How to improve the healing effect of silicon-based bioceramics?

Silicon-based bioceramics can heal health conditions such as infarcted myocardium and chronic wounds. How can they treat these conditions? Silicon-based bioceramics are bioactive, meaning that the materials have actions in the body that promote good health. In this article, we review several research articles on silicon-based bioceramics in the state-of-art research conducted in the preclinical phase.

1 Silicon-based composites

Fabricating composites can combine the advantages of the different components.

1.1 Bioactive SiO_4^{4-}

Si ions (here SiO_4^{4-}) are bioactive as they promote the generation of angiogenic (blood vessel forming) growth factors (proteins/hormones for cell growth) directly and the paracrine effect (promoting cell-cell communication, Section 2.3). SiO_4^{4-} also promotes the expression of cardiac-specific genes as well as cardiomyocytes.[1]

1.2 Other bioactive ions

Another angiogenic ion include Fe^{2+}. Fe^{2+} is more angiogenic than Fe^{3+} but easily oxidized into Fe^{3+} in an O_2-included environment. Therefore, Fe^{2+} containing material needs antioxidant compounds (such as chitosan) to maintain its reductive state Fe^{2+}.[2] Having both Fe^{2+} and SiO_4^{4-} in the bioceramics can induce more enzymes that favor growth, such as vascular endothelial growth factor (VEGF), etc.
Besides SiO_4^{4-}, for heart tissue repair, we can also consider other elements in the composite such as K^+,[3] Zn^{2+},[4] Li^+,[5] and Mg^{2+}.[6]

1.3 Chitosan

We often utilize the biocompatible polymer chitosan to form a composite with the silicon-based inorganic materials for several reasons:

- Composites with polymers allow for the slow release of ions/drugs. [7,8]
- Hydration effect. Chitosan is a hydrogel that is important for wound healing because of its high moisture content.
- The photothermal effect permits mild heat treatment. Photothermal materials produce heat upon irradiation of electromagnetic waves. Chitosan emits heat by near-infrared light (808 nm laser) (Section 2.1).
- Antioxidant. Chitosan as an antioxidant that can prevent/slow down the oxidation of Fe^{2+} into Fe^{3+}.

2 Treatments vs. conditions: mechanisms except for the bioactivity

We design different materials and treatment methods according to different health conditions (Table 1).

Table 1 Challenges and how to overcome them for specific disease/ health conditions. The listed healing effect does not include the bioactivity of ions (Section 1).

Health condition	Challenges	How to overcome the challenges
Tumor [7]	• Tumor sites are not targeted • High temperature causes tissue burn.	• Nd-Ca-Si silicate /alginate hydrogel composite extract*. • Target the tumor site by intravenous injection.

	• Difficult to accurately track and control the in-situ temperature.	• Photothermal treatment by Nd^{3+} and hydrogel. • Temperature monitoring by Fluorescent component: Nd^{3+}.
Chronic wound [2]	• Obstruction of blood vessels. • Dehydration.	• Fe_2SiO_4/N, O-carboxymethyl chitosan. • Fe^{2+} and SiO_4^{4-} together can induce more enzymes that favor growth. • Photothermal effect of the chitosan. • Hydrogel moisturizes the wound.
Infarcted myocardium [1]	• The generated cardiomyocytes need orientation during growth.	• Calcium silicate/chitosan scaffold*. • The anisotropic nanofiber structures promote cardiomyocyte orientation, maturation, and contractile function.
Acute myocardial infarction (AMI) [9]	Implanted biomaterials and transplanted cells have • Poor maintenance and growth, • Difficulties in implantation/transplantation, • Degradation.	• Calcium silicate extract * • Injection can overcome the drawbacks of implantation. • Paracrine effect stimulated by SiO_4^{4-} (Section 2.3).

*Extracts of the composites are obtained by immersing the biomaterials in a medium followed by centrifugation.
*The composite scaffold can be fabricated using the electrospinning technique.

2.1 For tumor and chronic wound: photothermal treatment

2.1.1 Mild heat treatment by photothermal effects

Near-infrared (NIR) light can penetrate deeply into tissue, thereby enabling photothermal treatment where the photothermal material is.[10] Mild heat treatment at its targeted area can improve blood circulation (at 30-45 °C) as well as angiogenesis (at 40-41 °C).[11] Except for chitosan, some rare-earth ions can be photothermal and incorporated into the bioceramics, e.g. Nd^{3+}.[7] Mild heat treatment can stimulate the production of enzymes that favor the growth of blood vessels and other cells, e.g. VEGF.

2.1.2 Challenges vs. solutions

For mild heat treatment, surrounding tissues risk being burned at temperatures above 45 °C. We can monitor the in-situ temperature by incorporating fluorescent materials (Section 2.1.3).
For tumor treatment, it is challenging to target tumor sites. Ma et al. proposed targeting the tumor sites by intravenous injection of the composite extract followed by the photothermal effect of the material.[7]
For chronic wounds, the main problems are obstruction of blood vessels and dehydration. Therefore, angiogenesis and hydration are important and can be provided by photothermal hydrogel.

2.1.3 Fluorescent material for thermometry

Rare earth metal ions such as Nd^{3+} are fluorescent.[7] The material Nd-Ca-Si silicate and its alginate hydrogel composite show linearity between their fluorescence intensity vs. temperature that can be used for thermometry.[12] Thermometry by fluorescent material has a variety of advantages such as high precision and high sensitivity.[13]

2.2 For infarcted myocardium (heart attack): nanofiber-structured composite scaffold

Infarcted myocardium is a heart attack that occurs when blood flow decreases or stops at a part of the heart, causing damage to the heart muscle. We often replace part of the heart tissue and regenerate the

heart tissue, called cardiac tissue engineering. The mature cardiomyocytes (heart muscle cells) are highly aligned around a dense vascular network. Therefore, a major challenge for the material to initiate effective cardiomyocyte growth involves orienting the generated cardiomyocyte. In this case, chitosan can be fabricated into a highly oriented nanofiber structure that promotes cardiomyocyte orientation, maturation, and contraction.

2.3 For acute myocardial infarction: paracrine effect

In the case of acute myocardial infarction (AMI), we conventionally implant biomaterials or transplant tissues. However, the implantation and transplantation are difficult. Additional issues include their poor maintenance and growth, as well as degradation. Yi et al. proposed the use of injections instead of implantation.[9] The injected SiO_4^{4-} can stimulate angiogenesis as well as promote cardiomyocyte survival by the paracrine effect. The paracrine effect is the process in which a donor cell signals a patient's cell to change its behavior (Figure 1).

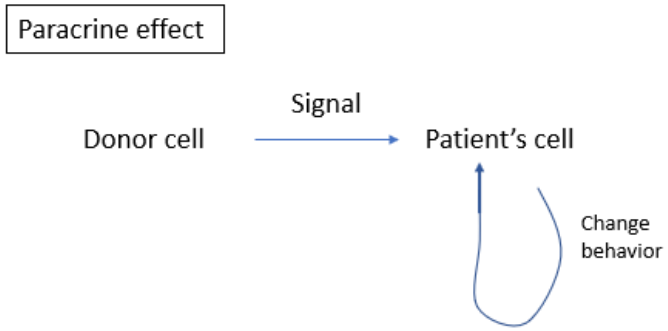

Figure 1 Simple scheme of paracrine effect.

The SiO_4^{4-} (4.53–9.08 ppm) can promote cell-cell communication by enhancing the connexin 43 (Cx43) expression. Cx43 is a protein that participates in all forms of cell communication. Such communication promotes the generation of enzymes that stimulate angiogenesis, reconstruct blood flow, and inhibit apoptosis (cell death).

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