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Review

# Physiochemical characteristics and bone/cartilage tissue engineering potentialities of protein-based macromolecules — A review

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A B S T R A C T

Protein-based macromolecules such as keratin, silk fibroin, collagen, gelatin, and fibrin have emerged as potential candidate materials with unique structural and functional characteristics. Despite many advantages, the development of tissue-engineered constructs that can match the biological context of real tissue matrix remains a challenge in tissue engineering (TE). The tissue-engineered constructs should also support vascularization. Protein-based macromolecules, in pristine or combine form, provide a promising platform to engineer constructs with unique design and functionalities which are highly essential for an appropriate stimulation and differentiation of cells in a specific TE approach. However, much work remains to be undertaken with particular reference to in-depth interactions between constructed cues and target host tissues. Thus, modern advancements are emphasizing to understand critiques and functionalization of protein-based macromolecule that organize not only cellular activities but also tissue regenerations. In this review, numerous physicochemical, functional, and structural characteristics of protein-based macromolecules such as keratin, silk fibroin, collagen, gelatin, and fibrin are discussed. This review also presents the hope *vs.* hype phenomenon for tissue engineering. Later part of the review focuses on different requisite characteristics and their role in TE. The discussion presented here could prove highly useful for the construction of scaffolds with requisite features.



**Contents**



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## 1. Introduction

Proteins are promising candidates for tissue engineering purposes due to their unique structural and functional characteristics that include biocompatibility, biodegradability, functional entities, overall cost-effective ratio, abundance, and reduced ability to tissue inflammatory responses, *etc.* Many efforts have been made to develop tissue-engineered constructs using various protein-based macromolecules [1,2]. Most of them suffer from two major drawbacks, *i.e.*, (1) the mechanical properties of the synthetic scaffold for bone tissue engineering are far away from the healthy bone, and (2) there is no or weak interaction of synthetic bone with the host bone. Being the interdisciplinary research fields of medicine and bioengineering, TE has overcome the drawbacks, such as insufficient numbers of the donor for biological and immunological reactions [3]. To overcome these limitations, researchers have attracted towards the hierarchical structure of natural biomaterials as a promising candidate for improvement and development of innovative and high-performance biomaterials for TE [4–6]. Particularly, the motivation for new biomaterials for tissue engineering has been resulting from design and structural analysis different scales of extracellular matrix that cells used to manage themselves for tissues [7]. Thus, it is highly requisite to understand the sophisticated functionality of the biological system and design new biomaterials for tissue engineering.

For bone tissue engineering, basic knowledge of bone regeneration is necessary, and the bone is composed of a porous material whereas soft tissues are made of collagen [8]. There are other types available in calcified tissues such as proteins which are typically involved in orientation, size regulations and crystal pattern of mineral deposition [9]. The relationship between porous inorganic material and a network of soft matter provide appropriate mechanical strength along with hardness, compressive and fracture toughness to the host bone [10]. A suitable scaffold should have the features of the interconnected open porous 3-D structure, biocompatible, biodegradable, huge surface area and porosity with enhanced mechanical strength. Such scaffolds also provide new cell attachment and facilitate cell proliferation and differentiation that ultimately leads towards the bone regeneration [11].

Considering various requisite features for TE, herein, an effort has been made to present various protein-based macromolecules such as keratin, silk fibroin, collagen, gelatin, and fibrin with TE potentialities. Following a brief introduction, the hope *vs.* hype phenomenon for TE is discussed. In the next part, numerous physicochemical, functional, and structural characteristics of protein-based macromolecules are discussed. Later part of the review focuses on different requisite characteristics such as porosity, mechanical strength, swelling ability, biomineralization, and protein adhesion and their role in TE. Towards the end information is also given on current challenges, opportunities, concluding remarks and future perspectives of TE.

## 2. TE: hope *vs.* hype

The use of scientific principles to construct, design, and modifying the living tissues through the use of factors, cells, and biomaterials is known as tissue engineering [12]. A scaffold having a source of cell attachment and cell maintenance function with a rich source of osteoprogenitor cells in combination with selected osteoinductive growth factors is referred as skeletal tissue engineering. Up till now, a mechanically competent vascularized osteoinductive/conductive construct remains to be documented. Understanding how cells function and form matrix, the fabrication of materials to provide appropriate scaffolding, conducive to cell attachment and maintenance of cell function, are key concepts in bone TE.

Undeniably, the loss of tissue as a result of disease or injury provide reduces the quality of life at the socioeconomic level [13]. This is compounded by the observation that artificial prostheses, which do not integrate with the surrounding tissue, are subjected to wear and, eventually, fails. On the other hands, the joint replacement surgeries have significantly improved the living standard in elderly population through osteoarthritis, rheumatoid arthritis, and osteoporosis [14–16]. This clinical approach fascinated the interests in developing new therapies for bone regeneration and provided a hope that TE may be able to address the problem. The generation of new tissues can be carried out, for example, cartilage involves *in-vitro* expansion of cells isolated from a biopsy, commonly using bioreactor technology and appropriate 3-D scaffolds [7].

## 3. TE potentialities of protein-based macromolecules

TE depends on the improvement and development of appropriate scaffolds. This provides a friendly biocompatible environment for cell proliferation and differentiation that leads to tissue formation. TE scaffolds are cultured *in-vitro* for test implantation functionality, or they can be implanted cell seeding and let to growing *in situ* [17]. For TE, protein-based macromolecules are excellent and attractive candidates because of their unique properties like bioactivity, biocompatibility, and biodegradability. Fig. 1 illustrates several protein-based candidate macromolecules which have already been used or being employed for TE applications. Suitable scaffold for bone tissue structure and design should have the features like structure reliability, interconnected porosity and degradability rate with elucidation with extracellular matrix

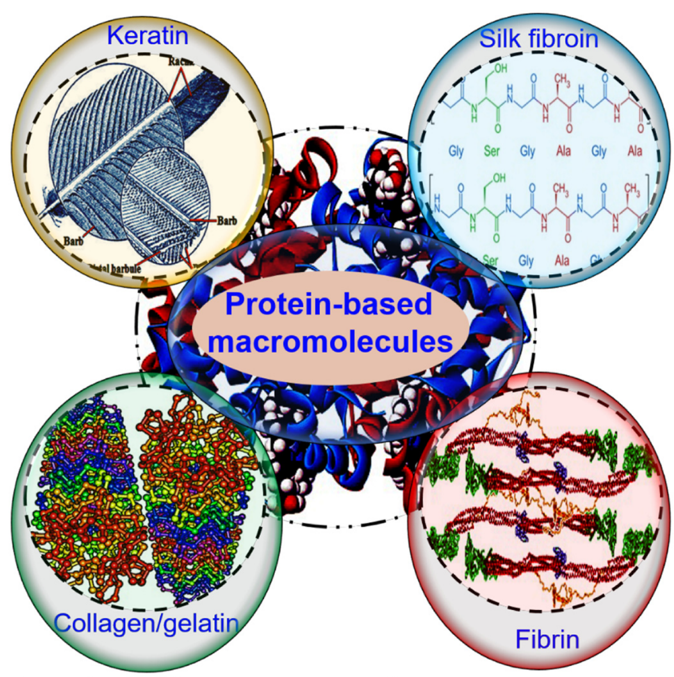


**Fig. 1.** Protein-based candidate macromolecules.