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Nanomaterials modulating stem cells behavior towards cardiovascular cell lineage

Hamidreza Arzaghi a,g#, Bahare Rahimi a#, Bashir Adel b#, Golbarg Rahimi c, Zahra Taherian b, Afsaneh L Sanati d*, Amin Shiralizadeh Dezfuli e,f,g*

a Department of Medical Biotechnology, Faculty of Allied Medical Sciences, Iran University of Medical Sciences (IUMS), Tehran, Iran

b Department of Biology, Faculty of Sciences, The University of Guilan, Rasht, Iran

c Department of Cellular and Molecular biology, University of Esfahan, Esfahan, Iran.

d Institute of Systems and Robotics, University of Coimbra, 3030-194 Coimbra, Portugal

e Radiation Biology Research Center, Iran University of Medical Sciences (IUMS), Tehran, Iran

f Young Researchers and Elite Club Shahr-e-Qods Branch, Islamic Azad University, Tehran 37515-374, Iran

g Ronash Technology Pars Company (AMINBIC), Tehran, Iran

# H. Arzaghi, B. Rahimi and B. Adel contributed equally to this work.

* Corresponding authors: Afsaneh L Sanati and Amin Shiralizadeh Dezfuli
Abstract
The cardiovascular system, which is one of the complex and indispensable systems in the body, is responsible for the circulation of nutrition, oxygen, carbon dioxide, hormones to other parts of the body. Injuries and scar formation in various parts of the cardiovascular system could be overwhelming due to the limited regenerative ability of cardiomyocytes. Furthermore, surgeries for cardiovascular complications have major risks, and the shortage of organs is inevitable. However, cardiovascular tissue engineering is promising since it can promote cardiovascular regeneration. Although tissue engineering and regenerative medicine could offer solutions to overcoming these challenges, the interactions between nanomaterials and stem cells are not fully understood. Therefore, controlling the behavior of stem cells is challenging due to the limited knowledge in this area. In this review, we discussed various nanomaterials, which were utilized in cardiovascular tissue engineering recently. Moreover, we highlighted the effects of these nanomaterials on stem cells' behaviors, with specific emphasis on proliferation and differentiation. It is expected that a better understanding of stem cell and nanomaterials interactions would facilitate the design of nanomaterials for regenerative medicine and cardiovascular tissue engineering applications.
1. Introduction

Cardiovascular diseases (CVDs) are one of the major health problems in the world, especially in developing countries. According to the world health organization, CVDs are the number one cause of death worldwide, and it is estimated that 17.9 million people died in 2016 (Garcia and Burkle 2018). Myocardial infarction (MI) and coronary artery diseases are the primary causes of CVDs related death (Lopez et al. 2006; Beaglehole and Bonita 2008). Moreover, ischemia can cause necrosis and apoptosis, which can lead to scar formation and permanent damage to the heart structures, thereby reducing the contractile ability following heart failure in severe conditions. Furthermore, the regeneration ability of the cardiomyocytes is extremely limited, and the only options for the treatment of CVDs are surgical methods such as heart transplant and reperfusion therapy (Lamendola et al. 2009; Laflamme and Murry 2011; Mentzer 2011; Rentrop and Feit 2015; Vunjak-Novakovic et al. 2011).

Stem cell transplantation has been utilized as a novel therapeutic method for the treatment of several diseases such as liver (Ordovás, Park, and Verfaillie 2013), kidney (Yokote and Yokoo 2012), brain (Tsukamoto et al. 2013), spinal cord (Mothe and Tator 2013), heart diseases (Assmus et al. 2002), etc. After transplantation, it is expected that the stem cells differentiate to the target cells in response to their microenvironment. In the past decade, stem cell therapy has been used for myocardial repair and heart regeneration. For instance, Bartunek et al. utilized the bone marrow-derived mesenchymal stem cells in the C-CURE clinical trial for the patient with heart failure, and they reported the safety and possibility of stem cell therapy in chronic heart failure (Bartunek et al. 2013). However, stem cell therapy has some limitations since the transplantation or injection of stem cells may result in low retention and poor survival of the cells in the body (Al Kindi et al. 2008; Templin et al. 2012; Mayfield et al. 2014). Moreover, in this method, there is no control over directing the stem cells fate, which completely limits its therapeutic applications. Several stem cell behaviors such as proliferation, differentiation, migration, and cell adhesion can be controlled by manipulating intracellular signaling pathways utilizing different transcription and growth factors. This control over the fate of stem cells is an essential key component for regenerative medicine and tissue engineering methods (Hofmann 2014).

In the past decades, various nanomaterials were utilized to design practical tools for therapeutic and diagnostic purposes in medicine. With the emerging of nanotechnology, the first use of nanomaterials was gene and drug delivery for modulating stem cells behavior by encapsulation of
drug/gene in polymers and lipid-based nanomaterials. Furthermore, several biomaterials are synthesized with nanostructure featured to induce microenvironment cues, wherein stem cells can proliferate and differentiate to target cell lineage (Chandra and Lee 2015; Poustchi et al. 2020; Pacelli et al. 2020; Amani et al. 2021). Most researcher’s interests focused on designing new fabrication methods for therapeutic and imaging applications, the interactions between nanomaterials and stem cell behavior are not investigated thoroughly. It has been shown that not only utilizing nanomaterials as scaffolds can change the differentiation and proliferation of stem cells but also the aqueous suspension of nanoparticles has the ability to induce stem cell differentiation (Arzaghi et al. 2020). This viewpoint can be utilized in the design and fabrication of nanomaterials for cardiac tissue engineering since acquiring regenerative medicine methods to replace the damaged cardiac tissues is promising in CVDs complications, especially in myocardial repair (Fujita and Zimmermann 2017). For example, it has been shown the conductive properties of carbon-based and metal-based nanomaterials can enhance the electrical signals passing through cardiomyocytes and promote both proliferation and differentiation of stem cells (Yao et al. 2018). Therefore, we provide a comprehensive review of nanomaterials utilized in cardiovascular tissue engineering focusing on the effect of nanomaterials on cellular behaviors. It is expected that the increase in knowledge of nanomaterials and stem cell interactions will be beneficial in the design and synthesizing novel therapeutic methods in tissue engineering and regenerative medicine.

2. Cardiovascular system overview

The circulatory or cardiovascular system consists of the lymphatic system, heart, and blood vessels, which circulate blood, nutrition, oxygen, carbon dioxide in the body, thereby stabilizing its conditions such as temperature, pH, and homeostasis (Wirkner and Richter 2013; Whittemore 2014).

In the center of the cardiovascular system therein lies the heart that pumps blood within the blood vessels to provide continuous flow throughout the body, and it is located between the lungs in the middle mediastinum. The human heart consists of four chambers (two lower ventricles and two upper atria) and four one-way valves. This giant muscular organ consists of three layers in the wall (endocardium, myocardium, and epicardium) that are surrounded by the pericardium. The endocardium is the most inner layer of the heart wall, which consists of single squamous epithelium. This tissue is structurally similar to the endothelial cells, which cover the internal
structure of blood vessels. This layer not only controls the heart development in the embryo but also regulates the myocardium functions. Furthermore, it controls the contractility and electrophysiological environment of cardiomyocytes. Cardiomyocytes join together with the intercalated discs and coated mainly with collagen fibers as an extracellular matrix, which forms the cardiac muscles or myocardium. Cardiac muscle is an involuntary muscle similar to skeletal muscle with contraction ability due to the electrical stimulation of action potentials through the release of calcium from the sarcoplasmic reticulum. The action potentials are initiated by pacemakers cells in the sinoatrial node located in the right atria and depolarized neighboring contractile cells via gap junctions in the intercalated discs. These action potentials reach the other pacemaker cells in the Atrioventricular node by the electrical conduction system of the heart. If the initiation of action potentials in SA nodes is compromised, therefore the cells located in Purkinje fibers become responsible for the heart contractions. Cardiac fibroblasts are other cells located in the heart, and they play a crucial role in creating the extracellular matrix of cardiomyocytes, whereby they can repair an injury by secretion of collagen. Furthermore, cardiac fibroblasts can transform to the myofibroblast with a contracting ability during myocardial infarction (reduction in blood flow to the heart) (Sakmann, Noma, and Trautwein 1983; Yaniv et al. 2015; Burkhard et al. 2017; Piccoli et al. 2017; Maiullari et al. 2018; Liang et al. 2019).

Diseases that involved the myocardium are the most important clinical problems, which are the leading cause of death in developing countries. Coronary artery disease (CHD) or ischemic heart disease (IHD) is the most prevalent condition of the heart, which is the reduction of blood flow to the heart due to atherosclerosis. Consequently, the lack of oxygen leads to myocardial infarction and damage to the cardiomyocytes. Another condition that damages the cardiomyocytes is the inflammation of the myocardium (myocarditis or inflammatory cardiomyopathy) due to various circumstances such as viral or bacterial infections, autoimmune diseases, and alcohol and drug usage (Al Badarin et al. 2017; Ashtari, Nazari, Ko, Tebon, Akhshik, Akbari, Alhosseini, Mozafari, Mehravi, Soleimani, et al. 2019; Vunjak-Novakovic et al. 2011).

The pericardium is the outermost layer of the heart, and it is made up of two layers: Fibrous pericardium and Serous pericardium (epicardium). The pericardium is consists of dense and loose connective tissue, which protects the heart from any external damage or infections as well as lubricating the heart for better functioning during the heartbeat. The lubrication of the heart is
carried out by serous fluid secreted by the pericardium, and it fills the pericardial cavity (Hoit 2017; Chong and Angeli 2019).

Another component of cardiovascular systems is blood vessels that transport blood throughout the human body and are divided into five types: veins, arteries, venules, arterioles, and capillaries. In the blood circulatory system, arteries and arterioles transport oxygenated blood from the lungs to other parts of the body, but the veins and venules have reverse functions that transport deoxygenated blood from the body to the lungs. Trauma and mechanical damage to the blood vessels may lead to internal or external hemorrhagic, which can cause ischemia or myocardial infarction. In contrast, hypertension or an increase in blood pressure through the vessels may lead to stroke or heart failure (Plein et al. 2018; Sheng and Zhu 2018). Valvular heart disease is another cardiovascular disease, which involves the dysfunction of one or more valves in the heart. Irrespective of the disease process, stenosis, and insufficiency/regurgitation is the most common consequence of valvular heart disease. The former is the thickening of the valve, which can lead to narrowing the blood flow, and the latter is the capability of the heart valve to prevent the backflow of the blood. Valvular heart disease, similar to other cardiovascular diseases, can be life-threatening, and the treatments require the surgical repair or replacement of the valve. (Maganti et al. 2010; Iung and Vahanian 2011).

3. Stem cells in cardiovascular tissue engineering

Stem cells are unspecified cells, which capable of both self-renewal and differentiation into a variety of specialized cell types under certain conditions. Mostly, stem cells are classified into three types of Embryonic Stem Cells (ESCs), Induced Pluripotent Stem Cells (iPSCs), and Adult Stem Cells (ASCs). In this section, we review some of the important stem cells that have been utilized in cardiovascular tissue engineering.

3.1. Embryonic Stem cells (ESCs)

Embryonic stem cells (ESCs) are pluripotent stem cells derived from the inner cell mass of blastocysts. Not only ESCs have the self-renewal ability but also they capable of differentiating to all the cells in the body such as hepatocytes, chondrocytes, pancreatic cells, and cardiomyocytes (Mahla 2016). Several studies have been reported the utilizing of ESCs to improve the seizures
associated with infarcted myocardium, blood pressure, and ventricular function in various animal models. For instance, Liu et al. utilized human embryonic stem cell-derived cardiomyocytes (hESC-CMs) transplantation as grafts for restoring the heart’s function after myocardial infarction in macaque monkeys. They suggested that hESC-CMs grafts can re-muscularize substantial amounts of infarcted myocardium and reduce the scar size, thereby enhancing the overall cardiac function. Furthermore, they did not observe any teratoma formation despite the several reports on this possibility by employing pluripotent stem cells (Liu, Chen, Yang, et al. 2018). In a related study, Romagnuolo et al. successfully tested the capacity and stability of hESC-CMs transplantation in the pig model as a next step in the preclinical development of hESC-CMs (Romagnuolo et al. 2019). Moreover, in the first human clinical trial, Menasché et al. confirmed that hESCs have a good potential for transplantation in patients with severe ischemic left ventricular (LV) dysfunction, reliably giving rise to clinical-grade cardiovascular progenitors under defined conditions. To ensure the differentiation of hESCs into cardiovascular progenitors, they measured co-expression of the transcription factor ISL1 (a marker for cardiac and vascular lineages) and stage-specific embryonic antigen-1 (SSEA-1; a marker for the loss of pluripotency) (Moretti et al. 2006; Mummery et al. 2012). Then the cells-loaded fibrin patch, were transferred onto the epicardium of the infarcted area through the surgical procedure. As a result, with an increased systolic motion of the cell-treated segments, all patients were symptomatically improved and it showed hESC-derived cardiovascular progenitors have short- and medium-term safety for cell therapy (Menasché et al. 2018). However, the ethical concerns behind ESCs usage limit the application of these cells in tissue engineering and regenerative medicine, which can be solved by acquiring the iPSCs.

3.2. Induced Pluripotent Stem Cells (iPSCs)

Following the repudiation of utilizing the ESCs cells in regenerative medicine by the Japanese Ministry of Health, Labour and Welfare in 2006, simultaneously, Yamanaka and his colleagues Takahashi introduced the iPSCs from the somatic cells (Takahashi and Yamanaka 2006; Nagoshi and Okano 2018). The iPSCs characteristics are comparable to ESCs such as pluripotency, embryoid formation, and teratoma formation. The iPSCs technology has been used as autologous cells to decrease immune rejection after transplantation. Moreover, it can overcome the ethical concern behind the ESCs, which created a novel way towards cell therapy and regenerative
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medicine. Similar to the ESCs culture methods, IPSCs can differentiate into the cardiomyocytes through a variety of stimuli. Therefore, IPSCs are suitable for cardiovascular cell therapy and tissue engineering applications. For example, Nelson and co-workers utilized IPSCs delivery for treating the myocardial infarction in the mice. They reported that the transplanted IPSCs differentiate into the cardiomyocytes, smooth muscle cells, and endothelial cells, and it improved the cardiac function significantly (Perez-Terzic, Ikeda, and Terzic 2009). In another work by Maiullari and coworkers, They utilized a 3D-bioprinting approach to fabricate vascular cardiac tissues with Human Umbilical Vein Endothelial Cells (HUVECs) and induced pluripotent cell-derived cardiomyocytes (iPSC-CMs). The results suggest that these approaches can be considered for reconstructed therapy by revascularization of ischemic and damaged organs (Maiullari et al. 2018).

3.3. Adult Stem Cells (ASCs)

3.3.1. Cardiac Progenitor Cells (CPCs)

Previously, it was considered that the adult cardiac tissue does not have self-renewal ability and incapable of regeneration. However, recent evidence indicated the presence of a heterogeneous group of cells, which are distributed throughout the heart. Endogenous cardiac stem cells or cardiac progenitor cells (CPCs), which are identified in 2003 by the expression of tyrosine kinase receptor and c-Kit in the adult mammalian heart. These cells have self-renewal ability and multi-potent characteristics, which can contribute to the restoration of adult cardiomyocytes and vascular cells after injury (Hsieh et al. 2007; Bergmann et al. 2009; Senyo et al. 2013). Several Studies isolated the CPCs from different species and demonstrated that these multipotent cells can differentiate into cardiomyocytes, vascular smooth muscle cells, and endothelial cells (Laugwitz et al. 2005; Bearzi et al. 2007; Chong et al. 2011). Therefore, CPCs can be utilized in stem cell therapy and tissue engineering. For example, Gaetani and coworkers construct a cariogenic scaffold by combining the human cardiac-derived cardiomyocyte progenitor cells, biomaterials, and 3D printing technology (Gaetani et al. 2012). Moreover, Streeter et al. design polycaprolactone (PCL) nanofiber-based patches with the electrospinning method for the delivery of CPCs (Streeter et al. 2019).

3.3.2. Mesenchymal stem cells (MSCs)
Mesenchymal Stem Cells (MSCs) are a group of adult stem cells, which are used widely in tissue engineering and cell therapies due to their extraordinary potential for retaining the post-natal capacity of self-renewal and multi-lineage differentiation. MSCs have excellent properties such as limited immune response, secretion of a variety of anti-inflammatory, and antifibrotic mediators as well as high potential for activation of resident precursors (Golpanian et al. 2016). Due to the spectacular differentiation potential, safety, and feasibility of mesenchymal stem cells, many investigations proposed the MSCs as one of the most promising types of stem cells that can be used in cell therapy and tissue engineering (Karantalis et al. 2014; Heldman et al. 2014; Caplan 2009). It is also reported that MSCs can transdifferentiate into mesodermally derived cell types including cardiomyocytes (Guo et al. 2018). Recently, several studies have been conducted utilizing MSCs as a source for cardiac regeneration (Swaminathan et al. 2018). For instance, knowing that mechanical and electrical forces are one of the important regulators of gene expression and cellular function in cardiac tissue, Llucià-Valldeperas and colleagues used cardiac adipose-derived hMSCs (cATMSCs) implantation within a fibrin patch for treating infarcted myocardium in a murine model. These findings indicate that electrical stimulation on cATMSCs improved synchronous contractions, tissue homogeneity, and immunomodulatory properties, which could be a promising therapeutic strategy for heart repair after myocardial infarction (Llucià-Valldeperas et al. 2017). In a related study, Chen et al. focused on improving the poor survivability and lower retention of implanted stem cells for cardiac infarction. By using the Chitosan/silk (CS/SF) fibroin modified nanofibrous cardiac patch loaded adipose tissue-derived mesenchymal stem cells (AD-MSCs), they show that CS/SF-modified multilayers patches improve left ventricular ejection fraction (LVEF), cell viability, cardiac function, and reduced adverse ventricular remodeling in rat myocardial infarction model (Chen et al. 2018).

4. Nanomaterials controlling cellular behaviors

Until now, the effect of nanomaterials on stem cell behavior has been studied extensively. Nanomaterials not only can be utilized as nanoparticles, which can easily cross through the cell membrane and affecting the intracellular signaling pathway but also they can be utilized as a three-dimensional substrate for culturing the stem cells. The interaction between nanomaterials and stem cells has not been entirely understood, but we know that the bulk properties or physicochemical parameters and surface properties of nanomaterials play a major role in controlling cellular
behavior. However, the underlying mechanisms of various nanomaterials in which they can promote or inhibit adhesion, migration, differentiation, or proliferation, need further investigations. Here, we briefly discuss the bulk (Figure 1) and surface properties (Figure 2) of nanomaterials and their effect on cellular behavior, which can be utilized in the treatment of cardiovascular diseases.
4.1. Bulk properties

4.1.1. Size and shape
Nanoparticles can activate certain signaling pathways since they can act as a mechanical stimulus for inducing or inhibiting a wide range of behaviors in stem cells. However, nanoparticles should have the proper size to internalized to the cells. It has been shown that the optimal size for the differentiation of stem cells is around 20 to 70 nm (Li, Zhang, et al. 2016). However, the toxicity of the nanoparticles is relative to their size. For example, it has been shown that the particles with a smaller size (less than 50 nm) have shown more toxicity compare to large particles (Li, Zhang, et al. 2016; Lv et al. 2015). For example, in a study by Abdelhalim, GNPs with the size of 10 and 20 nm showed hemorrhage and excess extravasation of red blood cell, which indicated heart muscle damage in rats. However, the rats treated with 50 nm GNPs showed normal heart muscle (Abdelhalim 2011). It has been suggested that the production of the higher ROS molecules is the main toxicity mechanism of smaller GNPS since the smaller particles have a relatively high surface to volume ratio compared to larger particles. Therefore, smaller particles tend to produce more ROS molecules and oxidative stress in heart muscles (Abdelhalim 2011). Moreover, the shape of nanomaterials can control cellular behavior since the cellular uptake of nanoparticles is size and shape-dependent. It has been shown that the uptake of spherical nanoparticles is higher compare to nanorods and other shapes when the size of particles lower than 100 nm (Rivera-Gil et al. 2013; Albanessa and Chanw 2012).

4.1.2. Nanomaterial source
The source of nanomaterials is another factor, which should be taken into account since different kinds of materials have various effects on cellular biological response. Numerous scaffolds have been fabricated with different synthetic or natural materials. The advantage of utilizing natural materials such as hyaluronic acid, fibrinogen, collagen, and chitosan is the similarity of their components with the native ECM (Zamboni et al. 2018; Sridhar, Lakshminarayanan, et al. 2015). The RGD sequence that can be found in scaffolds synthesized with natural materials facilitates the adhesion of cells to the surface of nanomaterials and providing a suitable environment for
controlling the cell fate. In contrast, the synthetic nanomaterials may require further modification (Schacht, Vogt, and Scheibel 2016). Moreover, the hydrophobicity and the low number of attachment sites in synthetic nanomaterials may result in weak cell adhesion and unfavorable cellular response. However, synthetic materials can be used to overcome weak mechanical properties and lack of ideal chemical functional groups (Hossain, Mohamed, and Shafri 2020).

4.1.3. Porosity
The Porosity and pore size of scaffolds affect cellular response and cellular behavior, which lead to determining the phenotype of the cells. It has been demonstrated that nanoporous scaffold with pores smaller than 1 μm can improve cell-surface interactions. However, cell-cell communication relies on the 1 to 3 μm pores sizes. Furthermore, the optimum pore sizes for cell migration is ranging from 3 to 12 μm (Bružauskaitė et al. 2016). However, suitable pore size in scaffold for different tissue regeneration is varied and depends on the source and the size of cells. For instance, it was shown that the higher ratio between cells and pore size increases cell migration and cell invasion (Bružauskaitė et al. 2016). Turning to the cardiovascular system, it has been shown that the large pore size increase angiogenesis in porous PEG hydrogels (Artel et al. 2011). Culturing the vascular smooth muscle cells on L-PLA with 38–150 μm pore size showed cell proliferation and matrix deposition (Zeltinger et al. 2001). Moreover, Wang et al. showed the differentiation of iPSCs into smooth muscle cells on PLLA scaffold with the 60–150 μm pore size. Implanting this scaffold subcutaneously in nude mice showed the formation of vascular tissue (Wang et al. 2014).
Figure 2. Schematic representation of nanomaterials surface properties, which may modulate cellular behaviors towards cardiovascular cell lineage

4.2. Surface properties

The nature of the nanomaterials surface and the bioactive agents and biomolecules, which are utilized for functionalization can change the performance of nanomaterials in living tissue (Amani, Arzaghi, et al. 2019). Surface modification technology with bioactive agents and biomolecules can be employed as a proper tool for mimicking the tissue microenvironment (Ahn et al. 2018).
Whether nanomaterials are used as nanoparticles or 3D substrates for cardiac tissue engineering, understanding their surface properties and modifications techniques for changing the surface properties should be taken into account. The surface properties of nanomaterials such as surface charge, surface chemistry, surface topography, and surface wettability play major roles in cell adhesion, cell shape, cell proliferation, and differentiation (Yu, Cui, et al. 2017). These properties can be manipulated in designing nanomaterials for cardiovascular tissue engineering.

4.2.1. Surface Chemistry

The surface chemistry of nanomaterials is the main factor, which affect the cell-matrix interactions. Subsequently, these interactions can change a certain cells behavior, which can be utilized in designing new nanomaterials. Simpson and colleagues in 1994 demonstrated that the interactions between cardiomyocytes and collagen type I as a substrate, determined the phenotype of the cells (rod-like cell shape) by controlling the signaling pathways, which affect the cardiac alpha or beta integrin chain (Simpson 1994). The surface chemistry of nanomaterials can be associated with other surface properties such as wettability and surface charge affecting the cell adhesion, cell proliferation, and differentiation (Yu, Cui, et al. 2017). One of the crucial key components, which determine the nanomaterials surface properties is the chemical functional groups. Given that, the surface chemistry of substrate can be modified by utilizing various surface modification techniques. These methods can be used to add new functional groups (acetylation, fluorination, silanization, etc.) or changing the existing functional group (oxidation, reduction). For example, modification of substrates with Diethylenetriamine (DETA), which add primary amines on the surface of a substrate, can enhance cell attachment, differentiation, and long-term survival of rat embryonic cardiomyocytes (Das et al. 2004). Moreover, nanomaterials can be functionalized with specific biological molecules if certain functional groups are present on the surface. For instance, Kang and coworkers immobilized the Fibronectin onto PCL nanofibers modifying by initiated chemical vapor deposition (iCVD) polymer films. This nanofibers increased Umbilical-cord-blood-derived MSCs attachment, improved cardiac function, and angiogenesis in the rat myocardial infarction model (Kang et al. 2014).

Modifying various substrates with nanomaterials is another strategy utilizing surface chemistry. For example, mechanical and electrical properties of collagen can be increased by surface coating of collagen hydrogels with CNTs. Yu et al. found that the incorporation of carboxyl-functionalized
MWCNTs (30 ± 15 nm in diameter and 5-20 μm in length) with collagen type I hydrogel can improve the cardiac cell functions (Yu, Zhao, et al. 2017).

4.2.2. Surface Charge

Solid surface can become negatively and positively charge by changing the surface chemistry of nanomaterials with various chemical methods. It has been shown that the cell attachment on positively charge substrates is higher compare to negatively and neutrally charged surfaces (Castro et al. 2017; Park, Lee, et al. 2015). Moreover, It should be noted that the surface charge of nanoparticles is another factor that determines the uptake of nanoparticles, thereby affecting the biological response in the target cells (Jing and Bhushan 2013). Asati and coworkers functionalized the cerium oxide nanoparticles to produce neutral, negatively, and a positively charged nanoparticles. They found that aminated cerium oxide nanoparticles, which have positively charged surface, showed increased internalization and localization to cardiac myocytes (Asati et al. 2010). Furthermore, the surface charge can be used to form a complex structure with biomolecules such as DNA. For instance, Chang and colleagues synthesized AuNP loaded GMT(Gata4, Mef2c, and Tbx5) coated with PEI for the reprogramming of induced cardiomyocytes. They make a complex utilizing the electrostatic interactions between positive and negative charge of PEI and DNA, respectively. Moreover, they found that the AuNPs/GMT/PEI complex like other cationic nanocarriers has a high delivery efficacy (Chang et al. 2019).

4.2.3. Surface Wettability (Hydrophilicity/Hydrophobicity)

The adhesive force between the solid surface and liquid, which causes the spreading of the liquid across the solid surface is surface wettability (Lai et al. 2013). It has been shown that the proteins attract to hydrophilic surfaces compared to hydrophobic surfaces. Consequently, cell attachment and proliferation is higher on the hydrophilic surface (Arima and Iwata 2007). It should be noted that the surface wettability of nanomaterials can be adjusted by the manipulation of surface chemistry and surface topography (Ueda and Levkin 2013). For example, Wei and colleagues utilized plasma polymerization and oxygen plasma treatment to create a wide range of surfaces from 106° to 0° (hydrophobicity to hydrophilicity) wettability degree. They demonstrated that the rat fibroblast tends to spread on hydrophilic surfaces. Moreover, they showed that the fibronectin protein is attached to the hydrophilic surfaces to a higher degree compared to albumin, which is
absorbed on hydrophobic surfaces (Wei et al. 2007). Overall, cell spreading and cell attachment have a direct relationship with a positive cell surface and hydrophilicity and a negative relationship with negative surface charge and hydrophobicity (Guo et al. 2016). However, moderately wettable surface with the contact angle of 70–80° is preferable for cell attachment (Guo et al. 2016; Wei et al. 2007; Vickers 2017). Mehdinavaz Aghdam et al. synthesize a PCL/PGA blend nanofibrous scaffold, and they cultured the CPCs cells on the scaffold for the investigation of cell adhesion and proliferation. They used the PGA reinforcement to increase the mechanical properties of the scaffold. Moreover, increasing the PGA concentration is enhanced the hydrophilicity of the scaffold. They demonstrated that the 65:35 PCL:PGA ratio showed the highest cell adhesion and proliferation. However, increasing PGA by more than 50% reduces the cell proliferation and growth substantially (Aghdam et al. 2014).

4.2.4. Surface Topography
Another aspect of surface properties, which is crucial for cardiac tissue engineering is controlling cellular behavior through topographical features. One of the main challenges is to simulate the in vivo like orientation and elongation of cardiomyocytes in tissue engineering strategies. We can see this three-dimensional syncytium formation of cells in adult cardiomyocytes, which enables producing the electrical signals (Au et al. 2007). It has been shown that the topographical cues are the major determinant of cardiomyocyte orientations (Au et al. 2007). One of the most crucial aspects of surface topography is the surface roughness, which is calculated by measuring the protrusions and depressions of the surface (Xu et al. 2004). It has been shown that rough and smooth surfaces can induce different cell responses. For example, an increase in surface roughness can increase the adsorption of key ECM proteins such as fibronectin and vitronectin. Fibronectin can enhance cell attachment and cell growth by chemoattractant of various cell types such as fibroblasts and endothelial cells, which are essentials in wound healing after myocardial infarction (Grinnell 1984). Stout et al. utilized the carbon nanofibers (CNF) for increasing the roughness of PLGA with different ratios (100:0, 75:25, 50:50, 25:75, and 0:100 wt% CNF:PLGA). They observed that the increase of CNF into PLGA structures promote cell attachment and growth of cardiac muscle cells. They reported that the 50:50 ratio of PLGA and CNF with the 0.025 g/mL PLGA density showed the highest cardiomyocyte growth (Stout et al. 2012).
Another aspect of surface topography is the surface pattern, which can be classified into isotropic and anisotropic patterns. A surface with no directional orientation is isotropic. However, surfaces with nanotopographical patterns such as protrusions, pillars, circular, etc (Yao, Peng, and Ding 2013). Several studies investigate the effect of nano topographical features on protein absorption and cell behaviors such as growth and stem cell differentiation (Biggs et al. 2007; Ji et al. 2012; Ngandu Mpoyi et al. 2016; Dalby and Gadegaard 2007). It has been shown that these effects are the result of biochemical and biomechanical processes of adhesion and cytoskeletal conformation. Ngandu Mpoyi and coworkers designed a nanostructures polycarbonate surface with 150 nm diameter arranged in a square pattern and ≈90 nm deep pits (NSQ50) to investigate the adsorption of proteins and cellular behaviors. They utilized the C2C12 myoblasts to investigate the focal adhesion assembly and myogenic differentiation compared to the flat control groups. They found that the fibronectin absorption increase in globular clutters both on the interpits space and inside the nanopits, which increases the cell attachment to the surface. Moreover, C2C12 interacted with the edge of pits through filopodia and even enters the nanopits. Altogether, they concluded that the nanotopographical features can impact cellular behavior such as differentiation by changing the cell adhesion and cytoskeleton organization (Figure 3) (Ngandu Mpoyi et al. 2016). Au and colleagues demonstrated that the effect of topographical features on cardiomyocyte orientations is significantly stronger than the electrical stimulation (Au et al. 2007). Furthermore, it has been shown that cellular behaviors such as morphology, the velocity of action potential conduction, and cell-cell coupling proteins interactions can be controlled by controlling the size of nanogrooves (Kim et al. 2010).
4.2.5. **Mechanical properties**

Controlling cellular behavior can be achieved by mimicking the tissue-specific niche properties such as mechanical properties modifying. These modifications adjusting the cell-material interactions, which affect intracellular pathways regulating cellular behavior (Han et al. 2020). Material stiffness is the resistance of materials to deformation when a force is applied, which means that the materials with high stiffness can resist deformation, but materials with low stiffness, deform easily. Every tissue display a special stiffness values, which is determined by the
composition of the ECM and cross-linking proteins (Handorf et al. 2015). The interaction of stem cells with the metric stiffens is crucial for the regulation of stem cell fate such as the early stage of differentiation. These cells mechanically interact with the ECM by cell adhesion molecules (CAMs) such as integrins, which help them recognize the substrate stiffness. Consequently, these interactions convert to biochemical signals, which determine the cell behaviors and stem cell fate (Tatsumi et al. 2007; Yeung et al.; Han et al. 2020). Several studies revealed that mimicking the biomechanical properties of cardiac muscles is crucial in cardiac tissue engineering. First, the biomechanical cues may induce cardiac differentiation. Moreover, mechanical cues enable the tissue construct to be synchronized with the contraction of the heart, which induces mechanical transfer from the myocardial environment to the stem cells (Guan et al. 2011).

In recent years, several biomaterials have been used to mimic the mechanical properties of the myocardium. The similarity between the mechanical properties of the heart and biomaterials is crucial. It has been demonstrated that the young modulus for the heart is 10 to 20 kPa in diastole and 200–300 kPa at the end of systole. Therefore, relatively low young modulus with high elasticity and tensile strength is optimal for cardiac tissue engineering. Consequently, the materials with high stiffness are not desirable (Davenport Huyer et al. 2016). For example, it has been shown that biodegradable polyesters, such as polylactide (PLA) and copolymers are not suitable for such applications since they lack suitable stiffness (Wang et al. 2010). The flexible and soft polymers with a good elasticity futures such as polyurethane is a good candidate for myocardial tissue engineering. For instance, Guan and coworkers used electrospinning poly(ester carbonate urethane)urea (PECUU) nanofibers and electrospraying MSCs methods to synthesize a myocardium-like tissue construct. They showed that the anisotropic mechanical properties with areal strains at 10 kPa, and strains at 10 kPa were the same as the native myocardium (Guan et al. 2011). Moreover, Li et al., synthesized thermosensitive hydrogels based on N-isopropylacrylamide, N-acryloxysuccinimide, acrylic acid, and poly(trimethylene carbonate)-hydroxyethyl methacrylate with various mechanical properties (16 kPa, 45 kPa, 65 kPa). They observed that 76% hMSCs encapsulated in the hydrogel with the higher modulus (65 kPa), and they expressed the proteins essentials for contraction ability of the heart such as MYH6 and cTnI, which showed the successful differentiation of the MSCs into cardiomyocytes (Li et al. 2012). This study proved that the modulation of mechanical properties of the scaffold can induce higher differentiation of stem cells compared to traditional techniques such as co-culturing the hMSCs with cardiomyocytes.
or using 5-azacytidine. Despite the compositions, several factors can contribute to the mechanical properties of biomaterials, which can be modulated to change the elasticity of the hydrogel. For example, Davenport Huyer, and colleagues synthesized poly(octamethylene maleate (anhydride) 1,2,4-butanetricarboxylate)(124 polymer) with one step polycondensation reaction, which showed an ideal biodegradability, relatively low Young’s modulus with excellent elasticity properties, high elongation, and tensile strength. The hydrogel properties were tunable by UV light exposure, monomer composition, and porosity content. They utilized an experimental design to find the best relationship between these properties. Afterward, rat cardiomyocytes cell attachment ability was investigated by live/dead staining, which showed an excellent cell-substrate and cell-cell attachment (Figure 4) (Davenport Huyer et al. 2016).
Figure 4. A) Mechanical properties of 124 polymer construct. a) Elastic properties of 124 polymer suitable for cardiac tissue engineering (scale in mm). b) Young’s modulus to monomer ratio, UV exposure energy, and porogen content relationships. c) Stress-strain curve, which demonstrated the elastic characterization of 124 polymer d) Comparison between elastomeric properties of polymer 124 and poly(octamethylene maleate (anhydride) citrate. B) Culturing rat cardiac cells on 124 polymer for 7 days. a) bright-field image with 250 and 100 μm magnification. b) live (green)/dead (red) staining of rat cardiomyocytes image. c) Confocal microscopy of rat cardiac cells after staining with cardiac troponin-T (green) and F-actin (red), which demonstrated the formation of rat cardiomyocytes. d) Representation of intercellular connections and organized cardiac tissue by Connexion 43 staining (green) at cellular junctions (Davenport Huyer et al. 2016). (Figure has been reproduced from (Davenport Huyer et al. 2016) with permission from American Chemical Society, Copyright 2016).

5. Nanomaterials effect on cellular behavior and their application in cardiac tissue engineering

5.1. Metal-based nanomaterials

5.1.1. Gold nanoparticles

Gold nanoparticles (AuNPs) are the colloidal suspension of gold particles in waters with unique chemical, physical, thermal, optical, and biological properties. Gold nanoparticles have potential applications in various fields such as chemistry, physics, material science, biology, and medicine. Moreover, AuNPs are widely used in drug delivery and regenerative medicine since they can be designed, produced, and modified utilizing different functional groups, which provide antibodies and ligands conjugation (Jazayeri et al. 2016; Amani, Mostafavi, et al. 2019; Fathi-Achachelouei et al. 2019). Recent studies have demonstrated the impact of AuNPs on cell fate and cell behavior, as it can promote the differentiation of ESCs and MSCs into osteoblast and cardiomyocyte cells. It has been shown that different sizes of spherical AuNps significantly enhanced the differentiation of AD-MSCs into osteoblast with no cytotoxic effect (Ko et al. 2015). Li and coworkers used different sizes and shapes of AuNps (nanorods and nanostars) to investigate the shape and size of these nanoparticles on osteogenic differentiation of hMSCs. They showed that the expression of
osteogenic markers increased by Au nanorod (70 nm) and Au nanosphere (40 and 70 nm) (Li, Zhang, et al. 2016). Such findings suggested that different shapes and sizes of AuNPs can significantly affect cellular behavior, which can be beneficial in tissue engineering applications. Ravichandran and coworkers, increased the cardiomyogenic differentiation of MSCs by the synergic effect of 5-Azacytidine (5-aza) and AuNPs loaded nanofibrous scaffold. In this study, AuNps nanofibers were fabricated by a mixture of gold chloride (AuCl3), Polyvinylalcohol (PVA) and bovine serum albumin. Moreover, it showed that the pretreatment of MSCs with AuNps loaded nanofibers increase the expression of cardiac-specific markers such as a-actinin, Cx43, and Troponin-T (Ravichandran et al. 2014). It should be noted that AuNPs heart distribution is size-dependent. In a study by Zhang and colleges, using smaller sizes of AuNPs with less than 40 nm is recommended since the larger size of AuNPs may show cardiac toxicity. Moreover, they suggest that the 5 nm AuNPs did not accumulate in hearts compared to larger sizes, and it showed cardiac protective potential (Zhang, Xue, et al. 2018).

Another important factor that plays a crucial role in cardiac tissue engineering and directing the stem cells fate is the conductivity of AuNPs. Several studies showed that the various nanofibers can be decorated with AuNPs. For instance, decellularized scaffolds can be integrated with AuNPs, which is a novel electroconductive platform with high compatibility. Shevach and coworkers design a hybrid scaffold with the fibrous decellularized omental matrices, and they deposited different sizes of AuNPs (4 and 10 nm) on this scaffold. This novel autologous scaffold, showed strong biocompatibility, electroconductivity, enhanced mechanical properties. However, in vivo conditions, the AuNPs may dissociate from the scaffold, but it showed excellent stability in vitro conditions. The cardiac cells showed aligned and elongated morphology with massive striation and organized connexin 43 electrical coupling proteins. The AuNPs in this hybrid scaffold reduce the proliferation, thereby maintaining the ratio of contracting to non-contracting cells (Figure 5) (Shevach et al. 2014). Nevertheless, Baei et al. improved the conductivity of chitosan by the incorporation of gold NPs into the chitosan structure. This improvement showed the differentiation of MSCs into cardiac cells. Moreover, the rate of cardiac differentiation was higher compared to the pristine scaffold (Baei et al. 2016).
Figure 5. A) Schematic overview of producing 3D decellularized Omental scaffold decorated with AuNPs as a personalized cardiac patch for cardiac tissue engineering. B) Decellularization process of Gold Nanoparticle-Decellularized Matrix Hybrids a) Native omentum tissue b) Omentum tissue during decellularization process c) After complete decellularization process. C-a) Decoration of the omentum decellularized scaffold with 4 nm and 10 nm AuNPs. b-d) SEM images of AuNPs-Decellularized scaffold C) Immunostaining of cardiac cell organization on day 5 (cardiac α sarcomeric actinin (pink), connexin 43 (green), and nuclei (blue))). a) pristine scaffold b)
deposition of 4 nm AuNPs c) deposition of 10 nm AuNPs (Shevach et al. 2014). (figure reproduced from (Shevach et al. 2014) Published by American Chemical Society, Copyright 2014).

Besides conductivity, it has been shown that the integration of gold nanorods (AuNRs) with hydrogels can increase the stiffness of the scaffold, which enhance the neonatal cardiomyocytes adhesion. Navaei and colleagues fabricated a gelatin methacrylate (GelMA)/AuNRs hybrid scaffold with various concentrations of AuNPs with an aspect ratio of 3.15 (16 ± 2 nm width and 53 ± 4 nm length). Moreover, they utilized different AuNRs concentrations (0.5, 1, 1.5 mg/mL) in the scaffold, which the 1.5 mg/mL group demonstrated the best results in cell retention and cytoskeleton organization. Moreover, it showed the cell-matrix interactions by enhancing the integrin 1 and cardiac-specific markers such as troponin I and sarcomeric -actinin. Moreover, the conductive properties of this hybrid scaffold resulted in high cell-cell interactions and electrical signal propagation by increasing the Cx43 gap junctions expression level and synchronized calcium signaling in cardiomyocytes (Navaei et al. 2016).

In addition to the features that we discussed above other properties of AuNPs can be used in designing new scaffolds for cardiac regeneration. Recently, a cardiac patch was developed by albumin electrospun fibers decorated with gold nanorods, which have the ability to absorb and convert the light (808 nm near IR laser) to thermal energy. This thermal energy can change the molecular structure of the scaffold, which can help the integration of the patch to the wall of the heart. Scanning electron microscopy (SEM) images of the sliced heart confirmed a close interaction between the heart and the cardiac patch (Figure 6). Cardiac cells showed an excellent contract ability, and a high expression of Cx43 between cardiomyocytes, which resulted in the synchronous function of these cells (Malki et al. 2018).

In another study by Sridhar and co-workers, a nanofibrous scaffold constructed by AuNPs (16 nm in size) embedded in polycaprolactone (PCL), Aloe Vera (AV), Vitamin B12, and Silk fibroin (SF) scaffold. They demonstrated that the chemical composition and the stiffness of the scaffold are responsible for the proliferation and differentiation of MSCs. Moreover, the AuNPs and vitamins improved the surface area of the scaffold as well as enhancing the cellular properties such as sarcomeric structures. Nevertheless, the scaffold with the AuNPs significantly enhanced the initial cell proliferation on day 5 (Sridhar, Venugopal, et al. 2015).
Figure 6. A-a) Schematic representation of gold nanorods-based engineered cardiac patch for suture-free engraftment by near IR. b) The cardiac patch after integration with rat heart. B-a) High-resolution TEM AuNPs. b, c) SEM image of albumin electrospun nanofibers d, e) Adsorption of AuNPs on the albumin nanofibers (Malki et al. 2018).

Table 1. A summary of Gold nanomaterials which impact the cellular behavior and their applications in cardiac tissue engineering.

| Gold nanomaterials | Scaffold | Result | Cell type | Applications | References |
|--------------------|----------|--------|-----------|--------------|------------|
| 1                  | AuNPs/5-aza/BSA/PVA | Induce cardiogenesis | MSCs | Cardiomyogenic differentiation | (Ravichandran et al. 2014) |
| 2                  | AuNPs + Decellularized omental tissue | Promote cardiac cell growth and enhance cardiac patches functions | Fibroblast | Suitable for engineering more homogeneous cardiac patches with heart function improvement | (Shevach et al. 2014) |
| 3                  | AuNPs + Chitosan thermosensitive hydrogels | Induce cardiac differentiation and maintain viability and growth rate of MSCs | MSCs | Enhances the properties of myocardial constructs | (Baei et al. 2016) |
| 4                  | AuNPs/PCL/SF/AV/Vit B12 | Enhance MSCs proliferation and differentiation into cardiogenesis | Cardiomyocytes + MSC | Potential suitable constructs for myocardial regeneration and repair | (Sridhar, Venugopal, et al. 2015) |
|   | Material/Method                        | Effect                                                                 | Cell Type                          | Description                                                                 | Reference               |
|---|---------------------------------------|------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------|-------------------------|
| 5 | AuNWs/alginate scaffold               | Improve electrical interaction between adjacent cardiac cells           | neonatal rat CMs and CFs           | Provide a promising scaffold for the therapeutic value of current cardiac patches. | (Dvir, Timko, Brigham, et al. 2011) |
| 6 | GelMA- Gold nanorod (GNR)             | Induce high cell retention and enhance expression of cardiac specific markers | Cardiomyocytes                     | Functional cardiac patches with superior electrical and mechanical properties | (Navaei et al. 2016)    |
| 7 | Au loaded laponite (Lap)/ECM hydrogel | Enhance cell survival rate, cell retention behaviors and cell expression of cardiac specific markers | Cardiomyocytes                     | Suitable cardiac regenerative material for the repair of infarcted myocardium | (Zhang, Fan, et al. 2019) |
| 8 | AuNPs/thiol-HEMA/HEMA scaffold        | Improve cell-cell communication and enhance Cx43 protein expression     | neonatal rat CMs                   | AuNPs/thiol-HEMA/HEMA Scaffold may facilitate cardiomyocyte function        | (You et al. 2011)       |
| 9 | AuNPs/PCL/gelatin fibers              | Enhance cell growth and proliferation with promote Actn protein expression | NRVMs                              | AuNPs/PCL/gelatin fibers can be used to improve the function of the infarcted heart | (Shevach et al. 2013)   |
| 10| AuNRs/GelMA hydrogel                  | Promote expression of Actn and Cx43 proteins and improve cell-cell communication, cell adhesion, spreading and alignment | neonatal rat CMs                   | Suitable functional cardiac patches for infarcted myocardium                 | (Navaei et al. 2017)    |
| 11| AuNRs/GelMA via 3D bioprinting        | Enhance cell adhesion, organization and expression of several cardiac specific genes with improve cell–cell coupling and synchronized contraction | neonatal rat CMs and CFs           | Potential application for cardiac tissue engineering                        | (Zhu et al. 2017)       |
| 12| AuNPs/collagen substrate              | Promote expression of several cardiac specific genes and improve cell adhesion, spreading, alignment, elongation, and striation | NRVMs                              | Potential applications of AuNPs/collagen substrate in regenerative medicine  | (Li, Shi, et al. 2016)  |
5.1.2. Silver nanoparticles

Silver nanoparticles (AgNPs) have potential applications in medicine, electronics, textiles, and cosmetics due to their superior antimicrobial properties. Different techniques can be used in AgNPs synthesis including laser ablation, gamma irradiation, electron irradiation, photochemical approach, and some biological mechanisms (Iravani et al. 2014).

Antiviral and antiseptic properties of AgNPs have been utilized for the production and development of biological instruments such as artificial cardiac pacemakers. Antimicrobial properties of AgNPs have been reported in tissue engineering and regenerative medicine studies especially in wound healing (Fathi-Achachelouei et al. 2019). All the beneficial applications of AgNPs along with the manipulation of their size, shape, concentration, functionalization, and exposure time, generate significant developments for cardiovascular disease diagnosis and prognosis (Gonzalez et al. 2016). The first cardiovascular usage of silver in the clinic was a silver-coated prosthetic silicone heart valve designed to reduce bacterial infection and the host inflammation response (Ge et al. 2014). In a study by Fu and co-workers, chitosan/heparin multilayer films were constructed, and not only showed an antibacterial effect on E. coli but also the incorporation of AgNPs into these multilayer films substantially improves its bactericidal properties. This study suggested that the nanosilver multilayer film could be useful in the surface of medical devices, especially in cardiovascular implants (Fu et al. 2006). In another study by Angelina et al. a pyrolytic carbon (PyC) biomaterial was constructed as an artificial heart valve. 

| 13 | AuNWs/PU scaffold | Enhance cell alignment, spreading, and proliferation | H9C2 rat CMs | Suitable cardiac regenerative material for future applications in cardiac tissue engineering | (Ganji et al. 2016) |
| 14 | peptide-functionalized AuNPs/ polymethylglutarimide fibers | Enhance cardiogenic differentiation and cell-cell communication | hPSCs | Suitable material for cardiac tissue engineering | (Jung et al. 2012) |
| 15 | AuNPs/reverse thermal gel | Promote expression of Cx43 protein and long-term cardiomyocytes survival | NRVMs and CFs | Potential application for cardiac tissue engineering | (Peña et al. 2019) |
and coated with a thin layer of AgNPs. The AgNPs give the PyC excellent antibacterial properties, and improve its haemocompatibility (Angelina et al. 2017). However, there are substantial concerns about their effects on human health since AgNPs can be released into the environment and interact with physiological fluids. Oxidization of the elemental Ag(0) to (Ag+) and the subsequent binding of Ag+ to protein ligands led to a toxic effect of AgNPs (Behra et al. 2013). It has been shown that extremely low concentrations of the ionic form of Ag such as silver chloride and silver nitrate can increase ventricular hypertrophy in cardiovascular systems which are associated with high blood pressure, the elevation of hemoglobin, and hematocrit concentrations (Espinosa-Cristobal et al. 2013). Nevertheless, there is insufficient information about the impact of AgNPs on the cardiovascular system. Some studies suggest that these NPs produce reactive oxygen species (ROS), which can induce cardiotoxicity (Bostan et al. 2016; Yu, Hong, and Zhang 2016). In a recent study by Ferdous and co-workers, the cardiovascular mechanism of pulmonary exposure to two different citrates (CT) and polyvinylpyrrolidone (PVP) coated with AgNPs was evaluated. They reported that AgNPs exposure induced oxidative stress which increases cardiac cell apoptosis and DNA damage. Besides, the time of thrombotic obstruction in cerebral microvessels and platelet aggregation increased after lung exposure to AgNPs (Ferdous et al. 2019). Moreover, Manuel and coworkers utilized a Langendorff heart (isolated perfused heart) preparation to demonstrated that the low concentrations of AgNPs (0.1 and 1 μg/mL) increased nitric oxide level, but the cardiac contractility or coronary vascular tone in normal Wistar rats were intact. However, high concentrations of AgNPs (10 and 100 μg/mL) increased reactive oxygen species, which led to the induction of cardiac contractility and vasoconstriction. Furthermore, this reactive oxygen species generated by AgNPs cause the degradation of muscle or rhabdomyolysis (Manuel et al. 2017).

Silver nanoparticles are often utilized in tissue engineering embedded in scaffolds that are subsequently cultured with MSCs. Moreover, AgNPs can induce a toxic effect in the mesenchymal stem cells. Furthermore, Wei and co-workers revealed that after uptake of AgNPs (30 nm) in hMSCs, apoptosis, necrosis, DNA damage, and reactive oxygen species increased and cell viability decreased (He et al. 2016).
Table 2. Silver nanomaterials applications in cardiac tissue engineering.

| Silver nanomaterials | Scaffold | Result | Cell type | Applications | References |
|----------------------|----------|--------|-----------|--------------|------------|
| 1                    | AgNPs/Pyrolytic carbon (PyC) | Direct effects of AgNPs on bacterial colonisation | - | Improved haemocompatibility properties and antibacterial effect by using pulsed laser deposition of silver nanoparticles | (Angelina et al. 2017) |
| 2                    | AgNPs | Direct effects of AgNPs on ion channels at the nanoscale level leading to loss of excitability of in mice cardiomyocyte | Cardiomyocyte | Warning about the use of AgNPs in nanomedical application | (Lin et al. 2017) |
| 3                    | AgNPs/collagen fibers | Improve electrical conductivity, cell proliferation and expression of connexin-43 gene | rat cardiomyoblasts | AgNPs/collagen fibers prevent biofilm formation but did not activate macrophages | (Allison et al. 2017) |
| 4                    | AgNPs | Induce oxidative stress and cardiac inflammation | - | AgNPs can decrease cardiac contraction via downregulation of related genes | (Bostan et al. 2016) |

5.1.3. Titanium dioxide

Titanium dioxide nanoparticles (TiO$_2$ NPs) are made in large quantities globally, which can be used in a variety of applications due to their anti-corrosive, high stability, and photocatalytic characteristics. Recently, a variety of techniques have been used to synthesized TiO$_2$ NPs such as the sol-gel methods, reverse micelles, chemical vapor deposition, etc (Nyamukamba et al. 2018). These nanoparticles are being studied in the field of nanomedicine as a beneficial tool in advanced imaging and nanotherapeutics (Shi et al. 2013). Several studies have revealed that TiO$_2$ NPs can be utilized in various biodegradable polymers as good filler materials since they can enhance cell attachment and proliferation. Moreover, unique physicochemical characteristics make TiO$_2$ NPs suitable for controlling cellular behavior such as migration and differentiation of stem cells (Park et al. 2007). In vivo studies showed the systemic distribution of TiO$_2$ NPs to all tissues and organs in the body after initial absorption (Hong et al. 2017). Due to the growing use of TiO$_2$ NPs in tissue...
engineering, the study of toxicity is crucial. For instance, Jawad and coworkers investigated the cellular toxicity of TiO$_2$ NPs on three different cardiac cell types including fibroblasts, adult rat ventricular cardiomyocytes, and human embryonic stem cell-derived cardiomyocytes (hESC-CM). The lowest test dose of TiO$_2$ NPs (10 mg/mL) showed a reduction in the beating rate of hESC-CM, but there was no significant impact on myocyte cell viability or acute contractility of the myocytes observed in 24 hours. The cultivation of fibroblasts in 5–150 mg/mL TiO$_2$ NPs stimulated cell death and decreased cell proliferation significantly in 4 days. However, there were no arrhythmias or discontinuation of the beating in three different cell types (Jawad et al. 2011). It should be noted that the toxicity effect of TiO$_2$ NPs highly depends on various factors such as concentration and exposure time which could affect cellular behavior by activation or suppression of related cell signaling pathways (Chen et al. 2015). The inflammatory reaction generated by TiO$_2$ NPs is known to be one of the major causes of cardiovascular system dysfunction. In a recent study, Zhang et al. investigated the mechanism of cardiovascular toxicity induced by dermal exposure to TiO$_2$ NPs. This study displayed that TiO$_2$ NPs treatment highly elevated the reactive oxygen species and 8-hydroxy-2'-deoxyguanosine. Besides, it increased the inflammatory biomarker rates, such as soluble intercellular adhesion molecule-1, immunoglobulin E, hypersensitive C-reactive protein, and interleukin-8. Furthermore, exposing human umbilical vein endothelial cells (HUVECs) to TiO$_2$ NPs reduces cell viability and a rise in caspase-3 levels, which induces cytotoxicity and cell apoptosis (Zhang, Liu, et al. 2019). In another study, Hong and coworkers revealed that the exposure of mice to TiO$_2$ NPs for six months, damage the heart muscle by disrupting the cytokine expression link to Th1 or Th2 (Hong et al. 2015). Chen and colleges investigated the effect of TiO$_2$ NPs on the cardiovascular system after oral intake. After regular gastrointestinal administration of TiO$_2$ NPs (0, 2, 10, 50 mg/kg) for 30 and 90 days, they investigated the rate of heart injury by measuring the heart rate, biochemical parameters in the blood, cardiac histopathology, and blood pressure. TiO$_2$ NPs exposure increased the inflammatory responses such as increased concentrations of interleukin 6, tumor necrosis factor α, white blood cells count, and granulocytes. Even low concentrations of TiO$_2$ NPs can cause harmful cardiovascular effects after 30 days or 90 days of oral exposure (Chen et al. 2015). However, TiO$_2$ nanofilm showed good blood cells, endothelial cells, and smooth muscle cells compatibility in a work by Xiang and coworkers (Xiang et al. 2015). Moreover, it has been shown that TiO$_2$ nanotube provides a favorable template for bone growth and differentiation but there is no evidence of
favorable cell proliferation and differentiation in cardiovascular tissue reconstruction (Popat et al. 2007).

Table 3. Titanium dioxide nanomaterials applied in cardiac tissue engineering applications

| Titanium dioxide nanomaterials | Scaffold | Result | Cell type | Applications | References |
|-------------------------------|----------|--------|-----------|--------------|------------|
| 1                             | TiO₂ NPs | Induce accumulation of ROS, leading to oxidative stress | HUVECs | Cardiovascular toxicity identification | (Zhang, Liu, et al. 2019) |
| 2                             | TiO₂ NPs | Direct toxicological effect of TiO₂-NPs on myocardial tissue. | Cardiomyocytes | Cardiovascular toxicity identification | (Savi et al. 2014) |
| 3                             | TiO₂ NPs | Induce oxidative stress and DNA damage, leading to abnormal cardiac differentiation | hESCs | TiO₂ NPs could affect pluripotency and differentiation properties of hESCs | (Pan et al. 2018) |
| 4                             | TiO₂-PEG/CTS hydrogels | Enhance cell retention and cell adhesion of cardiomyocytes | cardiomyocytes | TiO₂-PEG/CTS hydrogel is potentially suitable cardiac patches for cardiac repair applications | (Liu, Chen, Zhuang, et al. 2018) |
| 5                             | Micro/nano composite TiO₂ films | Enhance blood cells, endothelial cells, and smooth muscle cells compatibility | endothelial cells | Potential application for cardiovascular implanted devices | (Xiang et al. 2015) |
| 6                             | TiO₂ NPs | Increase the inflammatory response | Cell type | TiO₂ NPs can cause harmful cardiovascular effects | (Chen et al. 2015) |

5.1.4. Magnetic nanoparticles

Magnetic nanoparticles (MNPs) are one of the important classes of nanomaterials, which have potential applications in nanomedicine. MNPs are synthesized using several methods such as thermal decomposition, microwave-assisted, chemical vapor deposition, combustion, carbon arc, laser pyrolysis, etc (Majidi et al. 2016). MNPs can be detected and controlled by magnetic fields, which opens up a wide range of possibilities for their clinical usage. MNPs have been utilized for
a variety of clinical applications including delivery of drugs and genes, magnetic imaging, and hyperthermic treatment (Wu et al. 2019). Iron oxide magnetic nanoparticles (IONPs) have crucial diagnostic properties in clinical applications. Regulation of synthetic procedures such as surface functionalization, size, and magnetization is crucial for contributing to specific properties such as stability, physicochemical, and biological fate (Mohammed et al. 2017). Recently, several studies reported the tracking of stem cell fate by IONPs conjugated growth factors (Willmann and Dringen 2018; Giannaccini et al. 2017; Marcus et al. 2015). Moreover, Iron oxide NPs showed HRP and catalase-like activity, which can reduce ROS due to their antioxidant properties. Furthermore, IONPs have been utilized in regenerative medicine and tissue engineering applications (Jansman and Hosta-Rigau 2019; Panahi et al. 2020). Huang et al. showed the beneficial impression of Ferucarbotran nanoparticle labeling, on human mesenchymal stem cells (hMSCs) proliferation. Superparamagnetic iron oxide (SPIO) nanoparticle has an intrinsic peroxidase-like activity, which can decrease intracellular H$_2$O$_2$. After internalization into hMSCs, it increases the progression of the cell cycle regulation by the free iron released from lysosomal degradation (Huang et al. 2009). Moreover, IONPs are beneficial tools for cardiovascular protection. In a study by Xiong and co-workers, a rat coronary artery ligature model was used to evaluate the effect of 2,3-dimercaptosuccinic acid modified Fe$_2$O$_3$ NPs in cardiovascular disease. This study showed that IONPs, which can preserve the heart from ischemic injuries in vitro and in vivo conditions without toxic effect, is a clinically good candidate for the treatment of cardiovascular disease (Xiong et al. 2015). In a different study, Han and co-workers used IONPs to stimulate the cardiac mesenchymal stem cell differentiation. In this research, the H9c2 cardiomyocytes that were treated with IONPs, co-cultured with MSCs. The Internalization of IONPs in H9c2 has increased the Cx43 expression, which is an important factor to trigger gap junctional signaling pathways and improve communications with hMSCs. Furthermore, the expression of cardiac-specific genes increased in hMSCs, which induced the cardiac differentiation; thereafter, H9c2 cells were separated from differentiated hMSCs, and they were utilized to treat the myocardial infarction by reduction of ventricles diameter and the systole and diastole time in a rat model (Han et al. 2015). Recently, superparamagnetic IONPs were used for the labeling of MSCs for cardiac tissue regeneration. IONPs were PEGylated and then IONP-labeled MSCs were administered into a rat model with cardiac disease. The MRI was employed to track MSCs labeled with IONPs, and they utilized a magnetic field for the targeted delivery of IONPs to the heart. In the presence of the magnetic field,
myocardial hypertrophy and heart function improved by utilizing SPION-labeled MSCs, but fibrosis formation reduced (Naseroleslami, Aboutaleb, and Parivar 2018). Moreover, IONPs can be used in the embedded scaffold structures for cardiovascular tissue engineering. For instance, Mou and co-workers treated the cardiomyocytes with different concentrations of 2,3-dimercaptosuccinic acid (DMSA) modified IONPs. After the internalization of IONPs to the cells, IONPs showed peroxidase-like activity, which decreased ROS level in the cardiomyocytes. DMSA-IRONs peroxidase-similar activity imposes positive effects for enhancing the myocardial infarction remodeling (Figure 6) (Mou et al. 2015). Another study showed that the supplementation of DMSA-coated IONPs with cardiomyocytes led to overexpression of Cx43 in the cells, which promote gap junctions, desmosomes, and adherent junctions between the cardiomyocytes (Mou et al. 2018).
Figure 7. A-a) TEM image of Fe$_2$O$_3$@DMSA NPs (9.8 nm). b) TEM image of Fe$_2$O$_3$@DMSA NPs of (35.2 nm). B) The heart sections stained with triphenyl tetrazolium chloride solution a) Sham-operated control (Sham) b) Normal saline-treated (CAL) c) Fe$_2$O$_3$@DMSA NPs-treated (CAL 1 Fe$_2$O$_3$@DMSA NPs). d) Different sizes of the infarcted area in the heart sections in different groups. C-a) Different concentrations effect of iron oxide modified with 2, 3-dimercaptosuccinic (DMSA-IRONs) on cardiomyocytes with double immunofluorescence staining (α-actinin (green) and connexin 43 (red) nucleus (blue)). b) Effect of different concentrations of DMSA-IRONs on cardiomyocytes with double immunofluorescence staining (phalloidin (green) and N-cadherin (red) nucleus (blue)) (Mou et al. 2015; Xiong et al. 2015). (this figure has been reproduced from (Xiong et al. 2015) with permission from John Wiley and Sons, Copyright 2015).

Table 4. Magnetic nanomaterials used in cardiac tissue engineering applications

| Magnetic nanomaterials | Scaffold | Result | Cell type | Applications | References |
|------------------------|---------|--------|-----------|--------------|------------|
| 1                      | IONPs   | Increase expression of cardiac-specific genes in hMSCs and lead to cardiac differentiation | MSCs + cardiac cells | IONPs are a clinically good candidate for the treatment of cardiovascular disease without toxic effect | (Yaniv et al. 2015) |
| 2                      | PEG-SPIONs | SPION-labeled MSCs in the presence of magnetic field might be able to improve cell homing of MSCs in the site of injury | MSCs | SPION-labeled MSCs could contribute to improvement of cardiac functions | (Naseroleslami, Aboutaleb, and Parivar 2018) |
| 3                      | IONPs   | Enhance a gap junctional communication between MSC and the cardiomyoblast via activation of connexin-43 | hBM-MSCs | potential therapeutic effect of IONP-cocultured MSCs | (Han et al. 2015) |
| 4                      | IONPs   | Labeling hBM-MSCs with IONP retain cell viability, proliferation rate and cardiogenic differentiation of hBM-MSCs | hBM-MSCs | IONP-labeled hBM-MSCs is safe and can be used in regenerative medicine | (Mohanty et al. 2018) |
Enhance the expression of cardiac functional genes in ECCs and supports cardiac differentiation mouse embryonic cardiac cells (ECCs) promising candidate for functional cardiac tissue patches (Nazari, Heirani-Tabasi, Hajiabbas, Salimi Bani, et al. 2020)

5.2. Carbon-based nanomaterials

5.2.1 CNTS

Carbon nanotubes (CNTs) are carbon allotrope with the 2D graphene sheet that enrolled in cylindrical to form 1D nanoscale structures, which were discovered in 1991 (Santhosh et al. 2016). Generally, CNTs can be classified into two types: single-walled carbon nanotube (SWCNT) and multi-walled carbon nanotube (MWCNT). Depending on the synthesis condition, the diameter of SWCNTs is usually less than 1 nm, while the diameter of MWCNTs is 1.4 nm to 100 nm, due to the multiple one-atom-thick sheets of carbon (Jia and Wei 2019; De Volder et al. 2013). Carbon nanotubes have unique properties such as mechanical and thermal transfer features, tensile strength, and electrical conductivity (Prato 2010; Ahadian, Obregón, et al. 2016), which makes them an excellent candidate for drug delivery (Hughes 2017), cancer therapy (Gai et al. 2018), immunostimulatory activity (Wang and Mooney 2018), biosensor (Gupta, Murthy, and Prabha 2018), gene delivery (Taghavi et al. 2017) regenerative medicine, and tissue engineering applications (Shrestha et al. 2018). Several methods have been utilized for synthesizing CNTs such as the electric arc discharge method (Zhang, Zhao, et al. 2018), laser ablation method (Mocan et al. 2016), chemical vapor deposition (Xu et al. 2018). The heart tissue is made up of collagen and elastin fibers, which make a specific molecular network, and it provides unique electrical and mechanical properties for the heart (Dvir, Timko, Kohane, et al. 2011). It has been demonstrated in recent years that tissue engineering scaffolds containing electrically conductive nanomaterials can mimic the myocardial ECM (Ashammakhi, Ahadian, Xu, et al. 2019), and Among all conductive nanomaterials, CNTs have received special attention in recent years due to their unique electrical conductivity, topographical, and mechanical properties (Ashtari, Nazari, Ko, Tebon, Akhshik, Akbari, Alhosseini, Mozafari, Mehravi, and Soleimani 2019). Despite the above-mentioned spectacular properties of CNTs, the biocompatibility and direct utilization of these nanomaterials are controversial. Several studies suggest that the aggregation and agglomeration of CNTs could cause toxicity and poor dispersibility of CNTs in polar solvents (Li et al. 2007; Bagheri, Abdouss, and Shoushtari 2010; Urankar et al. 2012). To overcome these limitations and
further improve the electrical and mechanical properties of these nanostructured materials, many studies incorporated the CNTs into various polymeric scaffolds for cardiac tissue engineering (Zhou et al. 2014; Kankala et al. 2018). For instance, Dominguez et al. utilized a Vapor Phase Polymerization (VPP) technique, which is widely used to deposit thin film layers of conductive polymers such as poly(3,4-ethylenedioxythiophene) (PEDOT) or PPy onto non-conductive substrates to provide electrical conductivity. They utilized sugar grains as a porogen to manufacture 3D porous scaffolds composed of PEDOT and CNT. The results showed that the impedance of PEDOT/CNT ($|Z_{\text{PEDOT/CNT}}| = 6 \, \text{k\Omega}$) scaffolds at 0.1 Hz was significantly lower than PDMS/CNT ($|Z_{\text{PDMS/CNT}}| = 50 \, \text{k\Omega}$) and naked electrode filled with electrolyte PBS solution ($|Z_{\text{PBS}}| = 90 \, \text{k\Omega}$). The result showed that PEDOT/CNT scaffolds are highly conductive with tunable electrical and mechanical properties, which can play a major role in electroactive cell growth (Dominguez-Alfaro et al. 2019). Another study by Martinelli et al. showed that CNTs can be utilized as scaffolds to encourage the growth of cardiomyocytes, formation of the functional syncytium, and electrophysiological maturation. They developed an elastomeric scaffold made of integrated MWCNTs into polydimethylsiloxane (PDMS) containing micrometric cavities. They found that the 3D-PDMS+MWCNT can promote cell viability, proliferation, and functional maturation of cardiac myocytes (Martinelli et al. 2018). In another study Ahadian and colleagues described the incorporation of MWCNTs into polymer 124, which enhanced the electrical conductivity, swelling ability, and tissue maturity. This scaffold showed an improvement in the excitation threshold of materials with 0.5% CNT content ($3.6 \pm 0.8 \, \text{V/cm}$) compared to materials with 0% ($5.1 \pm 0.8 \, \text{V/cm}$) and 0.1% ($5.0 \pm 0.7 \, \text{V/cm}$), suggesting greater tissue maturity (Ahadian, Huyer, et al. 2017). Furthermore, CNTs can be integrated into hydrogels, which can increase their biocompatibility and electrical activity (Sun et al. 2017). Hydrogel matrices have been widely developed for tissue engineering purposes. Various properties of hydrogels such as chemical, physical, and mechanical properties can be modified, which provide unique opportunities to enhance cell adhesion and cell viability for myocardium repair (Camci-Unal et al. 2014; Wu et al. 2017). For the first time, a study in 2014 proved that Electroconvulsive therapies (ECTs) based on CNTs could improve heart function. An SWCNT (1.5 mg/mL)/gelatin hydrogel was constructed to provide a microenvironment, which promotes cardiac contractility, the formation of gap junction, the expression of electrochemical associated proteins in vitro, and enhanced cardiac function in vivo (Zhou et al. 2014). Furthermore, several studies reveal that CNT
incorporation in natural hydrogels like collagen with enhanced elastic modulus could support the
growth of cardiomyocytes to increase the mechanical strength and electrical performance for
cardiac tissue engineering (Yu, Zhao, et al. 2017). For example, Sun et al. demonstrated that
incorporation of SWCNTs embedded in small concentrations (1 wt%) within Collagen hydrogels
can promote cell adhesion, cell elongation, cell alignment, and assembly of neonatal rat ventricular
cardiomyocytes (NRVM). However, cell viability was significantly decreased with concentrations
of CNTs up to 2 wt%, suggesting higher concentrations of CNTs incorporated within hydrogels
showed cell toxicity. The CNT/Collagen-hydrogel platform led to improved mechanical
contraction potential and better functionality of cardiac constructs (Sun et al. 2017). Recent
advances in tissue engineering by various methods for the fabrication of polymeric scaffolds have
significantly improved our ability to mimic native cardiac tissue. Among them, electrospinning is
well known for its capability of mimicking the fibrillary structure of myocardial ECM to
promoting cardiomyogenesis and tunability of the 3D architecture of the biodegradable scaffolds
to make effective propagation of electric potential among the cardiomyocytes (Kitsara et al. 2017;
Martinelli et al. 2012). For example, GelMA-coated CNTs were incorporated in PGS/gelatin
electrospun nanofibers to produce a CNT polymeric hybrid composite as a graft for cardiac tissue
constructs. In another study, Shin and colleagues fabricated aligned CNT forest microelectrode
arrays, which were embedded into flexible and biocompatible hydrogels. This construct showed
an excellent anisotropic electrical conductivity with control over actuation behavior. After
culturing the cardiomyocyte for 5–8 days, the cells showed homogeneous cell organization
(homogenous Cx-43 distribution), with improved cell-cell interactions, and maturation (Figure 8)
(Shin et al. 2015). Furthermore, Kharaziha et al. reported that incorporation of 1.5% CNTs within
the PG nanofibrous scaffolds (aligned CNT-PG hybrid scaffold) significantly enhanced fiber
alignment and improved electrical conductivity and mechanical properties of the scaffolds, which
showed enhanced beating qualities (3.5-fold lower excitation threshold and 2.8-fold higher
maximum capture rate) for the cultured cardiac tissue (Kharaziha et al. 2014). In a related study,
Liu et al. used coaxial electrospinning technique to fabricate highly aligned and hybrid fibers (D
= 2–3 µm) through incubation of 3% MWCNTs (10–20 nm in diameter, 10–20 µm in length) in
poly(ethylene glycol)-poly(D, L-lactide) copolymers (PELA) (Mw = 42.3 kDa, Mw/Mn = 1.23)
to increase electrical conductivity and promote cell growth, cell viability, cell elongation and
synchronous beating rates for cardiomyocyte (reached 75 ± 8 times/min) (Liu et al. 2016). Despite
all CNTs applications in the biomedical field, different studies have confirmed their various levels of toxicity (Muller et al. 2005; Lanone et al. 2013; Chen et al. 2014). Besides the effect of concentration and shape dependency, SWCNTs can produce more cytotoxicity compared to MWCNTs (Zhang et al. 2010; Wang et al. 2011). Moreover, several investigations have been reported high concentrations of CNTs could be toxic to cardiomyocytes (Helfenstein et al. 2008; Correa-Duarte et al. 2004). However, the main cause of these toxicities is mostly related to the structural, physical, and surface properties of CNTs. Therefore, surface modifications can significantly improve the biocompatibility of these nanomaterials (Kim et al. 2012; Moorthi, Tyan, and Chung 2017). Furthermore, other techniques such as the use of certain enzymes, functionalization of surface, and improving biodegradability by incorporating with polymeric scaffolds or hydrogels can effectively eradicate or reduce the toxicity of CNTs (Amani, Arzaghi, et al. 2019).

Figure 8. A) A Schematic illustrating the fabrication steps to generate vertically aligned CNT forest micro-electrode arrays in multilayer hydrogels sheet to engineer cardiac tissue based 3D biohybrid actuators. B-a) SEM images of thin-film arrays with the uniform alignment of CNT micro-
electrode (460 μm width, 300 μm height, 50 μm thick, and 200 μm spaced between each micro-electrode), B-b) magnified the surface of CNT forest micro-electrode c) 3D interconnected network of CNT with tortuosity morphology. B-d,e) High-resolution transmission electron microscopy (HRTEM) was utilized to characterize the diameter distribution of CNTs inside the CNT forests. B-f) the distribution of inner diameter of the MWNTs in the CNT forests. C-a) freestanding 3D biohybrid actuator image with an average beating rate of 108 BPM on day 8. C-b) A side view schematic illustration of the multilayer hydrogel sheet saturated with aligned CNT microelectrodes and the Phase contrast image of the boundary between the CNT forest electrodes boundary and the hydrogel layer. D) Immune staining of cardiac cells on CNT-GelMA (sarcomeric α-actinin (green), nuclei (blue), and Cx-43 (red)). E) CNT forest electrode displacement in the multilayer hydrogel sheet under electrical stimulation (Shin et al. 2015). (this figure has been reproduced from (Shin et al. 2015) with permission from John Wiley and Sons, Copyright 2015).

Table 5. Summary of studies that researched CNTs usage in cardiac tissue engineering

| CNTs nanomaterials | Scaffold | Result | Cell type | Applications | References |
|--------------------|---------|--------|-----------|--------------|------------|
| 1 | SWCNTs/Gelatin hydrogels | regulate the microenvironment of infarct myocardium to enhance the structural integration | Ventricular cardiac cells | therapeutic potential in engineering cardiac tissues to repair myocardial infarction | (Zhou et al. 2014) |
| 2 | EB-CNTs | lower proliferation and higher differentiation | embryoid bodies (EBs) | Enhance the cardiac differentiation and beating activity | (Ahadian, Yamada, et al. 2017) |
| 3 | PVA-CS-CNTs | enhance the adherence of MSCs to scaffold and non-toxic for cell growth | MSCs | Suitable platform for cardiomyogenic differentiation and cardiac applications | (Mombini et al. 2019) |
| 4 | CNT-Col substrates | improve cardiac differentiation | brown adipose-derived stem cells (BASCs) | More effective for cardiomyogenesis and potentially safer source for cardiac regeneration | (Sun et al. 2016) |
| 5 | SWCNT/collagen hydrogels | enhanced cell–cell alignment and functionality of cardiac constructs | cardiomyocyte | Candidate for pharmacologic treatments and serve as an injectable material for cardiac applications | (Sun et al. 2017) |
|---|--------------------------|-------------------------------------------------|----------------|---------------------------------------------------------------------------------|------------------|
| 6 | CNTs/GelMA hydrogels | support the cardiac differentiation of EBs via expression of several cardiac genes | mouse EBs | controllable platform for cell therapy applications | (Ahadian, Yamada, et al. 2016) |
| 7 | SWCNTs/gelatin scaffold | Improve cell proliferation, electrical excitability and enhance differentiation into cardiac phenotype | rat cardiomyoblasts | potentially enhance electrical excitability to make mature cardiac phenotype | (Cabiati et al. 2018) |
| 8 | MWCNT/decellularized pericardial matrix hydrogel | Increase cellular alignment and enhance connexin 43 expression of the hiPSC-derived cardiomyocytes | hMSCs and hiPSC derived cardiomyocytes | provide a promising material for stem cell therapy applications | (Roshanbinfar, Mohammadi, et al. 2019) |
| 9 | thiophene-MWCNTs/PCL | Induce cell proliferation and cell differentiation | cardiovascular progenitor cells (CPCs) | promising candidate for postmyocardial infarction myocardium | (Wickham et al. 2014) |
| 10 | MWCNTs/glass coverslips | Improve cell viability and proliferation and promote spontaneous electrical activity in cardiac myocytes | neonatal rat ventricular myocytes | MWCNTs are able to promote cardiomyocyte maturation | (Martinelli et al. 2012) |
| 11 | MWCNTs/glass coverslips | Induce the expression of cardiac-specific genes | neonatal rat ventricular myocytes | MWCNTs are able to promote physiological growth and functional maturation | (Martinelli et al. 2013) |
| 11 | MWCNTs/PDMS | Improve cell viability, proliferation, elongation, alignment, and retention | neonatal rat ventricular myocytes | provide a promising material for innovative therapies for cardiac repair | (Martinelli et al. 2018) |
|   | Material System                                                                 | Effect                                                                 | Cell Type                          | Application                                                                                     | Reference |
|---|----------------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------|------------------------------------------------------------------------------------------------|-----------|
| 12| CNTs/GelMA hydrogels                                                             | Induce the expression of several cardiac-specific genes and promote cell adhesion, spreading, retention, and viability | neonatal rat CMs                   | Incorporation of CNTs into gelatin could be useful in cardiac cell therapy applications        | (Shin et al. 2013) |
| 13| alginate coated CNTs/methacrylate/d collagen 3D printed cardiac patch            | Enhance cell attachment, elongation, proliferation and migration of human coronary artery endothelial cells | HCAECs                             | Potentially suitable as pre-vascularized hybrid cardiac patches for cell therapy applications | (Izadifar et al. 2018) |
| 14| SWCNTs/PNIPAAm hydrogels                                                        | Induce cardiogenic differentiation and improve cell adhesion, spreading, and proliferation of BASCs | brown adipose-derived stem cells (BASCs) | Myocardial application of SWCNTs/PNIPA Am hydrogels for improvement of cardiac tissue engineering | (Li et al. 2014) |
| 15| CNTs/GelMA hydrogels                                                             | Enhance mechanical properties and cell viability, spreading and proliferation | NIH-3T3 fibroblasts and hMSCs      | CNT incorporated GelMA can be useful for in vitro cell studies                                | (Shin et al. 2012) |
| 16| SWCNTs/GelMA hydrogels                                                           | Improve cell proliferation, differentiation and maturation into cardiac phenotype and enhance | H9C2 rat cardiomyoblasts           | Gel-SWCNT scaffolds is promising candidate for cardiac tissue engineering                       | (Cabiati et al. 2018) |
| 17| CNT/PLA scaffold                                                                 | Enhance cell elongation and cardiogenic differentiation of hMSCs        | hMSCs                              | CNT/PLA scaffold is promising candidate for electroactive tissue repair applications           | (Mooney et al. 2012) |
| 18| SWNTs/PU/gelatin scaffold                                                         | Improve electrical conductivity of the scaffold and enhance cell proliferation and adhesion | H9C2 cells and HUVECs              | SWNTs/PU/gelatin scaffold can be effective for cardiovascular tissue engineering               | (Tondnevis, Keshvari, and Mohandes 2020) |
|   | MWCNTs /PU scaffold | Enhance cytocompatibility, cell adhesion, and cell proliferation | H9C2 cells and HUVECs | potential application in cardiac tissue engineering |
|---|----------------------|---------------------------------------------------------------|-----------------------|--------------------------------------------------|
| 19 |                      |                                                               |                       | (Shokraei et al. 2019)                           |
|   |                      |                                                               |                       |                                                  |
| 20 | amino benzyl-CNTs/lysine reverse thermal gel | improve cardiomyocytes survival, proliferation, alignment, and maturation with expression of Actn and Cx43 proteins | cardiomycocytes | potential application in cardiac tissue engineering | (Peña et al. 2017) |

### 5.2.2. Graphene-based nanomaterials

Graphene-based nanomaterials (GBNs) is a two-dimensional carbon structure, which developed as a novel class of material with remarkable physicochemical properties and various applications (Amani et al. 2018; Xia et al. 2019). The GBNs including several graphene structures such as Graphene Oxide (GO), Reduced Graphene Oxide (RGO), Graphene Nanosheets, Few-Layered Graphene (FLG) and, Ultra-Thin Graphite have different varieties in surface properties, purity, size, and lateral dimensions. Various methods can be used for the preparation of GBNs depending on their applications such as micromechanical cleavage, chemical vapor deposition, epitaxial growth on silicon carbide, electrochemical synthesis, total organic synthesis, and other methods (Lü, Zhao, and Wang 2012). Graphene can be functionalized with various molecules since they have great surface chemical properties, which enhance their variety of applications (Jastrzębska, Kurtycz, and Olszyna 2012). GBNs are expected to exhibit specific interaction with biomolecules, cells, and tissues based on their number of layers, chemical functionality, dimensions, hydrophilicity, etc. The high surface area of graphene facilitates its cellular interactions (Goenka, Sant, and Sant 2014). The specific properties of GBNs, such as high conductivity, flexibility, and adaption to smooth/rough surfaces make them ideal for structural strengthening of tissue-based materials, and it has the ability to enhance the differentiation, proliferation, and adhesion of stem cells. For instance, functional groups of a scaffold, such as carboxyl, hydroxyl, and amine groups are crucial to regulating cell functions (Darvishi, Ahadian, and Savoji 2019). Graphene oxide is one of the most popular GBNs, which can be easily modified due to the functional groups in its structure such as hydroxyl, carboxyl, and epoxy. In addition,
GO can be easily converted by thermal and chemical reduction into RGO, which makes GO a successful precursor for the production of G-based composites. GO, RGO and other GBN composites can be chemically manipulated for interaction with different biological molecules such as proteins, peptides. Furthermore, GBNs have a high antimicrobial activity, which promotes their function in tissue engineering by reducing infections (Li et al. 2017; Shareena et al. 2018). Besides, hybridization of GO and RGO with other nanoparticles such as AgNPs (de Faria et al. 2014; Zhu et al. 2013), TiO₂ NPs (Akhavan and Ghaderi 2009) and, Fe₃O₄ NPs (Deng et al. 2014) can increase their antibacterial activity. All these specific features of GBNs, make them a popular tool in tissue engineering (Nayak et al. 2011; Shin, Li, et al. 2016). For example, Nayak and co-workers showed the effect of graphene synthesized with chemical vapor deposition (CVD) on the enhancement of GBNs ability for the differentiation of human mesenchymal stem cells. They reported that the large-scale surface characteristics induced by the ripples in the CVD graphene play a vital role in cell adhesion and differentiation. Furthermore, graphene's capacity to withstand lateral stress was thought to provide adequate local cytoskeletal resistance for differentiation of the bone stem cells (Nayak et al. 2011). Furthermore, GBNs have shown great potential to regulate the in vitro and in vivo cardiac differentiation by improving the electrical and mechanical conductivity of scaffolds and providing appropriate morphological indications. In a study by Lee et al. the vitronectin (VN) coated graphene effect on cardiomyogenesis of human embryonic stem cells (hESCs) was evaluated. They cultured hESCs on three different substrates including VN-coated graphene (graphene group), VN-coated glass (glass group), and glass coated with Matrigel (Matrigel group). The cultivation of hESCs on VN-graphene stimulated the expression of genes, which led to the gradual differentiation into the mesodermal and endodermal lineage. Ultimately, Graphene improved the cardiomyogenic differentiation of stem cells because of its roughness and upregulation of the ERK signaling pathway. As a result, graphene can provide a new approach for stem cell therapy for ischemic heart disease by improving the cardiomyogenic differentiation of hESCs (Lee et al. 2014). In another study by Ahadian and co-workers, graphene integrated into the structure of mouse embryoid bodies (EBs), which significantly improved cardiac differentiation of EBs (Ahadian, Zhou, et al. 2016a). Furthermore, Park et al. reported that MSCs coupled with GO showed an excellent cell survival in vivo for cardiac repair since the GO preserved the cells against reactive oxygen species. They developed the GO flakes to protect the implanted MSCs from ROS-mediated death thereby improving the therapeutic efficacy of the
MSCs (Park, Kim, Han, et al. 2015). In another study, RGO flakes with the thickness of 1–2 nm and the size range of 2–5 µm were inserted into hMSC spheroids, which led to an increase in cardiac specific-biomarkers. The high electrical conductivity of RGO and hybridization of RGO with hMSCs spheroids, enhanced heart repair and its function compared to RGO alone or hMSCs alone. One of the best advantages of this hybrid method is the efficient delivery of cells to damaged tissue, and multiple pharmaceutical molecules can be loaded onto the graphene for sustainable drug release (Figure 9) (Park, Kim, Ryu, et al. 2015). GBNs can combine with different scaffolds and enhance their electrical conductivity and mechanical properties. . In a recent study, Norahan et al. showed different biological and antibacterial effects of RGO coating on collagen scaffolds for cardiac patch applications. They showed that rGO significantly improved mechanical properties and the electroactivity of the collagen scaffolds (1100 ± 31 kPa, 4 × 10−4 ± 1.20 S/m). Electroactive RG-collagen scaffolds enhanced the expression of cardiac-specific genes such as Cx43, troponin-T and, actinin-4 compared to collagen scaffolds counterpart. Also, the coating of collagen scaffolds with RGO increased the antibacterial activity against E. coli, S. aureus, and S. pyogenes, which can reduce the chance of the infection (Norahan, Pourmokhtari, et al. 2019).
Figure 9. A) Schematic illustration of RGO flake and MSC spheroids for the treatment of myocardial infarction. B) The effect of implanting MSC–RGO hybrid spheroids on cardiac function and regeneration a) Capillary density in the peri-infarct border zone assessed by immunostaining b) Masson's trichrome staining for the indication of cardiac fibrosis (blue). c) Expression of Cx43 (red) in the infarct zone by immunohistochemical staining. C) Characterization of gap junctions in MSC–RGO hybrid spheroids with calcein AM (green) and
Dil (red) staining (the yellow colors show the transfer from green to red) (Park, Kim, Ryu, et al. 2015). (this figure has been reproduced from (Park, Kim, Ryu, et al. 2015) with permission from John Wiley and Sons, Copyright 2015).

Table 6. Graphene-based nanomaterials applied in cardiac tissue engineering applications

| Graphene-based nanomaterials | Scaffold | Result | Cell type | Applications | References |
|-----------------------------|----------|--------|-----------|--------------|------------|
| 1                           | GO/alginate | Increase cardiac maturation and cell viability under oxidative stress | MSCs + cardiomyocytes | Improve cardiac function and high cell protection capacity | (Choe et al. 2019) |
| 2                           | Graphene substrate | Promote maturation hiPSC-derived cardiomyocytes | hiPSCs | Induce cardiomyocyte development and enhance electrophysiological function | (Wang et al. 2017) |
| 3                           | Vitronectin (VN) - coated graphene | Promote cardiomyogenic differentiation | hESCs | Suitable platform for the development of stem cell therapies for ischemic heart diseases | (Lee et al. 2014) |
| 4                           | GO/collagen | Induce angiogenesis and enhance expression of several cardiac genes | neonatal cardiomyocyte | Appropriate cardiac patch for cardiovascular applications | (Norahan, Amroon, et al. 2019) |
| 5                           | graphene film | Enhance biocompatibility, cell attachment, cell proliferation and normal contractile activity of CMs | adult rat CMs | graphene materials are excellent supports for the biological cells applications | (Kim et al. 2013) |
| 6                           | graphene embedded EBs | Enhance cell differentiation, mechanical and electrical properties but decrease cell proliferation of EBs | mouse embryoid bodies (EBs) | affect in directing the cardiac differentiation of EBs | (Ahadian, Zhou, et al. 2016b) |
|   | Material                      | Effects                                                      | Cell Types                        | Potential Applications                                                                 | References                      |
|---|-------------------------------|--------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------|----------------------------------|
| 7 | graphene coated coverslips   | Promote the cardiomyogenic differentiation of hMSCs and enhance expression of several cardiac genes and ECM-associated proteins | hMSCs                            | Suitable platform for stem cell therapies                                              | (Park et al. 2014)               |
| 8 | GO flakes                     | Enhance cell attachment, survival, and cell–ECM interaction  | hMSCs                            | GO can be utilized to protect therapeutic cells implanted into various ROS abundant damaged tissue | (Park, Kim, Han, et al. 2015)    |
| 9 | rGO flakes                    | Improve cell–ECM interaction and promote the expression of several cardiac genes and secretion of paracrine growth factors | hMSCs                            | GO can be utilized to improve cardiac repair and cardiac function of the infarcted myocardium | (Park, Kim, Ryu, et al. 2015)    |
| 10| PLL/GO nanofilm              | Promote cell viability, proliferation, elongation, organization, and maturation | neonatal rat CMs, ECs, and hMSCs | Potential application in cardiac tissue engineering                                     | (Shin et al. 2014)              |
| 11| rGO/GelMA hydrogel           | Enhance cell viability, proliferation, and maturation of cardiomyocyte | neonatal rat CMs                 | rGO incorporated hybrid hydrogels can potentially used for drug studies and cardiac tissue engineering | (Shin, Zühlmann, et al. 2016)    |
| 12| rGO/silk fibers              | Improve maturation of cytoskeleton structure and enhance the expression of several cardiac proteins such as Actn, cTnl, and Cx43 | neonatal rat CMs                 | Great potential of rGO/silk fibers for the regeneration of functional excitable tissues | (Zhao et al. 2018)              |
| 13| rGO/silk fibers              | Improve biocompatibility and enhance cell attachment with expression of several cardiac functional genes | TBX18-transduced hiPSCs          | Suitable candidate for cardiac tissue engineering                                       | (Nazari, Heirani-Tabasi, Hajiabbas, Khalili, et al. 2020) |
5.3. Polymeric nanomaterials

One of the main aspects of tissue engineering is controlling the stem cells’ behavior, which can be achieved by traditional ways such as utilizing growth factors and cell signaling molecules. However, such methods are inadequate, due to the erratic distribution, short half-life, limited tissue penetration, and enzymatic degradation of growth factors. These limitations can be overcome by the incorporation of growth and signaling factors with polymeric nanomaterials (natural or synthetic) as a vehicle for the delivery of growth factors. These factors can either load into or absorb to the surface of various polymeric nanomaterials structures such as polymeric nanoparticles (sphere or capsules) and hydrogels (Sharma 2019; Yadav et al. 2019). Other polymeric structures are conductive polymers such as Polypyrrole and Polyaniline that can be synthesized as a scaffold for cardiac tissue engineering, thereby, improving the cardiac cells migration, proliferation, and differentiation (Ashtari, Nazari, Ko, Tebon, Akhshik, Akbari, Alhosseini, Mozafari, Mehravi, and Soleimani 2019). Gelmi and coworkers investigated the culture of human iPSCs in PLGA fibers with a layer of Polypyrrole (PPy). The PLGA fibers coated PPy increased the cell viability and expression of specific cardiac markers (Actinin, Myh6, Nkx2.5, GATA4, c-kit) without any cytotoxic effects. This study showed the first application of PPy as an appropriate supportive conductive material and a dynamic mechanical stimulating fiber scaffold for hiPSCs (Gelmi et al. 2016). Also, some studies incorporated Polyaniline into different polymers and hydrogels to produce electrically conductive scaffolds for cardiac tissue engineering. Polyaniline is one of the commonly observed conductive polymers, offering simple synthesis, controllable electrical properties, and environmental stability (Cui et al. 2013; Qazi et al. 2014; Dong et al. 2016). Combining Polyaniline with various biological materials can improve its biocompatibility. For example, Moura and co-workers functionalized Polyaniline with
polyglycerol dendrimers with high hydrophilicity and showed this combination increased the capacity of the scaffold to support the cardiac cells adhesion and proliferation (Moura and de Queiroz 2011). In a recent study by Roshanbinfar et al. the effect of electrospun fiber mats with different conductive materials such as polyaniline, collagen, and hyaluronic acid on cardiomyocyte attachment and contraction was investigated. They tested various concentrations of polyaniline in the nanofibrous composite and showed fiber mats contained polyaniline (1.34%) had the most desirable properties with a longer contraction time, lower beating rates, and greater contractile amplitude (Figure 10) (Roshanbinfar et al. 2020). The unique feature of piezoelectric scaffolds such as Polypyrrole and Polyaniline in generating electric charge with little mechanical forces make them attractive in cardiac tissue engineering applications. Hitscherich and co-workers utilized a piezoelectric scaffold made from electrospun polyvinylidene fluoride-trifluoroethylene (PVDF-TrFE) and evaluated its effect on mouse embryonic stem cell-derived cardiomyocytes (mES-CM). They cultured mES-CM on PVDF-TrFE and showed that the expression of cardiac genes increased in the mES-CM, and these cells contracted automatically with an exhibition of well-organized sarcomeres. This study Illustrated the efficacy of PVDF-TrFE scaffolds as a suitable material for the production of engineered cardiovascular tissues using stem cells (Hitscherich et al. 2015).
Figure 10. A) Morphology properties of various electrospun scaffolds. B) Microstructure of various fiber mats with confocal microscopy (the yellow arrow shows the presence of polyaniline in the scaffold). C) Expression of the cardiomyocyte-specific markers (troponin I, sarcomeric-α-actinin) for neonatal cardiomyocytes cultured at day 5. D) Confocal image of cardiomyocyte-specific markers (troponin I, sarcomeric-α-actinin) for hiPSC-derived cardiomyocytes cultured on electrospun fiber mats at day 5 (Roshanbinfar, Vogt, et al. 2019). (this figure has been reproduced from (Roshanbinfar, Vogt, et al. 2019) with permission from John Wiley and Sons, Copyright 2015).
Table 7. Examples of the use of polymeric nanomaterials in cardiac tissue engineering

| Polymeric nanomaterials | Scaffold | Result | Cell type | Applications | References |
|-------------------------|---------|--------|-----------|--------------|------------|
| 1                       | Collagen–HA–PANI fibers | Improve electrical conductivity and mechanical properties as the native myocardium | cardiomyocytes | Suitable substrates for cardiac tissue engineering | (Roshanbinfar et al. 2020) |
| 2                       | PLGA + Simvastatin conjugated nanoparticles (SimNPs) | Induce Proliferation and Migration Activities of hAdSCs | AdSCs | Induce endogenous cardiac regeneration and improve cardiac function in myocardial infarction | (Yokoyama et al. 2019) |
| 3                       | PANI/PCL patch | promote the cardiomyogenic differentiation of hMSCs | hMSCs | PANI/PCL patch potentially enhance the regeneration of damaged myocardium | (Borriello et al. 2011) |
| 4                       | PGS/aniline trimer scaffold | enhance cell proliferation, alignment, and elongation of H9C2 cells | H9C2 cells | Suitable polymeric films for cardiac tissue repair and regeneration | (Hu et al. 2019) |
| 5                       | Silk/PPy composite scaffolds | Increase cell viability cellular organization and sarcomere development | hPSC-derived cardiac cells | appropriate substrate for cardiovascular applications | (Tsui et al. 2018) |
| 6                       | PU-AP/PCL scaffold | Enhance cell proliferation and expression of several cardiac genes | rat cardiomyocyte | PU-AP/PCL scaffold is useful for tissue engineering and regenerative purposes | (Baheiraei et al. 2015) |

6. Conclusion and future perspective

Cardiovascular diseases that involve the heart and blood vessels can be introduced as the number one cause of death worldwide in the past few years (Ashammakhi, Ahadian, Darabi, et al. 2019). The rapid development of nanotechnology provides various nanomaterials with diverse features. The combination of nanomaterials and stem cell research offers new approaches for the treatment of various cardiovascular diseases since the regeneration ability of cardiovascular tissues is quite limited compare to other organs. However, various bulk and surface properties of nanomaterials
can affect stem cell behaviors by modulating underlying intracellular pathways. Understanding these features and their effect on cellular behavior opens new effective ways to take control of stem cell fate, which is crucial in designing new nanomaterials suitable for cardiac tissue engineering. The surface properties of nanomaterials can control stem cell attachment. For example, hydrophilic surfaces enhance cell adherence and cell spreading on the surface of nanomaterials. Moreover, the surface topology is the determinant of cell arrangement and cell alignment on the surface of nanomaterials. After cell attachment, migration, proliferation, and differentiation are the next steps for directing stem cells towards cardiac cell lineage. For example, it has been shown that large pore sizes in biomaterials increase angiogenesis, cell migration, and proliferation (Zeltinger et al. 2001). Furthermore, various properties of nanomaterials can induce differentiation of stem cells into cardiac cells. Li et al. showed that controlling the mechanical properties is enough for inducing MSCs differentiation into cardiomyocytes by designing a hydrogel with a Young’s modulus of 65 kPa (Li et al. 2012). Nevertheless, before using nanomaterials in clinical applications, several factors should be considered thoroughly. For example, the toxicity of nanomaterials should be investigated in depth since some nanomaterials can be quite toxic. Generally, the metallic nanoparticles are more toxic compared to other nanoparticles. Moreover, soluble nanoparticles showed more toxicity compared to the particles, which bind to a substrate. Functionalization of a substrate with metallic nanoparticles could be an efficient way for cardiovascular tissue engineering. On one hand, the functionalization of a substrate can decrease the toxicity related to metallic nanoparticles and in another hand, the electrical conductivity of such particles can efficiently benefit the differentiation and alignment of stem cells. Furthermore, electroconductive nanomaterials not only can mimic the myocardial ECM but also can support the electromechanical integration of cardiomyocytes (Ashtari, Nazari, Ko, Tebon, Akhshik, Akbari, Alhosseini, Mozafari, Mehravi, and Soleimani 2019). In addition to metallic nanoparticles, graphene base nanomaterials and intrinsically conductive polymers (polypyrroles, polythiophenes, poly (3,4-ethylenedioxythiophene), polyanilines, etc) can be used in cardiovascular tissue engineering. Undoubtedly, the biocompatibility of carbon-based nanomaterials and the mechanical properties of conductive polymers should be investigated thoroughly. Consequently, numerous challenges should be overcome to utilized nanomaterials to address CVDs treatment’s obstacles in clinics.
Conflict of interest
The authors declare no conflict of interest.

Acknowledgements
# H. Arzaghi, B. Rahimi and B. Adel contributed equally to this work.
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