Curcumin: footprints on cardiac tissue engineering

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Abstract

Curcumin-based products are extensively being used as therapeutics in the treatment of cardiac disorders; however, there is no specific report on the potential usability of curcumin in cardiac tissue engineering applications. Having anti-oxidant, anti-inflammatory and anti-apoptotic properties, curcumin has been found highly promising for use in reconstructive strategies since it could promote the tissue healing process. Various tissue-engineered constructs containing curcumin (e.g., three dimensional (3D) scaffolds) have been developed for the management of soft tissue damages like wound injuries, and hence there are new hopes for the use of this amazing natural product for cardiac tissue engineering. However, some crucial questions should first be answered, including the optimum dosages of curcumin for promoting cardiac tissue regeneration, the type of carrier used (e.g., polymeric matrices), the preferable release profile, as well as the short- and long-term toxicity in the human body.

Keywords: Curcumin; Cardiac tissue engineering; Cardiac patches; Scaffold; Healing

1. Introduction

Cardiovascular diseases (CVDs) are among the most serious life-threatening disorders worldwide [1]. Myocardial infarction (MI) is commonly caused by the blockage of a coronary artery and leads to a massive cardiomyocyte loss in the heart tissue. Regarding poor regeneration of the heart, the lost cardiomyocytes are usually replaced with fibroblasts, and non-contractible scar tissue is created at the defect site resulting in a reduction in cardiac output. Therefore, the need for reconstructive interventions is absolutely demanded for patients suffering from heart diseases.

After being introduced in the 1980s, tissue engineering (TE) and regenerative medicine have created new hopes for the treatment of CVDs. On this object, researchers from different fields like materials science, medicine, and pharmacology are being trying to develop novel TE-based products to induce and improve the repair and regeneration of the damaged myocardium. The three building blocks of TE strategies are biomaterials (natural and synthetic), cells (differentiated and stem cells), and growth factors (native and recombinant) (see Figure 1) [2-4]. As it has been well-defined, the regeneration process of the heart tissue post-MI takes between six to eight weeks [5]. Hence, the substitutes designed for the replacement of the damaged heart tissue should have the ability to degrade over the regenerative period in order to avoid fibrous capsule formation and chronic inflammatory response in the cardiac tissue [6]. Moreover, a couple of other critical factors should be counted for materials and constructs used for MI reconstructive strategies, including the lack of local and systemic toxicity (i.e., biocompatibility), and the need for electromechanical integration with host myocardium (specifically, a good matching between the mechanical properties of host tissue and implant) [7].

Figure 1. Representative illustration of mechanisms involved in cardiac tissue repair and regeneration. Reproduced from Ref [8].

The use of natural plant products has recently appealed much consideration in TE strategies for soft tissue reconstruction [9]. These materials are considered as relatively inexpensive substances which can promote the wound healing process. Curcumin is one of the most widely-used natural extracts in TE strategies, especially in soft tissue healing. Although curcumin is historically identified as anti-cancer therapeutics due to anti-proliferative effects against multiple cancerous cells and inhibitory activity on the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) and downstream gene products (e.g., c-myc, Bcl-2, and COX-2) [10-17], this natural substance is recently found as an effective material in soft tissue healing. In this mini-review, we aim to propose curcumin as a great therapeutic natural product for cardiac TE. To the best of the authors' knowledge, it is the first report on the potential usability of curcumin as an additive in tissue-engineered constructs for cardiac regeneration.

2. Curcumin for cardiac tissue engineering

2.1. Exploring the question, weighing the merits

Curcumin, the main curcuminoid of the turmeric rhizome (*Curcuma longa*), is noted for its well-known anti-inflammatory, antioxidative, anti-apoptotic, and cardioprotective effects [18]. There is a large number of *in vitro* and *in vivo* studies showing that curcumin could reduce the generation of reactive oxygen species (ROSs), exert cytoprotective effects, and attenuate oxidative stress and inflammation [19-21].

Several mechanisms are involved in myocardial ischemia, and their role in ischemic myocardial cell injury and death have been well-characterized at the molecular level. As an illustration, the generation of ROSs in myocardial ischemia increases as a result of the loss of surface energy of the substrate [22]. The increased levels of ROSs can cause a variety of cardiomyocyte abnormalities like disturbed contractile activity[23]. Liu et al. clarified that the administration of curcumin (10, 20 or 30 mg/kg/d) as a supplement to rats results in reductions of oxidative stress (3-fold) and infarct size (2.5-fold) as compared to negative control groups [24]. Moreover, the percentage of infarct size in rats receiving curcumin (10, 20 or 30 mg/kg/d) after myocardium ischemia-reperfusion (MIR) showed a significant decrease (from 49.1% to 18.3%) as compared to the curcumin-free ischemia-reperfusion group. The authors proposed that the curcumin intake could reduce the risk of coronary heart disease via inducing JAK2/STAT3 signal pathway, decreasing oxidative damage and inhibiting myocardium apoptosis.

One of the main events occurring post-MI is cell apoptosis at the damaged sites, which causes hindering the ventricular remodeling of the remaining active myocardium [25]. Therefore, reducing apoptosis can be considered as one of the major targets for preventing heart failure progression of patients following MI. On this matter, Geng et al. showed that curcumin could protect cardiac myocytes against apoptosis induced by hypoxia in the most widely used inbred strain of mice, i.e., C57 black 6 (C57BL/6). They reported that curcumin exerts its protective effects via the up-regulation of miR-7a/b and the down-regulation of transcription factor SP1. In addition to decreasing these biochemical parameters, curcumin has been documented to modulate the SIRT3 signaling pathway and, hence, reduce the expression of other apoptotic

markers, like the pro-apoptotic protein Bax and acetylated superoxide dismutase 2 (AcSOD2) [26].

Although intense inflammatory responses triggered by MI are essential for cardiac repair, they could be implicated in the pathogenesis of post-infarction remodeling and heart failure. Having anti-inflammatory effects, curcumin is currently being used to attenuate the inflammation and thereby suppress the activation of a pro-fibrotic program [27]. In this regard, Lv et al. assessed the molecular mechanisms involved in curcumin-reduced inflammation after myocardial injury in rats [28]. They showed that the administration of curcumin at a dosage of 150 mg/kg/body weight results in an improvement in cell survival, reduction of infiltration of inflammatory cells, and thereby a decrease in proliferation of fibrous tissue. Their results revealed that curcumin exerts its anti-inflammatory effect through down-regulating the expression of nuclear factor-κB (NF-κB). Influence on the Nrf2-keap1 signaling pathway and suppression of the production of tumor necrosis factor (TNF) and the TNF-mediated cell signaling are also identified as other anti-inflammatory effects of curcumin [29,30].

Similar to the above-mentioned biological properties, anti-bacterial effects of biomaterials also are of great importance for cardiac tissue engineering. For instance, Mahmoudi et al. in 2016 developed infection-resistant MRI-visible patches for cardiac tissue engineering by incorporating superparamagnetic iron oxide nanoparticles (SPIONs) into this patch [31]. Based on the literature, it can be stated that curcumin possesses anti-bacterial features through the interaction with the essential cell division initiating protein FtsZ [32,33]. FtsZ is an essential protein in most prokaryotes, responding for bacterial cell division. It has been identified that the methoxy and hydroxyl groups of curcumin are indeed involved in its antimicrobial activity

[34,35]. The minimum inhibitory concentration (MIC) of curcumin has been previously evaluated on both Gram-positive and Gram-negative bacterial strains by Gunes et al. [36]. They reported that the curcumin showed anti-bacterial effects against *Pseudomonas aeruginosa* (175 mg/mL), *Bacillus subtilis* (129 mg/mL), methicillin-sensitive *Staphylococcus aureus* (219 mg/mL), methicillin-resistant *S. aureus* (217 mg/mL), *E. coli* (163 mg/mL), *Enterococcus faecalis* (293 mg/mL), and *Klebsiella pneumoniae* (216 mg/mL).

Figure 2. Schematic illustration of biological activities proposed for curcumin. Reproduced from Ref [37].

According to promising *in vitro* and *in vivo* results, pre- and clinical potential of curcumin has been evaluating in a large number of studies. For example, pharmacokinetic studies of curcumin were assessed in rodents like mouse, rat, and rabbit [38-42]. At the moment, near 198 clinical trials" (www.clinicaltrials.gov) on curcumin's therapeutic benefits have been registered. Among them, 11 studies are found for curcumin applications in cardiovascular diseases.

2.2. The challenges ahead

Up to now, a couple of physico-chemical restrictions have been counted for the wide use of curcumin, including its poor water solubility under acidic or neutral conditions, high decomposition rate in alkaline media and photo-degradation in organic solvents [9]. Moreover, the quick degradation of curcumin at physiological pH is considered as another complication regarding its use in the biomedical applications. However, researchers could overcome these

obstacles by developing complex formulations of curcumin and different carrier macromolecules, such as alginate and other polymers [43,44].

The use of the right concentrations of any substance for cardiac tissue engineering strategies should be determined through well-defined in vitro and in vivo assays. Although curcumin has no mutagenic and carcinogenic effects and has been "generally recognized as safe" (GRAS) by the US Food and Drug Administration (FDA) [45], there are a couple of studies showing that curcumin at high concentrations could cause nuclear DNA fragmentation in mammalian cell lines [46]. Moreover, some experimental data clarified that curcumin could inhibit the activity of the drug-metabolizing enzymes cytochrome P450, glutathione-S-transferase, and UDP-glucuronosyltransferase, which can lead to an undesired increase in the plasma concentrations of some drugs and thereby cause toxicity [47].

3. Expert Opinion

Today, curcumin has been widely proposed for the repair and regeneration of both hard and soft tissues. Based on the desired tissue to heal, researchers have developed and prepared a number of curcumin-containing implantable systems like micro- or nano-sized spheres, fibrous constructs and three dimensional (3D) scaffolds [9]. The carrier materials hosting curcumin molecules are typically designed as temporary matrices that degrade in vivo over time allowing a local and prolonged release of the active agent, thus minimizing the negative effects related to systemic toxicity and maximizing the therapeutic efficacy in situ.

It is worth pointing out that, although curcumin-delivering implants have been already developed for use in wound applications and osteochondral regeneration [9], no systems have

been specifically proposed for cardiac tissue engineering so far. Looking at this promising field of research, polymeric biomaterials seem to exhibit the most suitable physico-mechanical characteristics to be used in contact with the soft and delicate structures of the heart. A range of synthetic polymers, such as poly(glycerol sebacate), poly(ethylene glycol), poly(glycolic acid), poly(lactic acid, polycaprolactone, and polyurethanes, have been variously processed to obtain cardiac patches (or scaffolds) [48,49]. However, strategies of surface functionalization should be carried out so that curcumin molecules can bind to or be somehow encapsulated into these polymeric matrices for subsequent release. Furthermore, it cannot be ignored that synthetic polymers used in cardiac applications are mostly hydrophobic and lack cell recognition sites; thus, biofunctionalization of these biomaterials is also to be applied to enhance cell attachment and cell-material interactions [50].

Given the tendency of curcumin to degrade at physiological pH, encapsulation in polymeric micro- or nano-spheres rather than binding to the exposed surface of polymeric patches could be preferable [51-54]. In this regard, administration of curcumin-loaded polymeric spheres via injection would deserve to be considered. Biocompatible hydrogels with tunable swelling properties, porosity, degradation kinetics and permeability to biological fluids, nutrients, and oxygen could be investigated as promising carriers for curcumin. More specifically, injectable and smart hydrogels able to change their properties in response to different stimuli (e.g., temperature and pH) [55], thereby allowing a targeted release of curcumin, would be highly appealing.

Apart from polymeric biomaterials, other inorganic platforms such as mesoporous bioactive glasses (MBGs) have been widely investigated as drug delivery systems in tissue

engineering applications [56,57]. Given their inherent physico-mechanical properties (e.g., high stiffness) and apatite-forming capability, they have been mostly proposed for bone regeneration; however, incorporation of MBGs in polymeric matrices has also been recently proposed in the context of soft tissue repair [58]. At present, there are no studies dealing with the specific usage of MBGs for cardiac tissue engineering, and only one report has been published about the release of curcumin from MBGs (in the context of bone repair) [59]. In general, an important aspect that deserves to be mentioned when using MBGs in contact with soft tissues (including heart) is the risk of soft tissue calcification associated with the inherent bioactivity of these materials.

Regardless of the type of carrier material used, the optimal dosage of curcumin for promoting the repair and regeneration of cardiac tissue is a critical issue that still has to be comprehensively investigated. Appropriate in vitro (with cells) and in vivo (animal) models should be developed to elucidate this point as well as to test the potentially-suitable curcumin-loaded platforms.

Conflict of interest:

The authors declare no conflict of interest.

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Figure caption:

Figure 1. Representative illustration of mechanisms involved in cardiac tissue repair and regeneration. Reproduced from Ref [8].

Figure 2. Schematic illustration of biological activities proposed for curcumin. Reproduced from Ref [29].