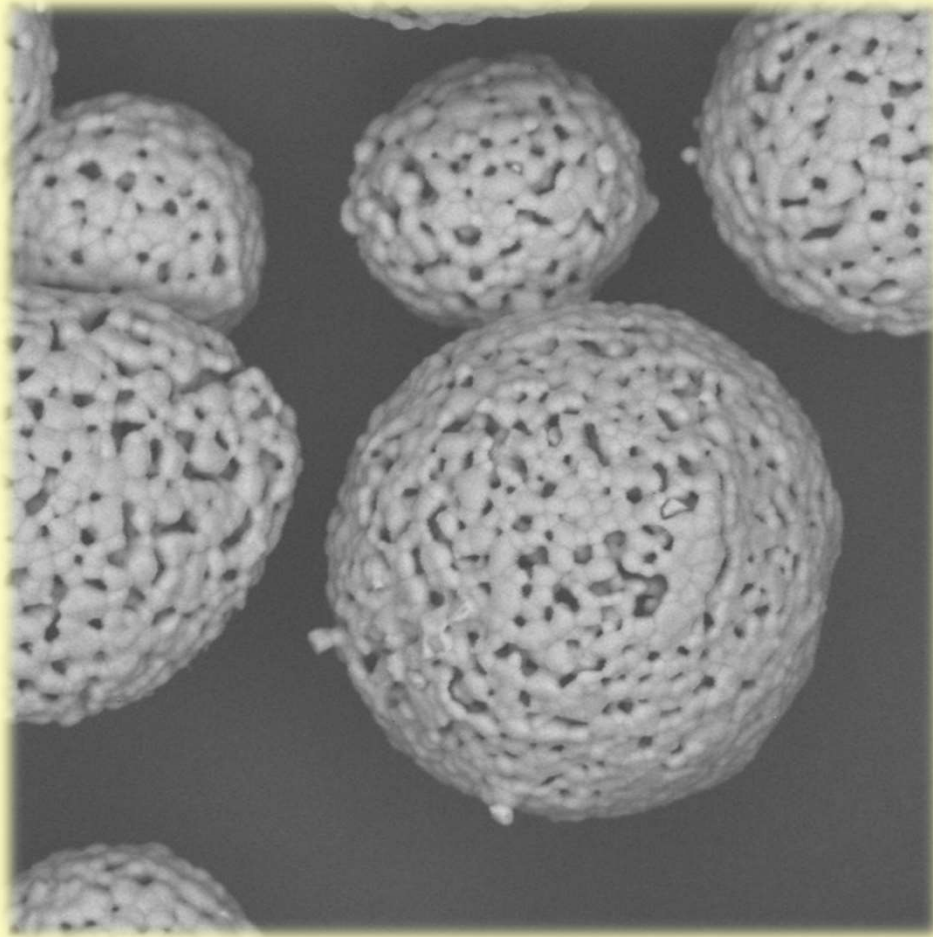




**BIOCERAMICS FOR STEM
CELL REGULATION AND
TISSUE REGENERATION**

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WHAT ARE BIO CERAMICS?

- Bioceramics are ceramic materials used for repair and reconstruction of diseased or damaged body parts.
- The term "bioceramics" often includes both crystalline and amorphous inorganic biomaterials.
- Strictly speaking:
 - Bioceramics: Synthesized inorganic materials with a crystalline structure.
 - Bioactive glass: Inorganic biomaterials with an amorphous structure.
- Bioceramics have a long history in healthcare, with calcium sulfate used for setting broken bones as early as 975 AD.

WHAT ARE BIO CERAMICS?

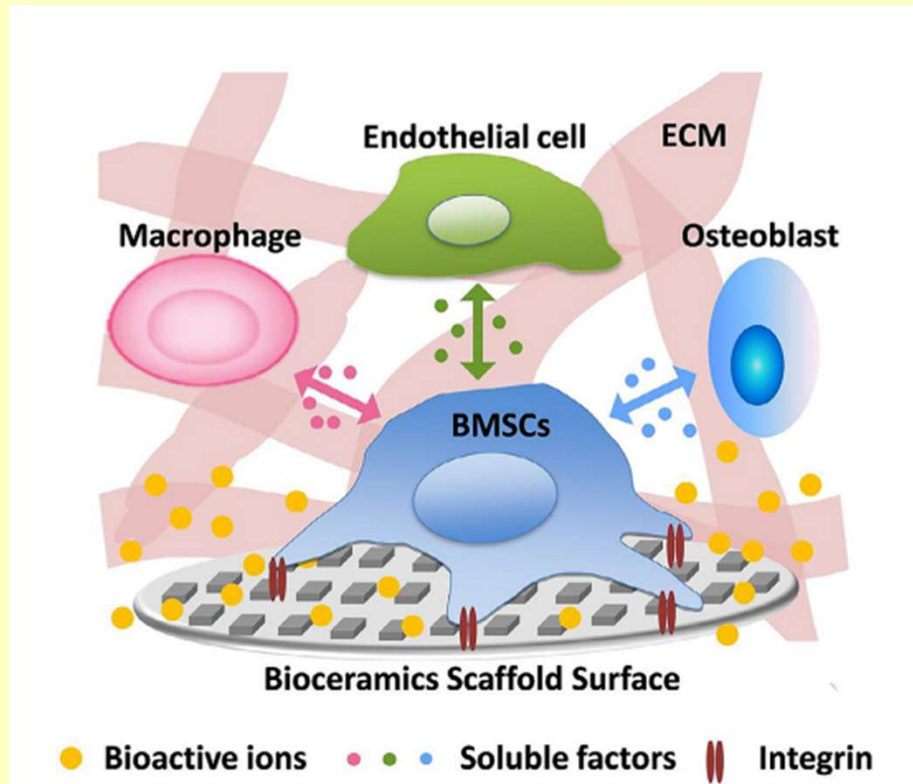
- Rapid development in the 20th century: from **alumina** and **zirconia** to calcium phosphate bioceramics.
- **Calcium phosphate** bioceramics are widely used for **orthopedic applications** due to excellent **biocompatibility**, **osteoconductivity**, and similarity to bone's inorganic component.
- In the early 1970s, **Bioglass®** was discovered to form interfacial bonding with bone tissue.
- Early clinical applications of bioceramics mainly focused on **mechanical properties** and biocompatibility.
- More recently, loading bioceramics with drugs for **antibacterial** and **anti-tumor effects** has been explored.
- Traditional reviews focused on material science perspectives like preparation and applications as **implants** and **drug delivery**.

THE NEW PARADIGM - ENHANCING TISSUE REGENERATION

- With an aging society, clinical demands for tissue regeneration and wound healing are increasing.
- This raises the question of whether biomaterials/bioceramics can be further improved for enhanced tissue regeneration or if we can regulate the process using specifically designed materials.
- Stem cells are crucial for tissue regeneration due to their self-renewal and differentiation potential.
- Stem cells reside in a complex microenvironment including cells, growth factors, cytokines, ECM, ions, and mechanical stimuli.
- Biomaterials can potentially regulate stem cell behavior to enhance tissue regeneration.
- Understanding cell-biomaterial interactions allows us to design biomaterials as extrinsic regulators of stem cell fate, directing their differentiation.

INTERACTION OF BIOCERAMICS WITH THE BODY

- When implanted, complex biological and chemical processes occur at the interface.
- These interactions determine the progress of tissue regeneration.
- Implanted bioceramics affect the cell microenvironment through their chemical and physical characteristics.



Schematic diagram of the inherent **chemical and topographical properties** of bioceramics, which may affect the stem cells microenvironment. After implantation of bioceramics scaffold into the body, the biodegradation products (**bioactive ions**) and the surface topography interact with the microenvironment of **BMSCs** via soluble factors (like growth factors), ECM and activation of tissue-specific cells (like **endothelial cell and osteoblast**) and immune cells (like **macrophage**).

ROLE OF BIOACTIVE IONS

- Degradation of Bioceramics is Crucial: Essential for implant materials.
- Ideal degradation rate: Should match bone ingrowth to maintain mechanical stability.
- Degradation mechanisms:
 - Calcium phosphate bioceramics: Solution-driven and cell-mediated processes.
 - Silicate bioceramics: Mainly solution-mediated dissolution.
- Degradation releases bioactive ions that stimulate cell behavior.
- In vitro degradation is often tested in simulated body fluid (SBF), PBS, Tris-HCl, and cell culture medium.

ROLE OF BIOACTIVE IONS

- Degradation rate and ion release profile depend on:
 1. Chemical composition
 2. Crystallinity
 3. Surface area
 4. Particle size
 5. Porosity
- Degradation rates of calcium phosphates: α -TCP > β -TCP > HAp.
- Doping with ions like Si or carbonate increases biodegradability.
- Lower crystallinity and higher specific surface area lead to faster degradation.
- Smaller particle size and high porosity accelerate degradation.
- Connective pores and high porosity facilitate tissue and blood vessel ingrowth.
- Biological parameters like defect location and size also affect degradation.

CONTROLLING DEGRADATION AND ION RELEASE

1. Synthesizing bioceramics with different compositions and physical characteristics containing bioactive ions.
2. Combining bioceramics with biopolymers for coating.
3. In vivo degradation differs from in vitro.
4. Degradation can change the surface microstructure, topography, and mechanical properties.

EFFECT OF BIOACTIVE IONS ON STEM CELLS

- Stem cells respond to various stimuli in their tissue niches.
- Bioactive ions have specific biological functions in tissue metabolism.
- Examples of ions in bone formation: Mn, Ca, Zn, Sr, Si.
- Examples of ions promoting angiogenesis: Cu, Co, Si, Ca, B.
- Inorganic ions can affect stem cell phenotype directly or indirectly.
- Calcium (Ca) ions enhance MSC proliferation, while both Ca and phosphate positively affect osteogenic differentiation.

EFFECT OF BIOACTIVE IONS ON STEM CELLS

- Local delivery of phosphate ions can trigger osteoinductive response.
- Sustained release of Ca ions may promote angiogenesis.
- Ionic extracts of silicate bioceramics promote osteogenic differentiation of BMSCs by activating osteogenic marker genes.
- Silicon (Si) is a key ion for the bioactivity of silicate bioceramics.
- Bioactive ions from silicate bioceramics can stimulate growth factor expression of BMSCs.
- For example, akermanite extracts stimulate BMP2 expression.
- Ionic extracts can also stimulate angiogenic growth factors like VEGF and EGF.
- Bioactive ions like Ca, Si, and P can stimulate ECM deposition.
- Si ions play a role in collagen and glycosaminoglycan production and mineralized nodule formation.

MECHANISMS OF ION BIOACTIVITY

- Detailed mechanisms of ion bioactivity are not fully understood.
- Studies are identifying activated signaling pathways.
- Calcium ions signaling cascade for osteogenic differentiation.
- Phosphate ions induce osteogenic differentiation via adenosine signaling.
- Silicon ions stimulate osteogenic differentiation via Wnt and SHH signaling pathways or by antagonizing NF- κ B activation via miR-146a.
- Nagelschmidtite activates the Wnt/ β -catenin pathway.
- MAPK signaling pathway (ERK, JNK, P38) is involved in cellular responses.
- Ions from akermanite activate the ERK pathway.
- Ca and Si ions from CS induce BMSC differentiation via AMPK/ERK1/2 signaling.
- Calcium silicate cement extracts promote odontogenic gene expression via the P38 pathway.
- Multiple signaling pathways can be activated depending on ion type, concentration, and cell type.

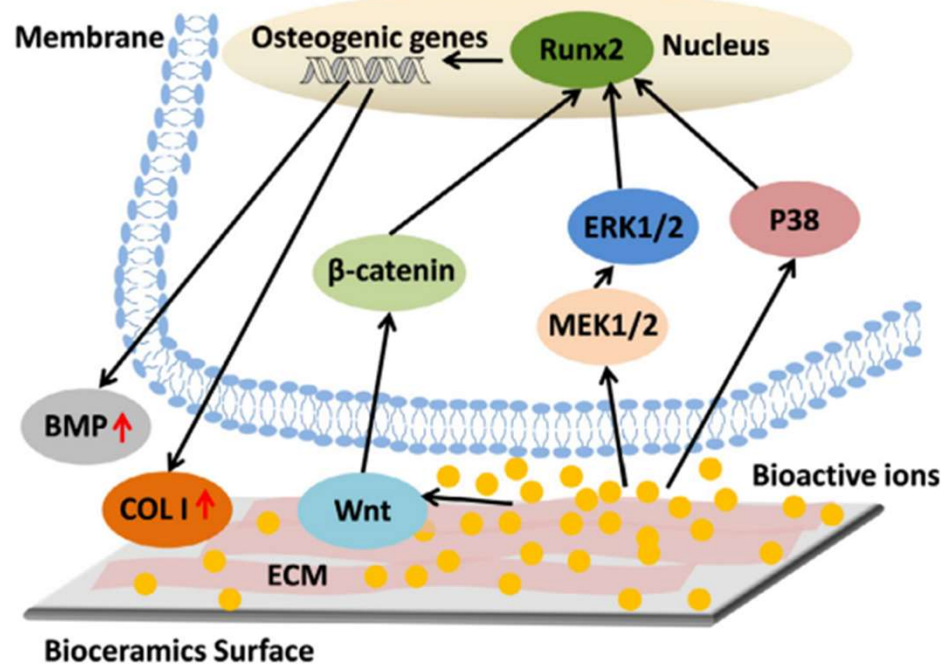


FIGURE 2

Signaling pathways activated by bioactive ions released from bioceramics in regulating the osteogenic differentiation of stem cells. Mainly three important signaling pathways are activated including P38, AMPK/ERK 1/2 and Wnt/ β -catenin signaling pathways.

EFFECT OF IONS ON TISSUE-SPECIFIC CELLS AND CELL-CELL INTERACTIONS

- Tissue-specific cells interact with stem cells and affect their microenvironment.
- Bioactive ions can affect the behavior of tissue-specific cells.
- Ca, P, and Si ions can induce osteogenesis and angiogenesis by stimulating growth factor and ECM protein expression in osteoblasts and fibroblasts.
- Bioglass 45S5 dissolution products stimulate IGF-II in osteoblasts.
- Dicalcium silicate extracts stimulate BMP2 in osteoblast-like cells.
- Si ions activate endothelial cells (ECs) and up-regulate angiogenic growth factors.
- Silicate bioceramics stimulate VEGF and bFGF secretion from endothelial cells and fibroblasts.

EFFECT OF IONS ON TISSUE-SPECIFIC CELLS AND CELL-CELL INTERACTIONS

- Bioglass 45S5 up-regulates CD44 and integrin $\beta 1$ in osteoblasts.
- Bioactive ions can indirectly affect stem cells through tissue-specific cell activation.
- Ions from CS affect cell-cell interactions (BMSCs and HUVECs) through paracrine signaling, stimulating VEGF in BMSCs and BMP2 in HUVECs.
- Cu ions in Cu-doped BG scaffolds stimulate BMSCs to secrete VEGF, promoting EC vascularization.
- Si ions up-regulate VEGF in HUVEC–HDF co-cultures, enhancing angiogenesis.

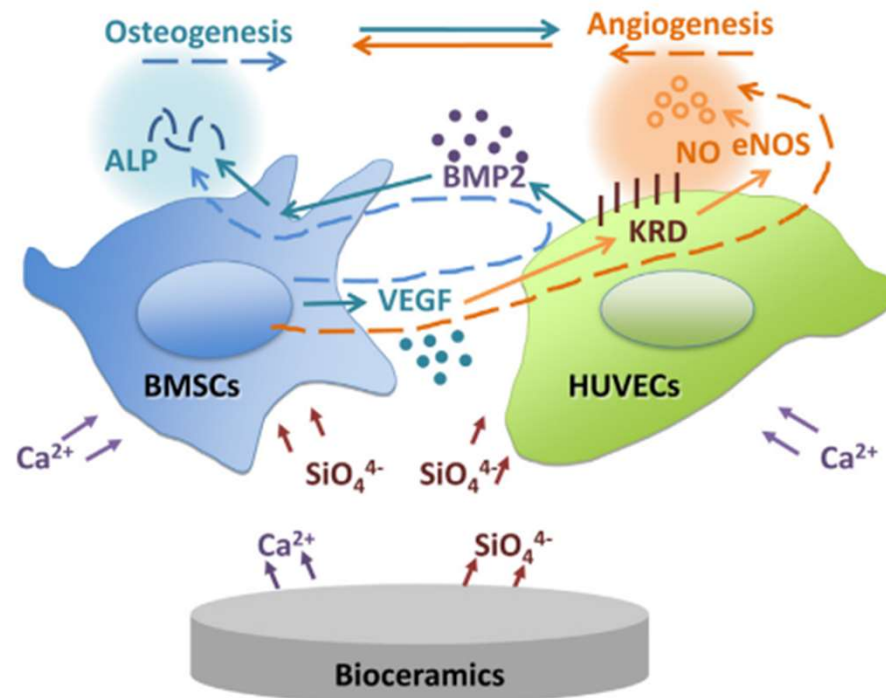


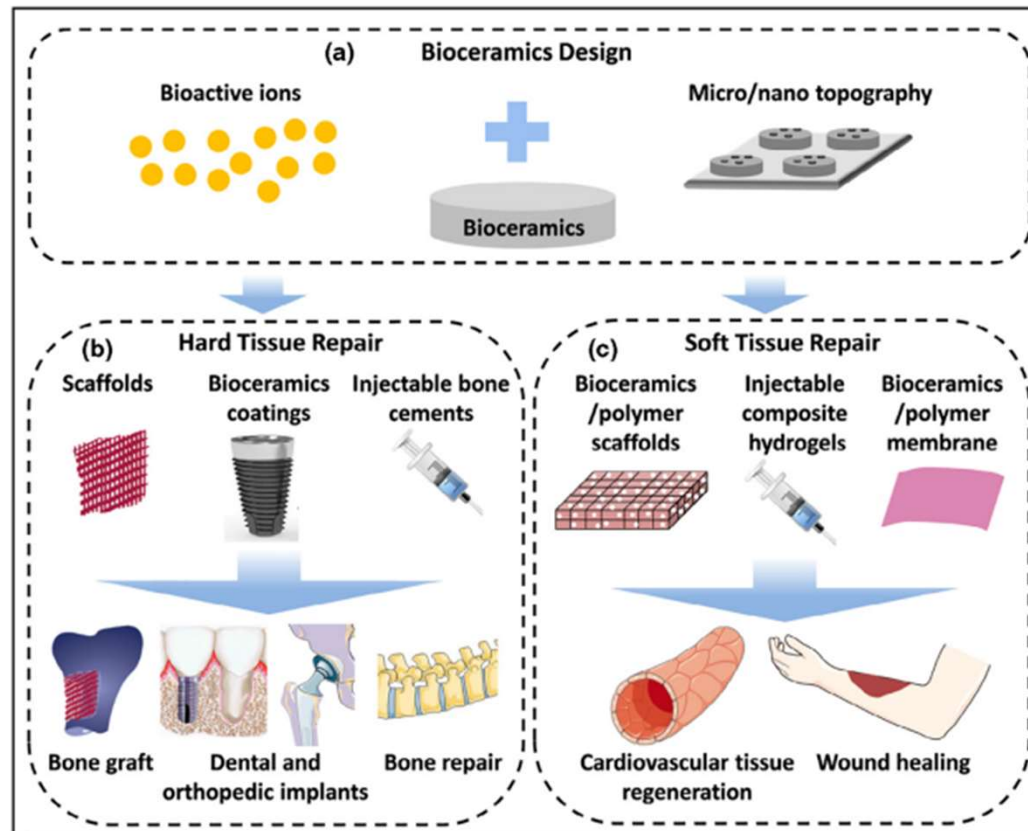
FIGURE 3

The proposed mechanism through which the bioactive ions stimulate the interactions between HUVECs and human BMSCs in co-cultures, which finally enhances the osteogenesis and angiogenesis/vascularization. (Reprinted with permission from Ref. [28]. Copyright 2014 Elsevier.)

PROTEIN ADSORPTION ON BIO CERAMICS

- Selective protein adsorption on specific topographies can indirectly affect stem cell microenvironment.
- HAp used for protein separation due to selective affinity.
- Calcium phosphate with specific microstructure can adsorb growth factors.
- Nanostructured calcium phosphate has strong adsorption for BMP2 and TGF- β 1.
- Selective adsorption of cell adhesion proteins (fibronectin, integrins) on nanostructured calcium phosphate contributes to stem cell regulation.
- Nanosheet, nanorod, and micro/nano hybrid HAp enhance adsorption of fibronectin and vitronectin, stimulating osteogenic differentiation.
- High specific surface area and Ca/P sites contribute to protein adsorption.
- Electrostatic forces and protein conformation also play a role.

APPLICATIONS OF BIOCERAMICS FOR TISSUE REGENERATION



CONCLUSIONS

- Bioceramics research is evolving towards bioactive materials regulating cell behavior and enhancing tissue regeneration.
- Predicting biological outcomes and designing bioceramics for specific clinical applications remains challenging.
- Chemical (ions) and structural (topography) characteristics affect stem cells and their microenvironment in multiple ways:
 - Directly affecting stem cell behavior.
 - Affecting tissue-specific cells and their interaction with stem cells.
 - Affecting macrophage behavior and immune response.
- Bioceramics with specific properties can regulate the stem cell microenvironment as a whole system.
- Applications are expanding to soft tissue regeneration due to angiogenesis stimulation.
- Bioceramics can be combined with biopolymers for various soft tissue applications.

REFERENCE

- Zhou, Yanling, Chengtie Wu, and Jiang Chang. "Bioceramics to regulate stem cells and their microenvironment for tissue regeneration." *Materials Today* 24 (2019): 41-56.