		[37][38]

2. Polymers

Silicon based materials have long been studied for their application in regenerative medicine either for their proangiogenic role^[1] or their use in scaffolds that mimic the structure and composition of bone tissue^[2]. In this field, the synthesis of silicate-containing hybrids by the sol–gel method is a new route to preparing bioactive implants with improved mechanical properties. These materials can be degraded by the physiological environment, which involves the eventual bone colonization and full tissue restoring. Actually, the research is focused on tailoring the hybrid implants for bone tissue regeneration rather than bone substitution. Silicate-containing hybrids must promote the osteogenic performance of the osteoblast-like cells^[3].

Interestingly, orthosilic acid, a unique soluble form of silicon, enhanced the bone morphogenetic protein2 (BMP-2)/RUNX2 and collagen I protein expression in preosteoblastic cells, promoting differentiation and mineralization of osteoblasts through the activation of the autophagic pathway^[4]. Moreover, an engineered bioactive silica-based nanoparticle formulation (NPs) was found able to stimulate in vitro differentiation and mineralization of osteoblasts and increased bone mineral density in young mice in vivo^{[5][6]}. In the search of the mechanisms underlying such results, Ha and collaborators^[7] found that the stimulation of autophagy and associated signaling suggests a cellular mechanism for the stimulatory effects of silica nanoparticles on osteoblast differentiation and mineralization. They notably suggested that it is the size of the nanoparticles (50 nm) that stimulates autophagy rather than the materials they are made of. These considerations are remarkably in line with what was found about gold nanoparticles: the 45 nm AuNPs were the most effective in promoting both autophagy and osteogenesis^[8].

Chitosan is a polysaccharide copolymer of glucosamine and N-acetylglucosamine derived by partial deacetylation of chitin from crustacean shells. Recently, many studies have investigated the effects of chitosan film or membrane on the morphology, stemness, and multi-differentiation abilities of mesenchymal stemc cells (MSCs). It has been demonstrated that MSCs cultured on chitosan film formed spheres and the expression of stemness marker genes increased significantly when MSCs were cultured using chitosan film compared with 2D monolayer culture systems^[9]. More importantly, culture on chitosan film resulted in an increased differentiation potential of MSCs into mesenchymal lineages, such as osteoblasts^[10]. In the same experimental model, mTOR signaling was activated especially in senescent cells, whereas its suppression or knockdown selected more primitive MSCs that are enriched in gene expression of pluripotency, in vitro osteogenesis, and in vivo bone formation^[11].

3. Metals

3.1. Titanium and Nanostructure

Most of the recent research on biomaterials is actually focused on titanium, the most often used material, due to its biocompatibility and mechanical properties, both for orthopedic and dentistry applications, in substitution of ceramics, polymers, and other metals^{[12][13]}.

In a lately published paper, an osteocyte-conditioned medium proved to inhibit osteoclast differentiation from bone marrow monocytes (BMMs) to osteoclasts. However, TiAl6V4 alloy particles (TiPs) attenuated this inhibitory effect by markedly decreasing the expression of interferon- β (IFN- β), an osteoclastogenesis-associated factor. Additional evidence suggested that TiPs decreased the expression of IFN- β in osteocytes via stimulation of autophagy^[14].

Among the others, one distinctive strategy used to improve the bio-functionality for titanium implants, was the use of exosomes derived by macrophage stimulated with BMP2, that were already known for their beneficial effects on osteogenic differentiation^[15]. The incorporation of BMP2/macrophage derived exosomes dramatically increased the expression of osteoblastic differentiation markers in MSCs. Remarkably, the pro-osteogenic role of the titanium nanotubes incorporated with BMP2/macrophage-derived exosomes is mediated by autophagy^[16].

In the biomaterial field of research, it is already known that biomaterials with varied surface topography have more biocompatible features and better interactions with the surrounding living tissues. Rough surfaces caused osteoblast differentiation via the autophagic-dependent PI3/Akt signaling pathway. One surface provoked the development of a third population of small, granular cells, responsible for cell cluster formation, which were important for the formation of bone noduli and mineralization. When autophagy was inhibited, both mature osteoblasts and small cells were absent, and the cell cluster formation was also prevented. Autophagy therefore has to play an essential role in the osteoblast differentiation on titanium-based surfaces with rough topography^[17].

The nanosized surface is well known for its ability to interfere with intracellular procedures and a nanotube structure was found able to enhance mTOR-independent autophagy in osteoblasts compared to a flat surface. Further analysis revealed that autophagy was temporally promoted by nanotubes in the initial day contact, and cell membrane stretching appeared to be the central regulation factor. The process was also reversible by exchanging the substrate nanotopographies in different cell lines. In summary, the nanotopographic surface is able to induce temporal and reversible autophagy, which may be used as a versatile method to control cell differentiation^[18].

Implant topography is associated with the functionality of osteogenic transcription factors directed by β -catenin in the nucleus. This protein can be degraded by YAP (Yes-associated protein) which is susceptible to autophagic flux. Nanotopography, in comparison with smooth surfaces, was associated with higher β -catenin nuclear translocation, osteogenic differentiation, and autophagy, and less cytoplasmic YAP in MC3T3-E1 cells. These results demonstrated an involvement of this pathway in the osteogenesis observed in response to titanium implants^[19].

3.2. Alumina

The osteoimmune environment plays indispensable roles in bone regeneration because the early immune environment that exists during the regenerative process promotes the recruitment and differentiation of osteoblastic lineage cells^[20]. Nanoporous anodic alumina with different sized pores had modulatory effects on macrophage responses and consequently on the osteogenic differentiation of bone marrow stem cells (BMSCs). The role of macrophages in osteogenesis was already suggested to be indispensable^[21]. The effect of the 50 nm nanoporous alumina structures on macrophage spreading and shape resulted in osteogenic differentiation of BMSCs, improving the osteogenic capacity of bone biomaterials with a mechanism related to autophagy activation^[22].

3.3. Silver

Silver is used in a variety of medical and general devices for its antimicrobial properties. It is, therefore, widely used in the form of nanoparticles in medicine, in order to retard and avoid bacterial infection^{[23][24]}. Despite their antimicrobial action, silver nanoparticles (AgNPs) lack toxicity towards eukaryotic cells, because of the induction of the autophagic process^[25]. Interestingly, linking the silver nanoparticles to thermosets made of materials commonly used in the dental practice resulted in further reduced cytotoxicity^[26], confirming that the adsorption of molecules on biomaterial surfaces can improve their biocompatibility.

Many results were recently achieved regarding effects of AgNPs on osteogenesis of stem cells^{[27][28][29]}. Again, the linking of AgNPs, whose potential toxicity raises serious concerns, on titanium surfaces proved to be a successful strategy^[30]. Moreover, AgNPs activated autophagy and osteogenesis. The administration of the autophagy inhibitor 3-methyladenine could reverse both processes, binding the occurrence of osteogenesis to the autophagic activity in human MSCs^[31].

4. Ceramics

Hydroxyapatite (HA) is a natural occurring mineral present in the human skeleton. In biomaterial applications it can be used in combination with alginate to study the improved osteoblast differentiation of dental pulp cells (DPSCs) ^{[32][33]}.

HA-nanoparticles (HANPs) promoted osteoblast differentiation in a dose-dependent manner the osteoblast cell line MC3T3E1. In addition, the internalized HANPs were located in typical autophagic vacuoles and increased the ratio of LC3II/LC3I, indicating HANPs induced cell autophagy. Moreover, the induction of autophagy was via the mTOR signaling pathway also in a concentration dependent manner. Collectively, these results revealed that HANPs modulates osteoblast differentiation by mediating autophagy in a dose-dependent manner^[34].

Polydopamine-templated hydroxyapatite (tHA) is a type of nano-biomaterial, designed as an alternative to the traditional hydroxyapatite (HA) that can promote osteogenesis in bone tissue engineering. The reinforcement of polycaprolactone (PCL) matrix with tHA enhanced cell adhesion, spreading, and proliferation of human mesenchymal stem cells. More importantly, tHA nanoparticles exposed on the surface of composite nanofibers could further promote osteogenesis of human MSCs in vitro^[35]. However, as already seen in other experimental

systems, the concentration is crucial. Indeed, high concentrations of tHA stimulated reactive oxygen species (ROS) production, resulting in cell injury and apoptosis in PDLSCs. Nevertheless, the triggering of the AMPK/mTOR signaling pathway when tHA is in combination with metformin, led to autophagy activation and consequent increased viability of human PDLSCs with a further improvement of the osteogenic effect^[36].

Interestingly, also the incorporation of fluorapatite (FA) crystals within the three-dimensional PCL nanofiber scaffolds provided a favorable extracellular matrix microenvironment for the growth, differentiation, and mineralization of human DPSCs^[37]. In a different cellular model, the inhibition of autophagy at earlier stages (days 1 to 3) could affect human adipose stem cell (hASCs) osteogenic capability and mineralization when grown on PCL+FA scaffolds. These results suggested that autophagy was indispensable during the early stage of osteogenic differentiation in this model^[38].

Concluding, the health of the bone tissue is strictly related to the differentiation of osteoblasts, the cell responsible for the deposition of organic osteoid and matrix mineralization, which leads to osteogenesis. Autophagy is thoroughly involved in the development of these cells, contributing therefore to bone homeostasis. Impairment of autophagic activity leads to disruption of the bone-remodeling balance, which leads to pathological state and failure of biomaterial implants. Autophagy modulation has been shown to have an intriguing potential as target for ageing, biomaterial design, and the therapy of various pathological conditions. Here the role of autophagy in osteogenesis promoted by different types of biomaterials is largely discussed. The knowledge of the conditions improving biomaterial bioactivity will help future research to design new biomaterial solutions.

Abbreviations

ASCs	adipose stem cells
BMMs	bone marrow monocytes
BMP	bone morphogenetic protein
BMSCs	bone marrow mesenchymal stem cells
DPSCs	dental pulp stem cells
FA	fluorapatite
HA	hydroxyapatite

MSCs	mesenchymal stem cells
NPs	nanoparticles
PDLSCs	periodontal ligament stem cells
PCL	polycaprolactone
ROS	reactive oxygen species

References

1. Khandmaa Dashnyam; Ahmed El-Fiqi; Jennifer Olmos Buitrago; Roman A Perez; Jonathan C Knowles; Hae-Won Kim; A mini review focused on the proangiogenic role of silicate ions released from silicon-containing biomaterials. *Journal of Tissue Engineering* **2017**, 8, , 10.1177/2041731417707339.
2. Irina Titorencu; Madalina Albu; Miruna Nemecz; Victor Jinga; Natural Polymer-Cell Bioconstructs for Bone Tissue Engineering. *Current Stem Cell Research & Therapy* **2017**, 12, 165-174, 10.2174/1574888X10666151102105659.
3. Daniel Arcos; María Vallet-Regí; Sol-gel silica-based biomaterials and bone tissue regeneration. *Acta Biomaterialia* **2010**, 6, 2874-2888, 10.1016/j.actbio.2010.02.012.
4. Hai Chi; Meng Kong; Guangjun Jiao; Wenliang Wu; Hongming Zhou; Lu Chen; Yini Qiao; Hongliang Wang; Wenzheng Ma; Yunzhen Chen; The role of orthosilicic acid-induced autophagy on promoting differentiation and mineralization of osteoblastic cells.. *Journal of Biomaterials Applications* **2019**, 34, 94-103, 10.1177/0885328219837700.
5. George R. Beck; Shin-Woo Ha; Corinne E. Camalier; Masayoshi Yamaguchi; Yan Li; Jin-Kyu Lee; M. Neale Weitzmann; Bioactive silica-based nanoparticles stimulate bone-forming osteoblasts, suppress bone-resorbing osteoclasts, and enhance bone mineral density in vivo.. *Nanomedicine: Nanotechnology, Biology and Medicine* **2012**, 8, 793-803, 10.1016/j.nano.2011.11.003.
6. Shin-Woo Ha; James A. Sikorski; M. Neale Weitzmann; George R. Beck; Bio-active engineered 50 nm silica nanoparticles with bone anabolic activity: therapeutic index, effective concentration, and cytotoxicity profile in vitro.. *Toxicology in Vitro* **2014**, 28, 354-64, 10.1016/j.tiv.2013.12.001.

7. Shin-Woo Ha; M. Neale Weitzmann; George R. Beck; Bioactive Silica Nanoparticles Promote Osteoblast Differentiation through Stimulation of Autophagy and Direct Association with LC3 and p62. *ACS Nano* **2014**, *8*, 5898-5910, 10.1021/nn5009879.
8. Yangheng Zhang; Na Kong; Yuanchao Zhang; Wenrong Yang; Fuhua Yan; Size-dependent Effects of Gold Nanoparticles on Osteogenic Differentiation of Human Periodontal Ligament Progenitor Cells.. *Theranostics* **2017**, *7*, 1214-1224, null.
9. Zhiqiang Li; Xiaojun Tian; Yan Yuan; Zhixiu Song; Lili Zhang; Xia Wang; Tong Li; Effect of cell culture using chitosan membranes on stemness marker genes in mesenchymal stem cells. *Molecular Medicine Reports* **2013**, *7*, 1945-1949, 10.3892/mmr.2013.1423.
10. Nai-Chen Cheng; Shan Wang; Tai-Horng Young; The influence of spheroid formation of human adipose-derived stem cells on chitosan films on stemness and differentiation capabilities. *Biomaterials* **2012**, *33*, 1748-1758, 10.1016/j.biomaterials.2011.11.049.
11. Hsiao-Ying Chiu; Yeou-Guang Tsay; Shih-Chieh Hung; Involvement of mTOR-autophagy in the selection of primitive mesenchymal stem cells in chitosan film 3-dimensional culture. *Scientific Reports* **2017**, *7*, 10113, 10.1038/s41598-017-10708-0.
12. Manmeet Kaur; K. Singh; Review on titanium and titanium based alloys as biomaterials for orthopaedic applications. *Materials Science and Engineering: C* **2019**, *102*, 844-862, 10.1016/j.msc.2019.04.064.
13. In-Sung Luke Yeo; Modifications of Dental Implant Surfaces at the Micro- and Nano-Level for Enhanced Osseointegration. *Materials* **2020**, *13*, 89, 10.3390/ma13010089.
14. Zhenheng Wang; Zhantao Deng; Jingjing Gan; Gang Zhou; TongGuo Shi; Zhenzhen Wang; Zhen Huang; Hongbo Qian; Nirong Bao; Ting Guo; Jiangning Chen; Junfeng Zhang; Feng Liu; Lei Dong; Jianning Zhao; TiAl 6 V 4 particles promote osteoclast formation via autophagy-mediated downregulation of interferon-beta in osteocytes. *Acta Biomaterialia* **2017**, *48*, 489-498, 10.1016/j.actbio.2016.11.020.
15. Fei Wei; Yinghong Zhou; Jing Wang; Changsheng Liu; Yin Xiao; The Immunomodulatory Role of BMP-2 on Macrophages to Accelerate Osteogenesis. *Tissue Engineering Part A* **2018**, *24*, 584-594, 10.1089/ten.tea.2017.0232.
16. Fei Wei; Mengting Li; Ross W. Crawford; Yinghong Zhou; Yin Xiao; Exosome-integrated titanium oxide nanotubes for targeted bone regeneration. *Acta Biomaterialia* **2019**, *86*, 480-492, 10.1016/j.actbio.2019.01.006.
17. Milena R. Kaluđerović; Marija Mojić; Joachim P. Schreckenbach; Danijela Maksimović-Ivanić; Hans-Ludwig Graf; Sanja Mijatović; A Key Role of Autophagy in Osteoblast Differentiation on Titanium-Based Dental Implants. *Cells Tissues Organs* **2014**, *200*, 265-277, 10.1159/000434625.

18. Wen Song; Mengqi Shi; Mingdong Dong; Yumei Zhang; Inducing Temporal and Reversible Autophagy by Nanotopography for Potential Control of Cell Differentiation. *ACS Applied Materials & Interfaces* **2016**, *8*, 33475-33483, 10.1021/acsami.6b11699.

19. Lingjie Li; Sheng Yang; Ling Xu; Yuzhou Li; Yiru Fu; He Zhang; Jinlin Song; Nanotopography on titanium promotes osteogenesis via autophagy-mediated signaling between YAP and β -catenin.. *Acta Biomaterialia* **2019**, *96*, 674-685, 10.1016/j.actbio.2019.07.007.

20. Lan Xiao; Yin Xiao; The Autophagy in Osteoimmunology: Self-Eating, Maintenance, and Beyond.. *Frontiers in Endocrinology* **2019**, *10*, 490, 10.3389/fendo.2019.00490.

21. Andy C. Wu; Liza J Raggatt; Kylie Alexander; Allison Pettit; Unraveling macrophage contributions to bone repair. *BoneKEy Reports* **2013**, *2*, 373, 10.1038/bonekey.2013.107.

22. Zetao Chen; Siyu Ni; Shengwei Han; Ross W. Crawford; Shifeier Lu; Fei Wei; Jiang Chang; Chengtie Wu; Yin Xiao; Nanoporous microstructures mediate osteogenesis by modulating the osteo-immune response of macrophages. *Nanoscale* **2017**, *9*, 706-718, 10.1039/c6nr06421c.

23. Sang Hun Lee; Bong-Hyun Jun; Silver Nanoparticles: Synthesis and Application for Nanomedicine. *International Journal of Molecular Sciences* **2019**, *20*, 865, 10.3390/ijms2004086 5.

24. Alexandra-Cristina Burduşel; Oana Gherasim; Alexandru Mihai Grumezescu; Laurentiu Mogoanta; Anton Ficai; Ecaterina Andronescu; Biomedical Applications of Silver Nanoparticles: An Up-to-Date Overview. *Nanomaterials* **2018**, *8*, 681, 10.3390/nano8090681.

25. Marialucia Gallorini; Viviana Di Giacomo; Valentina Di Valerio; Monica Rapino; Domenico Bosco; Andrea Travan; Mara Di Giulio; Roberta Di Pietro; Sergio Paoletti; Amelia Cataldi; et al. Silvia Sancilio Cell-protection mechanism through autophagy in HGFs/S. mitis co-culture treated with Chitlac-nAg. *Journal of Materials Science: Materials in Medicine* **2016**, *27*, 186, 10.1007/s10856-016-5803-5.

26. Silvia Sancilio; Viviana Di Giacomo; Mara Di Giulio; Marialucia Gallorini; Eleonora Marsich; Andrea Travan; Lorena Tarusha; Luigina Cellini; Amelia Cataldi; Biological Responses of Human Gingival Fibroblasts (HGFs) in an Innovative Co-Culture Model with *Streptococcus mitis* to Thermosets Coated with a Silver Polysaccharide Antimicrobial System. *PLOS ONE* **2014**, *9*, e96520, 10.1371/journal.pone.0096520.

27. Haiping Lu; Yi Liu; Jing Guo; H. L. Wu; Jingxiao Wang; Gang Wu; Biomaterials with Antibacterial and Osteoinductive Properties to Repair Infected Bone Defects. *International Journal of Molecular Sciences* **2016**, *17*, 334, 10.3390/ijms17030334.

28. Dan Hu; Xueping Gu; Weibing Si; Wei Qin; Jian Jiao; Yuefeng Hao; Biosynthesis of Silver nanoparticles using Bauhinia acuminate flower extract and their effect to promote osteogenesis of

MSCs and improve meniscus injury healing.. *Journal of Photochemistry and Photobiology B: Biology* **2019**, *197*, 111536, 10.1016/j.jphotobiol.2019.111536.

29. Ruizhong Zhang; Puiyan Lee; V C Lui; Yan Chen; Xuelai Liu; Chun Nam Lok; Michael To; Kelvin Yeung; Kenneth K Y Wong; Silver nanoparticles promote osteogenesis of mesenchymal stem cells and improve bone fracture healing in osteogenesis mechanism mouse model. *Nanomedicine: Nanotechnology, Biology and Medicine* **2015**, *11*, 1949-1959, 10.1016/j.nano.2015.07.016.

30. Huiliang Cao; Wenjie Zhang; Fanhao Meng; Jinshu Guo; Donghui Wang; Shi Qian; Xinquan Jiang; Xuanyong Liu; Paul K. Chu; Osteogenesis Catalyzed by Titanium-Supported Silver Nanoparticles. *ACS Applied Materials & Interfaces* **2017**, *9*, 5149-5157, 10.1021/acsami.6b15448.

31. Wei He; Yudong Zheng; Qingling Feng; Tarek A Elkholy; Xujie Liu; Xing Yang; Yansen Wang; Yajie Xie; Silver nanoparticles stimulate osteogenesis of human mesenchymal stem cells through activation of autophagy. *Nanomedicine* **2020**, *15*, 337-353, 10.2217/nmm-2019-0026.

32. Silvia Sancilio; Marialucia Gallorini; Chiara Di Nisio; Eleonora Marsich; Roberta Di Pietro; Helmut Schweikl; Amelia Cataldi; Alginate/Hydroxyapatite-Based Nanocomposite Scaffolds for Bone Tissue Engineering Improve Dental Pulp Biomineralization and Differentiation. *Stem Cells International* **2018**, *2018*, 1-13, 10.1155/2018/9643721.

33. Silvia Sancilio; Eleonora Marsich; Helmut Schweikl; Amelia Cataldi; Marialucia Gallorini; Redox Control of IL-6-Mediated Dental Pulp Stem-Cell Differentiation on Alginate/Hydroxyapatite Biocomposites for Bone Ingrowth.. *Nanomaterials* **2019**, *9*, 1656, 10.3390/nano9121656.

34. Renxian Wang; Hao Hu; Jianxun Guo; Qian Wang; Jingjing Cao; Honggang Wang; Guangping Li; Jianping Mao; Xuenong Zou; Dafu Chen; et al. Wei Tian Nano-Hydroxyapatite Modulates Osteoblast Differentiation Through Autophagy Induction via mTOR Signaling Pathway.. *Journal of Biomedical Nanotechnology* **2019**, *15*, 405-415, 10.1166/jbn.2019.2677.

35. Xiang Gao; Jinlin Song; Ping Ji; Xiaohong Zhang; Xiaoman Li; Xiao Xu; Mengke Wang; Siqi Zhang; Yi Deng; Feng Deng; Shicheng Wei; Polydopamine-Templated Hydroxyapatite Reinforced Polycaprolactone Composite Nanofibers with Enhanced Cytocompatibility and Osteogenesis for Bone Tissue Engineering. *ACS Applied Materials & Interfaces* **2016**, *8*, 3499-3515, 10.1021/acsami.5b12413.

36. Zun Yang; Xiang Gao; Mengjiao Zhou; Yunchun Kuang; Mingli Xiang; Jie Li; Jinlin Song; Effect of metformin on human periodontal ligament stem cells cultured with polydopamine-templated hydroxyapatite.. *European Journal of Oral Sciences* **2019**, *127*, 210-221, 10.1111/eos.12616.

37. T. Guo; Y. Li; G. Cao; Z. Zhang; S. Chang; A. Czajka-Jakubowska; J.E. Nör; B.H. Clarkson; J. Liu; Fluorapatite-modified Scaffold on Dental Pulp Stem Cell Mineralization. *Journal of Dental Research* **2014**, *93*, 1290-1295, 10.1177/0022034514547914.

38. Y. Li; T. Guo; Z. Zhang; Y. Yao; S. Chang; Jacques E. Nör; B.H. Clarkson; L. Ni; J. Liu; Autophagy Modulates Cell Mineralization on Fluorapatite-Modified Scaffolds. *Journal of Dental Research* **2016**, 95, 650-656, 10.1177/0022034516636852.

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