Chapter

Regulation of Angiogenesis Using Nanomaterial Based Formulations: An Emerging Therapeutic Strategy to Manage Multiple Pathological Conditions

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Abstract

Angiogenesis is an indispensable biological process, any aberrancy associated with which can lead to pathological manifestations. To manage different pathological conditions associated with abnormal angiogenesis, Nanomaterial based formulations have been tested in *in vitro* and *in vivo* models by different groups. The research advancements pertaining to the applications of major candidate nanomaterials for the treatment of pathologies like tumor, cardiovascular diseases, diabetic retinopathy, age related macular degeneration, chronic wounds, impaired osteogenesis and nerve tissue degeneration, have been briefed in this chapter.

Keywords: angiogenesis, nanomaterials, tumor, cardiovascular diseases, diabetic retinopathy, age related macular degeneration, chronic wounds, osteogenesis, nerve tissue degeneration

1. Introduction

Angiogenesis is an important biological process which involves the development of new capillary network from the pre-existing vasculature [1, 2]. The process of angiogenesis is indispensable in supplying oxygen and nutrients to cells under hypoxia, and it has been implicated in different physiological processes such as wound healing, embryogenesis etc. It has also been reported to play key role in many pathologies including diabetic retinopathy and cancer [3]. Angiogenesis is a multi-step process, which commences when the primary, pro angiogenic cytokine, VEGF, is secreted by the cells experiencing hypoxia. Thereafter the interaction of VEGF with its receptor (VEGFR2) on the nearby endothelial cells (EC), leads to EC activation, proliferation, migration, extra cellular matrix (ECM) remodeling, tube formation followed by loop formation leading finally to neo vessel formation and vascular stabilization [4, 5].

The process of angiogenesis is regulated by multiple factors, which may be pro- or anti-angiogenic in nature. The endogenous pro angiogenic factors include growth factors like VEGF, PDGF, FGF, EGF, angiopoietin-1, interleukin-8, placental growth

factor, angiogenin etc. The anti- angiogenic factors include endostatin, angiostatin, prolactin, fibronectin, vasostatin, interleukin-12, platelet factor 4 etc. [6, 7]. An equilibrium exists between the pro- and anti-angiogenic factors under physiological conditions, and any disturbance in that equilibrium would result in pathological manifestations [3]. Targeting angiogenesis therefore has drawn huge attention with respect to the therapeutics of pathologies were excessive or insufficient angiogenesis prevails [7]. One of the major approaches in angiogenesis targeted therapy involves targeting VEGF signaling pathway. Humanized monoclonal antibody targeting VEGFA, namely, Bevacizumab, with the approval of US Food and Drug Administration (FDA), has been employed in a combination therapy for the treatment of metastatic colorectal cancer [8]. In addition, an aptamer which inhibits VEGF 165, namely, Pegaptanib has been approved by FDA to treat Age related macular degeneration [9]. In spite of all such interventions, targeting angiogenesis demands much more explorations due to a variety of unresolved issues such as development of resistance to antiangiogenic therapy, lack of adequate treatment for ischaemic disorders etc. [10].

In an urge to overcome the limitations of conventional angiogenic therapy, researchers globally have focused on developing 'nanomedicines' for the treatment and diagnosis of various diseases associated with aberrant angiogenesis [11]. The field of nanomedicine involves the use of nanomaterials for biological and medicinal applications by virtue of their ability to interact with nucleic acids, proteins and membrane receptors effortlessly [10]. In this chapter, we have therefore focused on various research achievements pertaining to candidate nanomaterials that can be developed as potential drugs for angiogenic therapy.

2. Nanomaterials

The class of substances having at least one dimension less than 100 nano meters are called nanoscale materials and the field of science that deals with the synthesis, study of structure, physical and chemical properties and applications of various types of nanoscale materials is referred as Nanotechnology [12]. Nanomaterials usually occur as zero, one, two and three-dimensional structures. Generally, the nanoparticles are comprised of three layers called the surface layer, the shell layer and the core. The core is the central portion of the materials surrounded by the shell and surface layer. The shell layer is chemically different from the core and the outer layer. The surface layer permits surface modification with a variety of moieties like polymers, metal ions, and surfactants [13]. The physical and chemical properties of bulk materials are independent of their size, however, when converted into nano scale materials their optical, physical, mechanical and chemical properties vary according to their size [14]. Such properties include solubility, color, toxicity etc. The major reason for these improved properties of nanomaterials are due to their high surface mass ratio as compared with the bulk [15]. Due to their unique size, shape, structure and solubility they have found application in the biomedical, optical, sensor, electric and energy harvesting fields. Many nanomaterials are already being explored for their use in biomedical imaging [16], bio/chemical sensing [17], targeted gene and drug delivery [18]. We here focus on candidate nanomaterials which are potential nanomedicines in the field of therapeutic angiogenesis.

2.1 Classification of nanomaterials according to chemical composition

Based on the origin, size, morphology and chemical composition, nanomaterials are divided into various categories. In the present chapter we are focusing on some of the important classes that have found applications in biological field.

2.1.1 Metal nanoparticles

Metal nanoparticles are those particles which may be the pure metal or metal compounds like metal oxide, hydroxides, sulphides etc., exhibit size in the sub-micron scale. A variety of metal nanoparticles has been synthesized with varied structural morphology, size and compositions [19]. These metal nanoparticles can be synthesized from various metal precursors and can be functionalized with several groups [20]. The metal nanoparticles permit surface modification with various chemical functional groups and further allow them to be conjugated with polymers, ligands, antibodies etc. The improved surface mass ratio, shape, morphology and functionality, quantum confinement and plasmon excitation make them suitable for the applications in the field of energy, catalysis, electronics, and medicine [21]. However, they show some demerits such as tendency to get agglomerate and chances of formation of impurities due to their high reactivity. Many of the nanomaterials except gold, silver, and platinum exhibits high cyto-toxicity.

2.1.2 Carbon-based nanomaterials

Among the various carbonaceous nanomaterials, the zero-dimensional carbon-based quantum dots (CQDs and GQDs), one-dimensional carbon nanotubes (CNTs) and two-dimensional graphene (GR) are currently the most popular nanocarbon representatives in biological applications [22]. Carbon-based QDs are the recent extension in the nano carbon family with fascinating properties like biocompatibility, resistance to photobleaching and attractive photoluminescence. These outstanding properties make them smart candidates for bioimaging, sensing, drug delivery and cancer therapy [23, 24]. CNTs have a unique 1D nanostructure, with sp^2 hybridized carbon atoms rolled up to design a cylindrical shape. They exist as both single-walled CNTs and multi-walled CNTs depending on the number rolled-up graphene sheets. Due to their exceptional structural, mechanical, and electrical diversities, they deliver remarkable flexibility, strength, and electrical properties suitable for various biological applications like medical diagnostics, sensing and treatment of diseases. Graphene represents the 2D nano allotrope of carbon illustrating a planar graphitic structure with sp^2 hybridized carbon network. Its surpassingly large surface area, easy functionalization and chemical purity makes it a potential candidate for drug delivery. Moreover, it is also widely explored for *in vivo* imaging and cancer detection.

2.1.3 Polymeric nanoparticles

Polymeric nanoparticles are constructed with the aid of natural or synthetic polymers. As compared to other nanoparticles, they offer advantages like non-toxicity and biocompatibility suited for specific biological applications. Although they are used for biosensing and bioimaging, the major purpose of polymeric nanoparticles lies in the field of drug delivery [25]. Biomolecules or drugs are encapsulated into polymeric nanoparticles to obtain a gradual and continuous release of the drugs at the specifically targeted sites.

2.1.4 Ceramic nanoparticles

Nanoscale ceramics, which include various ceramic nanoparticles of zirconia, hydroxyapatite, alumina and titanium oxide have also found potential biological applications. Some of the distinct features like high load capacity, stability and effortless incorporation to hydrophilic and hydrophobic systems enhance

their efficiency in the field of biomedicine, however, work on scaling down its cytotoxicity remains to be addressed before its full-fledged use in the biological system [26].

2.1.5 Semiconductor nanoparticles

Semiconductor nanoparticles, particularly QDs have been heavily explored for a wide variety of biological applications like biosensing, molecular imaging, live-cell labelling and drug delivery. They possess unique optical properties like a long fluorescence lifetime and low photobleaching when correlated with conventional organic dyes and fluorescent polymers [27]. Although, the toxicity of the traditional semiconductor QDs is a typical concern that has to be addressed for *in vivo* applications.

2.1.6 Lipid-based nanoparticles

Lipid-based nanoparticles, consisting of liposomes, nanostructured lipid carriers and solid lipid nanoparticles have gained tremendous attention in the field of cancer treatment and drug delivery. These nanoparticles exhibit very low toxicity, can act as a carrier for both hydrophilic and hydrophobic molecules and ensures controlled release of drugs. Due to its versatility and biocompatibility, liposomes are the extensively utilized lipid-based nanoparticles [28].

3. Nanomaterial mediated therapy for pathologies with aberrant angiogenesis

Abnormal or excessive angiogenesis has been reported to be involved in the progression of a wide variety of diseases affecting different organs. For example, aberrant angiogenesis has been implicated to promote diseases like tumor, auto immune disorders and infectious diseases caused by the pathogens inducing angiogenesis and such diseases have been reported to affect multiple organ systems [29]. Further, it has also been reported to be involved in the advancement of skin tissue associated diseases like psoriasis, allergic dermatitis, blistering disease, scar keloids etc. In addition, it has been reported to be the major cause for diabetic retinopathy and choroidal neovascularization associated with wet type AMD, which affect the eyes [29]. Abnormal angiogenesis has also been reported to be involved in the progression of blood vessel associated disorders like atherosclerosis, transplant arteriopathy etc. [30]. The involvement of angiogenesis has also been reported in the progression of primary pulmonary hypertension, asthma and nasal polyps [29]. In addition, it has also been reported in the progression of diseases that affect the reproductive system, which include ovarian hyper stimulation, endometriosis etc. [31]. Aberrant angiogenesis has also been the leading cause for the progression of diseases like osteomyelitis which is characterized by impaired osteogenesis [29]. It has also been reported to promote nerve system associated diseases like diabetic neuropathy and amyotrophic lateral sclerosis, which are characterized by nerve tissue degeneration [32]. The process of angiogenesis has also been reported to promote physiological processes like wound healing and discrepancy associated with that could lead to complications like development of chronic wounds [33]. Different candidate disorders associated with aberrant angiogenesis and the candidate nanomaterials that can be developed as potential drugs for the treatment of such disorders have been detailed below.

3.1 Tumor

The essentiality of angiogenesis in the progression of tumor growth was a breakthrough finding by Judah Folkman way back in 1971, which opened up an era of investigations, concerned with targeting angiogenesis for cancer therapeutics. It has been established that a tumor cannot grow beyond 2 mm in diameter without a steady supply of oxygen and nutrients by means of angiogenesis [34–36]. Therefore, preventing the neovascularisation has been suggested as one of the key strategies for cancer therapeutics. Angiogenesis in a tumor micro environment, unlike that under physiological conditions, is characterized by the formation of immature, leaky blood vessels, resulting in a continual state of inflammation. This happens mainly due to the increased expression of a variety of pro angiogenic factors including VEGF, angiopoietin, integrins etc. and such factors are being targeted for anti-angiogenic therapy. Anti-angiogenic agents targeting VEGF, such as Bevacizumab has been approved by FDA, however, release of other pro angiogenic factors over ruled the efficiency of such mono-therapies [37–40]. Therefore, combination therapies using multiple anti-angiogenic agents were more appreciated to quick fix resistance to angiogenic monotherapy.

Nanoparticles (NPs) could be employed as a vehicle to deliver multiple drugs, targeting different molecules and pathways associated with tumor angiogenesis [37, 41]. The therapeutic drugs are generally loaded on to the NPs either by chemical conjugation or by encapsulation [38]. The NP-based drug delivery can either be passive or active in mode. The presence of leaky blood vessels in the vicinity of tumors facilitates the passive extravasation of NPs with size less than 200 nm into the tumor site by the Enhanced Permeability and Retention effect (EPR) and such NPs are later on cleared by the liver [39, 42]. In addition, limited lymphatic drainage facilitates the retention of NPs at the site of tumors which in turn promotes sustained drug delivery [39]. It has been reported that NP conjugated Doxorubicin [43, 44] and small molecule inhibitors of angiogenesis [45] could accumulate in the tumor micro environment by EPR effect, which lead to the stoppage of tumor angiogenesis and tumor growth [38]. Further, Caplostatin (TNP-470), an angiogenic inhibitor, has been reported to get selectively piled up in the blood vessels associated with tumors by EPR effect which in turn blocked tumor associated vascular hyperpermeability [46, 47]. The Active targeting of tumor vasculature by NPs is achieved by means of ligands presented on NP surfaces. The ligands would selectively bind to receptors which are over expressed on tumor cells as well as on tumor associated ECs, such receptors include VEGFRs, αvβ3 integrins etc. [38, 48].

NP mediated targeting of different miRNAs have also been tested for their therapeutic efficacy [49]. For instance, treatment with NP containing anti-miR-21 (CTX-SNALP-anti miR-21) has been reported to silence miR-21 in patients with glioblastoma resulting in an increase in the levels of its target gene RhoB both at mRNA and protein levels. Further, NP mediated administration of anti-miR-21 has been reported to inhibit tumor proliferation, induce apoptosis and promote survival rate in the animal model [49]. Exosomes are endogenous lipid-based NPs which are involved in the transfer of biomolecules like RNA and proteins between cells. It has been reported that miR-23a encapsulated exosomes could effectively induce angiogenesis in CAM model as well as in *in ovo* xenograft model by regulating the expression of SIRT1 gene [50].

Different metal NPs like gold and silver NPs have been reported to be effective for anti-angiogenic therapy. It has been reported that gold NPs (AuNPs) are capable of binding to the heparin binding domains of various growth factors like VEGF165 and bFGF leading to the conformational changes associated with the impaired functioning of such growth factors. AuNP mediated inhibition of VEGF was found

to be negatively regulating the phosphorylation of VEGFR2. The inhibitory effect of AuNPs on Heparin binding growth factors (HB-GFs) was found to be greatly depended on the size of AuNPs, further, AuNPs with 20 nm in diameter exhibited maximum inhibitory effect. In addition, AuNP with bare surface was found to be essential for the inhibitory effect on HB-GFs. Further, AuNPs have been reported to block of MAPK pathway in tumor cells which lead to the inhibition of epithelial to mesenchymal transition (EMT) and thence, the process of metastasis [51, 52].

AuNP has also been used as the carrier tool for drug delivery. It has been used to deliver an anti-EMT agent, Quercetin (Qu) and AuNP-Qu was found to be more effective when compared to free Qu, in inhibiting cell migration in MDA-MB-23 and MCF-7 cell lines [53]. In addition, recombinant human endostatin (rhES), an anti- angiogenic molecule, which in conjugation with AuNP-PEG (rhES-AuNPs-PEG), when administrated, targeted tumor cells more efficiently and exhibited better performance when compared to rhES. Moreover, the administration of rhES-AuNPs-PEG in combination with 5-flouro uracil (5-FU) facilitated improved localization of 5-FU on to the tumor site with subsequent reduction in tumor size than that in case of mono therapeutic administration of 5FU [54].

Silver NPs (AgNPs) have been reported to inhibit VEGF induced cell proliferation, migration and tube formation in bovine retinal endothelial cells (BRECs). It has also been reported to inhibit vessel formation in matrigel plug assay system. AgNP mediated anti angiogenic effect was found to involve negative regulation of PI3K/Akt pathway [55, 56]. According to a different study, AgNP has been reported to exert anti angiogenic effect by inhibiting HIF-1 in a dose dependant manner [57].

In addition to metal NPs, NPs based on cationic polysaccharides like chitosan has also been explored for biomedical applications taking an advantage of their relatively low toxic nature and high biodegradability and biocompatibility. Chitosan NPs (CNPs) showed anti-cancer effect in the xenograft model of hepatocellular carcinoma by inhibiting the expression of VEGFR2 and thereby negatively regulating the process of tumor angiogenesis [58]. Further, CNPs in conjugation with Ursolic acid (CH-UA-NPs) have been shown to inhibit cell migration and tube formation in human umbilical vein endothelial cells (HUVECs) *in-vitro*. In addition, CH-UA-NPs have also been reported to inhibit the expression of VEGF in hepatoma cell xenografts [59]. CNPs have also been utilized as a vehicle for the co delivery of psiRNA VEGF and pIL-4 in MCF-7 cells which caused relatively huge reduction in the levels of VEGF protein when compared to the cases where the plasmids were used individually [60].

Ruthenium modified selenium NPs (Ru-SeNPs) have also been reported to exhibit anti angiogenic properties, in CAM model as well as in HUVEC cells, mainly by inhibiting the phosphorylation of Akt, FGFR1 and Erk1/2. Further, it has been shown that SeNPs protected with Ru (II)-thiols (Ru-MUA@Se) was endocytosed by the cells by clathrin mediated mechanism [61]. SeNPs have also been used as a carrier tool for siRNA delivery. A pH sensitive, modified SeNP carrying VEGF-siRNA, namely, G2/PAH-Cit/SeNPs@siRNA, has been shown to exhibit high efficiency in terms of cellular uptake, drug release and gene silencing [62].

The cerium oxide NPs (CONPs) have been reported to exhibit anti-oxidant activity and they are characterized by a cerium core and a shield with an oxygen lattice. Chen et al., have shown that CONPs are capable of inhibiting reactive oxygen species (ROS) induced angiogenic signaling pathways [63]. In addition, the nanoceria conjugated with heparin was reported to inhibit the proliferation of human coronary artery endothelial cells (HCAECs) in a better way than that by unconjugated nanoceria [64]. Nanoceria has also been reported to inhibit the

proliferation of ovarian cancer cells in xenograft model *in-vivo* [65]. Further, the nanoceria conjugated with folic acid has also been reported to inhibit proliferation and angiogenesis in xenografts of ovarian cancer cells *in vivo* [66]. The anti-angiogenic effect imparted by nanoceria was reported to involve the inhibition of VEGF signaling pathway leading to the decreased phosphorylation of VEGFR2 at Tyr1173 and Y951 [65]. However, a report by Das et al., have suggested that nanoceria might exhibit pro angiogenic effect also [67], making the use of these NPs as anti-angiogenic molecules doubtful under clinical setup.

Silica based NPs have also been reported to exhibit anti angiogenic properties. Silicate NPs (SiO_2 NPs) have been reported to inhibit VEGFR2 phosphorylation and ERK1/2 activation in human micro vascular retinal endothelial cells (HMRECs), thereby inhibiting angiogenesis [68]. Mesoporous silica based nanoparticles (MSNs) have been used as a vehicle for the targeted delivery of chemotherapeutic agent, doxorubicin hydrochloride (MSNs@DOX). MSNs@DOX has been reported to suppress the metastasis of lung cancer cells by inhibiting VEGF induced angiogenesis [69]. Further RGD (Arg-Gly-Asp) modified MSN has been used as a carrier tool for the targeted delivery of anti-angiogenic agent, NAMI-A [70].

Further, MoS_2 nanoflakes containing ZnO NPs were found to inhibit tumor growth in *in-ovo* xenograft model by inducing apoptosis and by negatively regulating the processes of angiogenesis as well as EMT [71]. Similarly, the Tetraiodothyroacetic acid (Tetrac) based NPs have also been reported to be anti-angiogenic in nature in CAM model and in xenograft model of renal cancer cells [72]. Shereema et al., have formulated a green luminescent CQDs, which inhibited angiogenesis in CAM model by negatively regulating the expression levels of pro angiogenic factors including VEGF and FGF. The CQDs showed anti-cancer property *in vitro*, suggesting it to be a potential drug candidate for targeting tumor angiogenesis [73]. The applications of nanomaterials for anti tumor therapy have been represented schematically in **Figure 1**.

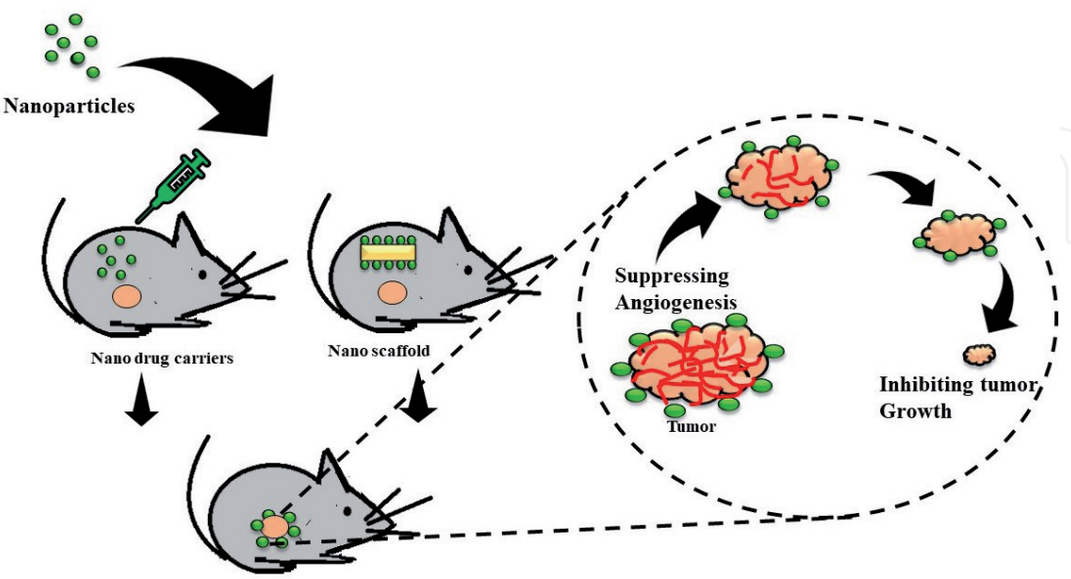

Figure 1.
Applications of nanomaterials in anti-tumor therapy. Many candidate nanomaterials possess intrinsic anti-angiogenic property and few could be used as vehicles for targeted drug delivery. Nanoparticles encapsulated/conjugated with anti- angiogenic drugs or nanoparticle based anti-angiogenic scaffolds, when administrated in in vivo models, precisely target tumor vasculature and inhibit tumor growth.

3.2 Cardio vascular diseases

Cardio vascular diseases (CVDs), which refer to a class of ailments encompassing coronary artery disease (CHD), peripheral arterial disease, cerebrovascular disease etc., account for the leading cause of death worldwide [74, 75]. Atherosclerosis is the most prevalent pathology behind CVDs, which involves the local accumulation of cholesterol within the walls of medium and large arteries leading to the emergence of atherosclerotic plaque [76, 77]. The process of angiogenesis has been implicated to play key role in plaque growth and intra plaque hemorrhage leading to plaque rapture [78, 79]. The application of nanomaterials has found its way in the diagnosis as well as treatment of CVDs. Integrin αvβ3 has been found to be over expressed in ECs actively involved in angiogenesis, thus, it has been targeted using NPs for CVD diagnosis [80]. For instance, in a murine model of hind limb ischemia, ^{76}Br- labeled multivalent dendrimers conjugated with integrin αvβ3 targeting peptides, were utilized for the detection of angiogenesis by positron emission tomography-computed tomography (PET-CT) [81]. In a different experiment using murine model of hind limb ischemia, a natriuretic peptide receptor C- targeted, ^{64}Cu labeled NP probe was used for the detection of angiogenesis [82]. Further, gadolinium-loaded perfluorocarbon (PFC) NP conjugated with a vitronectin antagonist peptide mimic, has been suggested to be a promising candidate for the detection of atherosclerotic lesions [83]. In addition, PFC NPs incorporated with anti-angiogenic drug, Fumagillin, have been implicated for the treatment of plaque angiogenesis [84].

3.3 Chronic wounds

Wounds are the disruption of the normal physiology of the skin, mucosal surfaces or organs, which occur as a part of a disease or etiology. The process of wound healing is divided into four distinct stages: hemostasis, inflammation, proliferation, and tissue remodeling. Injuries that show delayed healing up to 12 weeks after the initial insult are termed chronic wounds, often it happens because of various reasons such as persistent pathological inflammation [85], complications of ischemia, diabetes mellitus, or chronic venous insufficiency [86]. The application of growth factors has been employed to improve wound healing by promoting angiogenesis, but it possessed some drawbacks like rapid degradation of the candidate growth factors and the lack of controlled and localized delivery system.

Different NPs have been reported to promote wound healing, and many of them were implicated as drug carriers. Studies have shown that different metal ions-based nanomaterials possess the ability to promote angiogenesis and thereby induce wound healing [87, 88]. The metal ions such as Sr^{2+} and Co^{2+} when combined with nano bioactive glass showed pro angiogenic activity [89]. Colloidal AuNPs have been widely studied for biomedical applications due to their unique surface characteristics as well as optical and electronic properties [90]. AuNPs combined with epigallocatechin gallate and α-lipoic acid, reduced oxidative stress and inflammation and augmented angiogenesis, which led to cutaneous wound healing in rodent models [91]. The increased surface area of spherical AuNP helps in electron acceptance and also in scavenging reactive oxygen species that cause oxidative stress and impaired wound healing [92]. Formulation of AuNPs and scrambled peptides were reported to be suitable for angiogenic modulation in *in vivo* and *in vitro* models [93]. Moreover, NPs encapsulated in a microparticle developed by the microfluidic method provided a way to introduce a wide range of proteins including pro angiogenic agents to the injury site [94].

Low expression levels of angiogenic growth factors lead to impaired angiogenesis and wound healing. Heparin mimetic peptide nanofiber scaffolds have been used to overcome this situation, which showed improved vascular development associated with enhanced VEGF production in the treated animals. Also, hierarchically micro-patterned nanofibrous scaffolds with a surface modified nanosized bio-glass have been implicated in improving wound healing [95]. Xie et al. have developed an electrospun fiber nano composites containing different components such as antibacterial polymer chitosan, poly (ethylene oxide), VEGF and PDGF-BB loaded poly (lactic-co-glycolic acid) NPs. They have demonstrated that the application of such a nano composite would prevent bacterial attack in the vicinity of wound. In addition, they have demonstrated that the nano composite facilitated the early delivery of VEGF from the nanofiber and sustained delivery of PDGF-BB from the NPs, thereby accelerating tissue regeneration and remodeling in a full-thickness rat skin wound model [96]. Lino et al. have shown that light-responsive plasmonic gold nanocarrier could be used as a carrier vehicle for the delivery of microRNAs such as miR-302a and miR-155, which regulated the proliferation and survival of ECs thereby promoting wound healing [97].

Carbon nanotubes were functionalized with different side-chain moieties and they were applied for diagnosis as well as drug delivery purposes [98]. It has been shown that the Multi-Walled Carbon Nanotube (MWCNT) supports angiogenesis as the macrophages engulfing MWCNT, produce angiogenic cytokines such as VEGF and MMP9 [99]. Liu et al. have constructed a composite scaffold of VEGF165 loaded functionalized MWCNT, for the prolonged and sustained delivery of VEGF165, and it promoted tissue remodeling and repairing in the *in vivo* models [100].

Graphene based NPs have also been implicated to have massive applications in angiogenesis-based therapeutics [101]. Graphene, graphene oxide (GO) and reduced graphene oxide (rGO) have received great attraction as inorganic additive in biopolymers for developing biomaterial composites [102]. The Gelatin-methacryloyl (GelMA) hydrogel containing rGO has been indicated to promote cell proliferation and migration in *in-vitro* model of wound healing and it has also been implicated to promote angiogenesis in chick embryo model [103]. In addition, ZnO nanoflower based nanomaterials [104] and water-soluble CONPs [105] were also implicated to exhibit wound healing properties by modulating the process of angiogenesis. The candidate nanomaterials which possess the ability to promote wound healing, by promoting angiogenesis have been indicated schematically in **Figure 2**.

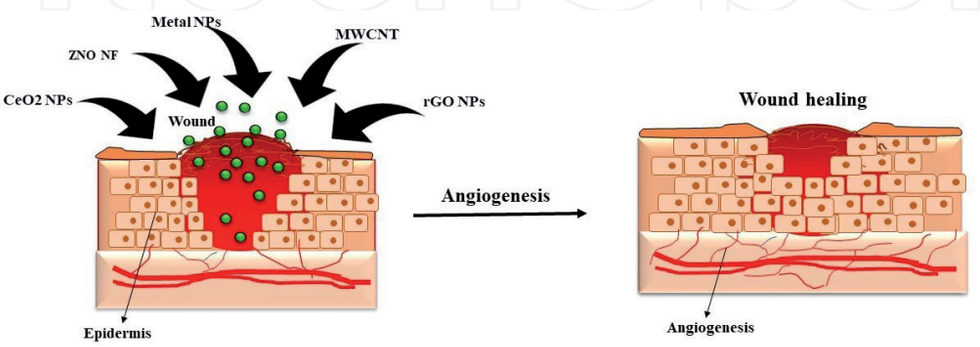

Figure 2.
Pro-angiogenic nanomaterials promote wound healing. Nanomaterials like cerium oxide nanoparticles, zinc oxide nanoflowers, multi walled carbon nanotubes, reduced graphene oxide nanoparticles and metal ion based nanoparticles like strontium ions and cobalt ions, promote wound healing in different in vitro and in vivo models by promoting the process of angiogenesis.

3.4 Diabetic retinopathy and age-related macular degeneration

Diabetic retinopathy (DR) is one of the critical leading causes of blindness and it is a secondary complication associated with Diabetic Mellitus. Diabetes affects the entire neurovascular regions of the retina, with ongoing neurodegeneration, gliosis, neuroinflammation, edema, angiogenesis, and fibrosis [106]. The changes in the vasculature cause perceptible abnormality in vision and lead to blindness. VEGFA, which gets upregulated in response to hypoxia, plays a central role in the initiation of DR. In addition to that, MMP9 has also been implicated to play key role in the onset and severity of DR [107].

The Age-related macular degeneration (AMD) is another complication where pathological angiogenesis is involved. AMD has been classified into two types. The type of AMD which is characterized by yellowish deposits in the macula is known as the Dry AMD, whereas, the AMD with characteristic choroidal neovascularisation (CNV) is termed as the wet type or neovascular AMD [108].

Laser photocoagulation and multiple intra ocular injections are the treatment strategies adopted for the diseases that affect the vascular structure of the posterior eye. It has complications like the destruction of healthy tissues. Though 'introducing protein drugs', was put forth as one of the treatment strategies, it possessed drawbacks like drug instability due to proteases action followed by drug injection. It therefore warranted novel treatment strategies to conquer these drawbacks. So, in an effort to develop alternative therapeutic strategies for ocular diseases, the efficacy of different candidate NPs, exhibiting innate anti angiogenic property or possessing the ability to carry drug, growth factors etc., to specific tissue sites, have been tested by different groups [109, 110].

The AuNPs, as mentioned earlier, possess anti angiogenic properties in addition to their unique electronic, biocompatible, and molecular-recognition properties [111]. It has been reported to induce the nano structural reorganization of VEGFR2 in HUVECs and consequently suppressed angiogenesis [112]. AuNPs have also been reported to suppress VEGF induced cell migration by negatively regulating the phosphorylation of Akt and eNOS in retinal endothelial cells [113]. It has also been reported to obstruct the proliferation of VEGF treated retinal endothelial cells by suppressing Src signaling pathways [114].

Kringle 5 (K5), a proteolytic fragment of plasminogen possessing 80 amino acids, has been shown to be highly effective in the inhibition of EC growth [115]. It has also been reported to inhibit ischemia-stimulated retinal neovascularization in the oxygen-induced retinopathy (OIR) model [116]. But it possessed the drawback of a short life span. An expression plasmid of K5 was encapsulated with PLGA polymer to form nanoparticles (K5-NP) which effectively inhibited VEGF expression and attenuated ischemia-induced retinal vascular leakage and retinal neovascularization in the OIR rat model [117]. Biodegradable NPs loaded with Fenofibrate (Feno-NPs) have been reported to be particularly useful for the targeted delivery and treatment of DR and neovascular AMD. Fenofibrate is a peroxisome proliferator-activated receptor α (PPARα) agonist, which is effective against DR. In diabetic rat models, at 8 weeks after the administration of Feno-NP by one intravitreal injection, the vascular leakage in the retina was found to be reduced. In addition to that the retinal leukostasis was inhibited, and further, the expression of VEGF and ICAM-1 were down regulated [118].

Octreotide (OCT), an analog of somatostatin, is an established neuroprotective and anti-angiogenic agent that targets VEGF. The intra ocular delivery of OCT combined with Magnetic NPs (MNP-OCT) has been suggested to improve the half-life and bio activity of OCT [119]. Polliner et al. have checked the possibility of receptor mediated targeting of NPs to capillary endothelial cells in the retina, and

they have demonstrated that Cyclo (RGDfC)-modified QDs specifically bind to the αvβ3 integrin receptors on the ECs and the cellular uptake mediated by receptor binding led to the accumulation of the NPs in the choriocapillaris and intraretinal capillaries [120].

Yandrapu et al. have formulated 'Nanoparticles in Porous Micropaticles (NPinPMP)', by encapsulating bevacizumab coated poly lactic acid NPs into porousifying PLGA microparticles (NPinPMP) using supercritical carbon dioxide (SC CO_2). Bevacizumab is a protein drug used to treat neovascular AMD and it was necessary to inject once in a month intravitreally. The *in vitro* studies revealed that, NPinPMP showed a sustained release of bevacizumab for a period of 4 months. In addition, bevacizumab has been detected for a period of 2 months after intravitreal injection of NPinPMP in rat model, while it was detected only for 2 weeks upon its intravitreal administration in individual form [121].

Likewise, Luo et al. have used, biodegradable PLGA nanoparticles conjugated with integrin-binding linear RGD peptide, as a carrier tool for the delivery of recombinant tFlt23k intraceptor plasmid possessing VEGF binding domains. The nontoxic RGD-functionalized NP delivery system was observed to be getting targeted directly to the choroidal neovascularization lesions after intravenous injection, and exhibited excellent vision restoration in both primate and murine AMD models [122].

Celecoxib is a cyclooxygenase-2 inhibitor, exhibiting anti-inflammatory and anti-angiogenic properties. Celecoxib-loaded poly (ortho ester) NPs were found to be highly effective against AMD and DR [123]. Interleukin-12 (IL-12) has been reported to exhibit anti-angiogenic property by reducing the levels of MMP9 and VEGFA [124]. Zheng and colleagues combined IL-12 with PLGA nanoparticles (IL-12-PNP) and proved it to be exhibiting better efficacy in terms of inhibition of VEGFA and MMP9 expressions in DR mouse retina and rat ECs. Further, the intra ocular administration of IL-12-PNPs showed reduced retinal damage in mice model with DR [125].

3.5 Impaired osteogenesis

Osteogenesis is referred to the process of regeneration of bones, which involves multiple steps such as the activation, migration and differentiation of different cell types [126]. The process of angiogenesis is crucial for the supply of growth factors, hormones, cytokines, chemokines, and metabolites required for osteogenesis. Any aberrancy associated with the vascular supply to the bone tissues would lead to different pathologies such as osteonecrosis [127], osteomyelitis [128], and osteoporosis [129, 130]. Discrepancy in angiogenesis has also been reported as one of the main reasons for the failure of osteogenesis after implantation. VEGF and HIFα are the major angiogenesis related factors that promote osteoblast differentiation and osteogenesis. So, it has been suggested that restoring angiogenesis would promote bone function and defect repair in pathologies with impaired osteogenesis.

Many candidate nanomaterials have been reported to be effective in improving the repair of bone tissues [131]. For example, synthesized chitin–$CaSO_4$–nanofibrin based injectable gel system showed enhanced osteo-regeneration via enhanced angiogenesis [132]. Further, the β $CaSiO_3$/PDLGA composite has been reported to induce the phosphorylation and activation of Akt and eNOS respectively in HUVECs with a resultant increase in the synthesis and release of NO and VEGF. Further the bone regeneration study in the rabbit femur defect model using β $CaSiO_3$/PDLGA composite has shown enhanced angiogenesis and osteogenesis [133]. Nano-hydroxyapatite has been reported to regulate the PI3K/Akt pathway for inhibiting migration and tube formation in HUVECs via inhibiting NO synthesis

and eNOS phosphorylation [134]. Similarly, calcium phosphate combined with electro spun poly (lactic acid) has been reported to promote VEGF expression in endothelial cells. It has also been reported to support vascular development and bone regeneration when injected subcutaneously in mice, by promoting the expression of proangiogenic factors like VEGF, IGF-2, GM-CSF, IL-1 beta, IL-6, IL-12p70 etc. [135]. Similarly, Nano bioactive glass, characterized by higher surface area and three-dimensional channel structure, is another material that could promote angiogenesis and bone regeneration [136, 137].

Nanomaterials can also act as carrier tools for different pro angiogenic small molecules and proteins like deferoxamine, adrenomedullin, VEGF etc. For example, Mesoporous silicate nanoparticles (MSNs) incorporated-3D nanofibrous gelatin (GF) scaffold has been employed for the dual-delivery of bone morphogenetic protein-2 (BMP2) and deferoxamine (DFO). DFO, being a hypoxia-mimetic drug, could trigger the stabilization of HIF-1α, and initiate subsequent angiogenesis. Further, it has been shown that DFO could significantly enhance BMP2 induced osteogenic differentiation in mouse and human stem cell models [138].

Ionic components have been utilized for the modification of vascularized bone tissue engineering scaffold. The Copper based nanomaterials could promote the expression level of VEGF, which in turn promoted the proliferation of ECs. Nano-structured surfaces on the Hydroxyapatite scaffolds in copper ion (Cu^{2+}) containing solutions under hydrothermal conditions could affect EC proliferation. Further, the nano-structured surfaces on the Hydroxyapatite scaffolds, promoted angiogenesis and bone regeneration. Dexamethasone (DEX), an osteogenic inducer combined with biphasic calcium phosphate nanoparticle (BCP NPs) scaffold, was found to induce the expression of VEGF and VEGFR2 and supported bone regeneration. The micro-grooves present in the scaffolds managed the assembly of HUVECs into tubular structures and promoted angiogenesis [139]. The gene encapsulated magnetic microspheres have also been used as a promising delivery system. For instance, introduction of VEGF165 with superparamagnetic (nano-Fe_3O_4) chitosan, induced *in vitro* and *in vivo* angiogenesis and bone regeneration [140].

The AuNPs have also been reported to induce angiogenesis during osteogenesis. AuNPs exhibited differences in angiogenic activity based on their surface charges and the presence of functional groups. The Gene profiling data revealed that in comparison with the cells (hMSCs) treated with AuNPs possessing amine or hydroxyl functional groups ($AuNPeNH_2$ or AuNPeOH), the cells treated with carboxyl group containing AuNPs (AuNPeCOOH) showed augmented expression levels of TGFβ and FGF-2, which in turn promoted cell proliferation over osteogenic differentiation [141].

3.6 Nerve tissue degeneration

Nerve tissue degeneration is a critical clinical challenge that leads to diseases like trauma or permanent paralysis, so research advancement in the field of nerve tissue regeneration is quite necessary. In the recent years, the applications of nanomaterials have received much attention from the research community focusing on nerve tissue repair.

The process of angiogenesis plays key role in supplying nutrients to the nerve tissue which in turn helps to repair segmental nerve defects. Recently, Lopez-Dolado et al. have designed a 3D scaffold containing partially reduced graphene oxide, which when implanted in the injured site in the spinal cord of a rat model, a remarkable induction in angiogenesis and axon regeneration was observed [142].

Further, GO/polycaprolactone (PCL) nano scaffolds have been implicated to promote angiogenesis by modulating Akt-eNOS-VEGF signaling pathway and it facilitated peripheral nerve regeneration *in-vivo* [143].

In addition, Xu et al. have formulated an acellular spinal cord scaffold (ASCS), namely, V-ASCS, for the sustained delivery of VEGF, and it was composed of VEGF165 encapsulated PLGA nanoparticles conjugated with ASCS. When V-ASCS was implanted at the injury site in a rat spinal cord hemisection model, it rendered significant progress in neovascularization [144]. Wen et al. fabricated a hyaluronic acid scaffold with brain-derived neurotrophic factor and VEGF loaded PLGA microspheres, which promoted angiogenesis and nerve fiber regeneration when implanted at the injured site in the spinal cord of rat model [145]. Yu and his co-workers have formulated PLGA microspheres encapsulated with VEGF, angiopoietin-1 and bFGF, and these angiogenic microspheres could release the angiogenic factors in a sustained fashion, which then induced angiogenesis and neurogenesis when administered at the injured site in the spinal cord of rat model [146].

Jian et al. have fabricated a nanohybrid hydrogel containing sulfated glycosaminoglycan-based polyelectrolyte complex nanoparticles (PCN), and it could accelerate neurogenesis and angiogenesis in *in-vivo* ischemic stroke model [147]. Amorphous non-fibrous hydrogel comprised of hyaluronic acid containing high cluster VEGF, when injected directly within the stroke cavity, stimulated the formation of a vascular and neuronal structures, that preceded to behavioral improvement *in vivo* [148].

Delivery of superparamagnetic iron oxide nanoparticle labeled Endothelial progenitor cells (EPCs) was found to induce the formation of vessel-like structures by the production of VEGF and FGF [149]. Similarly, superparamagnetic iron oxide (SPIO)-Au core-shell NPs incorporated with nerve growth factor (NGF) have been implicated to promote neuron growth and differentiation [150].

4. Conclusion

Aberrancy associated with angiogenesis pave the way for the progression of a number of diseases like tumor, cardio vascular diseases, diabetic retinopathy, age related macular degeneration etc. So, targeting angiogenesis presents itself as one of the key therapeutic strategies to tackle such complications. The currently available therapies though beneficial, do possess some limitations like acquisition of drug resistance by cells, fast decay of protein drugs by protease action, off target effects leading to decreased drug efficacy etc. Different candidate nanomaterials were implicated to possess anti- angiogenic properties, which were tested *in vitro* and *in vivo* to explore their additional properties like precise targeting of pathological angiogenesis, cellular uptake, efficacy etc. Nanoparticles have also been utilized as carrier tools for drug delivery. Surface modification of nanoparticles with RGD, VEGF etc. has reinforced them with specific targeting, internalization and sustained drug delivery. Growth factor encapsulated nanoparticle-based scaffolds were fabricated by different groups, to effectuate wound healing, osteogenesis and nerve tissue regeneration in *in vivo* models. On the whole, the application of nanomaterial-based formulations in pro or anti angiogenic therapy is a rewarding strategy for the treatment of complications associated with aberrant angiogenesis, which however, requires more explorations for translating from bench to bedside. The candidate disorders associated with aberrant angiogenesis and various applications of nanomaterials for the treatment of such disorders have been represented schematically in **Figure 3**.

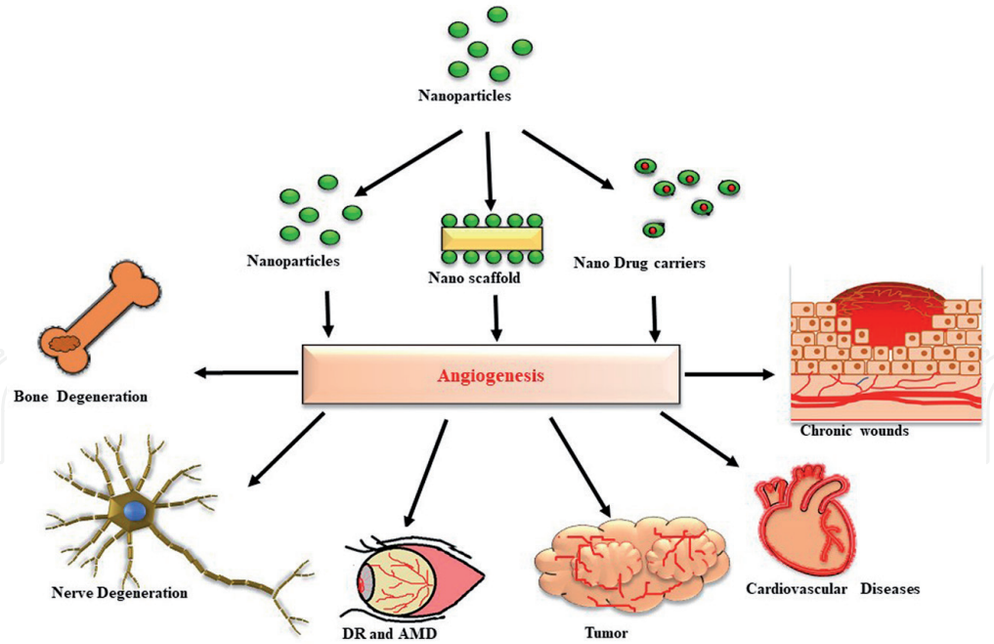

Figure 3.
Nanomaterial based formulations for the treatment of pathological conditions with aberrant angiogenesis. Abnormal angiogenesis promotes the progression of different diseases like tumor, cardiovascular disease, chronic wounds, diabetic retinopathy, wet type age related macular regeneration, bone and nerve tissue degeneration etc. nanomaterials possessing intrinsic pro- or anti- angiogenic property could be utilized individually or as a part of biodegradable polymer based-scaffolds for the treatment of such disorders. Different candidate nanoparticles with surface modifications with peptides like arginine-glycine-aspartate (RGD) and vascular endothelial growth factor (VEGF), could be utilized as carrier tools for targeted drug delivery.

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