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Current Status of Nanomedicine in Vascular Calcification

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Abstract

Vascular calcification (VC) is a serious condition which contributes to and is associated with a variety of cardiovascular diseases and therefore contributes too many of the leading causes of death in developed countries. While there are some drugs that have been shown to reduce VC, they often produce negative side effects due to their systematic and high dose approach of treatment. Here we discuss several approaches to address this issue using targeted nanoparticles. The nanoparticles produced were composed of polymers of BSA or PLA, were conjugated with rabbit anti-rat elastin antibodies for targeting of damaged elastin found in tissues affected by VC, and were loaded with the drugs BB-94 to inhibit MMP activity, PGG to protect elastin fibers from further degradation, or EDTA to resorb calcium deposits in the affected areas. Micelles, PLA, BSA nanoparticles have been used successfully and the elastin targeting method were universally successful, and the loaded drugs (both individually and, in one case, in conjunction with one another) had varying levels of success. Also discussed is a proposed method of treatment that involves the differentiation of macrophages in the affected areas into osteoclast-like cells to resorb calcification using vitamin D3 and M-CSF.

Keywords: Cardiovascular Disease; Macrophages

Abbreviations: VC: Vascular Calcification; AHA: American Heart Association; HD: Heart Disease; BSA: Bovine Serum Albumin; CKD: Chronic Kidney Disease; HSA: Human Serum Albumin; PAM: Peptide Amphiphile Micelle; HABP: HA-Binding Peptide; DTPA: Diethylenetriamine Pent Acetic Acid; EDTA: Ethylene Diaminetetraacetic Acid; MAC: Medial Arterial Calcification; AAA: Abdominal Aorta; M-CSF: Macrophage Colony-Stimulating Factor.

Introduction

Every year, a large percentage of people are affected by vascular calcification (VC). VC is an accumulation of mineral deposits in parts of the vascular system [1]. This process occurs as calcium travels through the blood allowing calcifications to gather in vessels, heart, or valves. There are different forms of vascular calcification which include intimal and medial calcification. Intimal calcification is associated with blood clots and blocked arteries, whereas medial calcification is associated with advanced age, kidney disease, diabetes, and hypertension and elastin calcification [1]. This process shares many features with proteins that are associated with embryonic bone formation, showing that this is an actively regulated process [2]. VC is known to be closely associated with atherosclerosis and accordingly increases an individual's risk of cardiovascular disease and major acute coronary events, especially when seen in the coronary artery [3,4]. Indeed, vascular calcification is associated with a 3-4 fold increase in risk of major cardiovascular events and related mortality [5].

According to the American Heart Association (AHA), heart disease (HD), stroke, and kidney disease are the number 1, 5, and 8 leading causes of death in the United states in 2016, respectively, and VC has been shown to be closely associated with all of these diseases and events (though VC is most likely a result of renal disease, rather than a risk/contributing factor to the disease) [5,6]. From 2014-

2015, CVD has cost the US $351.2 billion and has accounted for 840,679 deaths in 2016, at a rate of 220.7 cases of CVD death for every 100,000 people in the US from 2014 to 2016. CVD costs are expected to reach $1.1 trillion per year with 45% of the US population affected by some form of CVD by 2035. Therefore, the treatment of VC is a highly attractive method of reducing the risk of CVD, potentially saving the lives of hundreds of thousands of individuals in the US and saving the US billions of dollars per year.

Other therapeutic strategies used in patients with advanced kidney disease to reduce or prevent vascular calcification include lowering the circulating levels of phosphate or blocking calcium channels. These strategies have shown to reduce the overall presence of vascular calcification. However, the problem is with bone health and the inability to control where the drug migrates and takes effect. Since vascular calcification has the same mineral composition as bone, these therapies result in the breakdown of the tissues in bone throughout other areas of the body causing the development of osteoporosis [7]. Using nanoparticles to treat vascular calcification allows for a more targeted approach by delivering the drug to the intended site and minimizing the spread to other areas.

Previous studies

Targeting of VC

The first task at hand was to develop a method of targeting the affected/injured vasculature using nanoparticles to allow for successful specific drug delivery to the diseased vasculature. Several studies show that targeting vascular calcification with nanoparticles can be achieve by targeting damaged elastin in the ECM of the diseased vasculature. Different types of nanoparticles were used in studies to target calcified vasculature. In a study titled "Reversal of Vascular Calcification and Aneurysms in a Rat Model Using Dual Targeted Therapy with EDTA- and PGG-Loaded Nanoparticles," Bovine Serum Albumin (BSA) nanoparticles were crosslinked using heterobifunctional cross linker α-maleimide-□-Nhydrocysuccinimide ester poly (ethylene glycol) to achieve a sulfhydryl-reactive particle system. Targeting was achieved using anti-rat elastin antibody. Using EDTA NPs, removal of mineralization was observed. EDTA treatment helped improving the calcification from elastin but did not improve elastin regeneration. Targeting success was proved with the use of DIR dye in a rat model [8,9].

BSA nanoparticles were also used in another study titled "Systemic delivery of nanoparticles loaded with pentagalloyl glucose protects elastic lamina and prevents abdominal aortic aneurysm in rats", and were coated with an anti-elastin antibody. These nanoparticles targeted elastin present in the aorta using anti-elastin antibody. The results showed targeting of the aorta was successful. The nanoparticles targeted the injury site without affecting the uninjured aorta. Targeting success was also proved with the use of DIR dye and IVIS imaging [10]. In another study, using the same NPs, calcification in reverse chronic kidney disease (CKD) was targeted successfully [11].

The paper titled "Prevention of abdominal aortic aneurysm progression by targeted inhibition of matrix metalloproteinase activity with batimastat-loaded nanoparticles" discusses a study using poly (D,L-lactide) (PLA) nanoparticles conjugated with anti-elastin antibodies used to target elastin in the aorta. They concluded that the targeting of the injured aorta was a success by observing the fluorescence DIR dye [12]. No matter what the nanoparticle is made of, targeting was successful.

Recently another group in Germany has shown the successful targeting of calcification using human serum albumin (HSA) decorated with anti-elastin antibody. HSA was labeled with the fluorescent dye PromoFluor-633P-NHS-ester (PF633P) prior to NP formation in ttw/ttw and Abcc6-/- mice model which spontaneously developed calcification of elastic fibers in blood vessel walls [13]. Another group has developed a novel, fluorescently-labeled peptide amphiphile micelle (PAM) that uses a 12 amino acid HA-binding peptide (HABP) [SVSVGMKPSPRP] to target and detect atherosclerotic calcification (HA PAM) in 2019 and Successfully detected calcifications in atherosclerotic mouse models [14].

Treatment Methods using Nanomedicine

The current methods of treatment of VC are meant to address one or both of two treatment methods: attenuation/prevention of the progression of the disease and reversal of the disease. These methods used (or proposed the use of) the drugs to chelate calcium like diethylenetriamine pentaacetic acid (DTPA) and ethylenediaminetet raacetic acid (EDTA), and vitamin D3 and M-CSF to induce the differentiation of macrophages into osteoclast-like cells to resorb calcification. In term of reversal, Elastin regeneration has been the focus.

Chelating Calcification

Disodium ethylene diaminetetraacetic acid (EDTA) is a compound used for chelation therapy and has been found to be a safe treatment for atherosclerotic vascular disease, as well as to have a beneficial effect on cardiovascular risk profiles when compared to control [15,16]. Due to its ability to absorb mineral and metal deposits, EDTA has been found to have promise as a treatment in reversing vascular calcification. With relevant studies have shown that

elastin targeted EDTA nanoparticles may be administered in individuals with coronary artery disease by systemic infusion causes the removal of minerals from calcified elastin. In Vitro testing on EDTA loaded nanoparticles found that after three days of incubation both calcified porcine aortic elastin and Calcified human aortas from cadavers found that the NPs effectively removed minerals and from both calcified simples.

EDTA loaded nanoparticles therapy was successful When in Vivo testing was done on rats' after 28 days of feeding the adenine diet, which induces chronic kidney disease (CKD) associated Medial arterial calcification (MAC). As well as a group of rats 30 days after the initial $CaCl_2$ injury, which induces aneurysms in the abdominal aorta (AAA) of the rats. Elastin Targeted EDTA nanoparticles were found to effect on reverting vascular calcification on the experimental rat model of CKD. In the CKD rat model results showed no undue side effects in bone, mineral metabolism, and biomechanics.

The importance of these results becomes apparent when EDTA NP chelation therapy is compared with the standard intravenous EDTA chelation therapy. With historic data showing that traditional EDTA chelation therapy requires a high dosage and long treatment times, which cause side effects, such as hypocalcemia, bone loss, and renal toxicity. Diethylenetriamine pentaacetic acid (DTPA) is a chelating agent consisting of an aminopolycarboxylic acid with diethylene triamine backbone and five carboxymethyl groups possessing the ability to extract exchangeable, carbonate and organically bound metal fractions DTPA is approved as chelating agent by the FDA for the therapy of plutonium poisoning and can chelate calcium [17,18]. DTPA has been shown to be successful in removing calcium from Aortic ring culture in ex vivo culture.

Vitamin D3+ M-CSF

Because VC progression resembles the process of bone formation with osteoblast-like cells (the cells responsible for bone deposition in the remodeling process of bone formation) differentiated from VSMCs, pericytes, and monocytes found in vasculature, it was determined that the differentiation of macrophages into osteoclast-like cells (the cells responsible for bone resorption in the remodeling process of bone formation) may be possible as well. Therefore, another way to reverse VC proposed by the team of Bennett KA, et al. [19] is to induce differentiation of macrophages in the aorta into osteoclast-like cells using proteins such as dihydroxyvitamin D3 and macrophage colony-stimulating factor (M-CSF) loaded in NPs conjugated with rabbit anti-rat elastin antibodies to target degraded elastin in the calcified aorta, though this team has yet to publish achieved results. Although there are many other treatments for vascular calcification but the treatments, we mentioned were the ones that have been tried using nanomedicine.

Discussion/Conclusion

Targeting of vascular calcification using conjugated rabbit anti-rat elastin antibodies was successful for NPs as several studies showed significant targeting in different animal models of calcification. Additionally, NPs were seen to clear out of other organs as time progressed. These provide strong evidence that the use of anti-elastin antibodies is a viable way to target aneurysm for treatment while leaving both uninjured vasculature and other organs alone and unaffected.

While results have yet to be published, it has been proposed that vitamin D3 with M-CSF could be used to differentiate macrophages found in the calcified regions of the aorta into osteoclast-like cells to break down and resorb the calcification. If this is indeed possible, these factors could be loaded in NPs conjugated with anti-elastin antibodies as used in other tested drug delivery systems for targeting, and be delivered to the region of calcification to differentiate the plentiful macrophages found in AAA and calcified vasculature into osteoclast-like cells which would in turn break down and reverse calcification. Although dysfunctionality of osteoclast should be resolved [20].

Several drugs have been proposed to treat vascular calcification; however, the systemic delivery of the drugs requires high dosages and often results in unwanted side-effects, including the unwanted resorption of calcium in bones from the systemic use of calcium chelators, leading to the development of osteoporosis. Therefore, it is a greatly attractive approach to use drug-loaded nanoparticles to target and deliver the drug only to the desired area. As such, it is a great accomplishment to have successfully targeted the site of vascular calcification using nanoparticles. There are many diseases which involve vascular calcification that may be treated using the different targeting approaches discussed. Using NPs that target the site of VC to specifically deliver a drug to the affected site is a highly desirable approach for treating diseases involving VC, potentially preventing hundreds of thousands of deaths and saving billions of dollars per year.

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