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Functional Role of Inorganic Trace Elements in in Angiogenesis Part III: (Ti, Li, Ce, As, Hg, Va, Nb and Pb)

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Abstract

Many essential elements exist in nature with significant influence on human health. Angiogenesis is vital to developmental, repair, and regenerative processes, and its aberrant regulation contributes to pathogenesis of many diseases including cancer. Thus, it is of great importance to explore the role of these elements in such a vital process. This is third in a series of reviews that serve as an overview of the role of inorganic elements in regulation of angiogenesis and vascular function. Here we will review the roles of titanium, lithium, cerium, arsenic, mercury, vanadium, niobium, and lead in these processes. The roles of other inorganic elements in angiogenesis were discussed in part I and part II of these series. The methods of exposure, structure, mechanisms, and potential activities of these elements are briefly discussed. An electronic search was performed on the role of these elements in angiogenesis from January 2005-April 2014. These elements can promote and/or inhibit angiogenesis through different mechanisms. The anti-angiogenic effect of titanium dioxide nanoparticles comes from the inhibition of angiogenic processes, and not from its toxicity. Lithium affects vasculogenesis but not angiogenesis. Nanoceria treatment inhibited tumor growth by inhibiting angiogenesis. Vanadium treatment inhibited cell proliferation and induced cytotoxic effects through interactions with DNA. The negative impact of Mercury on cell migration and tube formation activities was dose and time dependent. Lead induced IL-8 production, which is known to promote tumor angiogenesis. Thus, understanding the impact of these elements on angiogenesis will help in development of new modalities to modulate angiogenesis under various conditions.

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Contributors

All authors contributed to the review outline. Asaturian and Orangi contributed equally to the literature search, creating the figures and tables, and writing the Review. Saghiri, Sorenson and Sheibani contributed equally to the literature search, writing and editing of the Review.

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Keywords

Angiogenesis; Endothelial cells; Inorganic elements

Introduction

Certain essential elements exist in nature, which influence human health through different mechanisms. Angiogenesis is of great importance in various pathological and physiological processes. Thus, exploring the role of these elements in such a vital process is of great clinical significance. Angiogenesis makes critical contribution throughout life with important role in successful regeneration and growth of new tissues. Blood vessels provide growing cells and tissues with oxygen and nutrients necessary for survival. In contrast, uncontrolled angiogenesis allows tumors to grow and metastasize, with serious adverse effects on human health.

There is increasing concern regarding the overall health impacts of exposure to various heavy metals in the environment. This is particularly true of mercury and less so with lead, and arsenic. Titanium, vanadium, and niobium are widely used in implant materials and have shown good results under in vivo conditions. Lithium and cerium are also used widely in solar cell batteries and fuel cells. Thus, in places where these elements are widely used, human health might be compromised.

Inorganic elements are an undeniable part of living organisms. Thus, it is important to know the activity and the role and tendency of these elements to maintain or alter angiogenic balance [1, 2]. In this last part of the review series, the role of titanium, lithium, cerium, arsenic, mercury, vanadium, niobium, and lead in regulation of angiogenesis was investigated.

Materials and Methods

This part of the study was preformed as previous parts of the series [1, 2]. Briefly, the potential effects of titanium, lithium, cerium, arsenic, mercury, vanadium, niobium, and lead in regulation of angiogenesis in peer-reviewed journals in the PubMed database, published in English from January 2005–April 2014, were included in this review. All Other articles which did not include these criteria, were excluded. The evaluation of the eligibility and finding relevant data were done by three reviewers independently (Saghiri MA, Orangi J, and Asatourian A) (α) The reviewers (Sorenson CM and Sheibani N) were selected to resolve any disagreement in mentioned processes, (β).

Titanium (Ti)

Fifty one related articles were found when the key word “Titanium in Angiogenesis” was searched. Among them 17 articles were satisfied the inclusion criteria and were selected for review [$\alpha = 22 - \beta = 7$]. The development and characterization of new materials capable of stimulating bone mineralization and angiogenesis has been a matter of concern among health professionals. The properties of Ti surfaces are considered as crucial factors for affecting the outcomes of clinical applications of Ti-based implants. Exposure to Ti often

occurs by way of Ti compounds that are added to cosmetics, sunscreens, paints, and food, while it is not a poisonous metal in the human body.

Nanoscale features of Ti surfaces affect osteoblasts differentiation [3]. However, the influence of these nanostructures on behavior of endothelial cells (EC) as well as on the interactions between EC and osteoblasts remain unclear. In a recent study of Raines et al. [4], the conditioned medium from MG-63 cells grown on different Ti surfaces was collected, and its effect on vessel formation by EC was investigated *in vitro*. Authors showed that vascular endothelial growth factor (VEGF) production was highest in MG-63 cells grown on SLActive surface, and this VEGF production stimulated differentiation and vessel formation by EC [5]. MG63 cells grown on rough Ti alloy increased the levels of active and latent transforming growth factor beta 1 (TGF- β 1) and osteoprotegerin in their medium, while it did not affect angiopoietin-1 level [4, 6].

The cellular responses of EC to Ti surfaces with different topographies and hydrophilicities are necessary, and they promote the differentiation of EC [7, 8]. *In vitro* studies showed that the modified hydrophilic surfaces increased absorption of plasmatic fibronectin [9], improved the differentiation of osteoblast-like cells, and up-regulated its related growth factors [10]. Peri-implant osteoblasts may create an environment that modulates angiogenesis around the implant and in the adjacent tissue. Thus, the chemistry of the implant plays an important role in determining the nature of the angiogenic milieu [6]. High surface energy and microrough surface topography of Ti substrates promoted the synthesis of pro-angiogenic growth factors, which resulted in an advancement of the human aortic EC differentiation *in vitro* [4], and improved neovascularization *in vivo* [11]. Osteoblasts produce VEGF-A [12], and basic fibroblast growth factor (FGF-2) [13]. The levels of these pro-angiogenic factors are regulated by 17 β -estradiol [14], 1,25 dihydroxyvitamin D3 [1,25(OH)2D3] [15], and bone morphogenetic protein-2 (BMP-2) [16], which stimulate osteogenesis.

The integrin $\alpha_2\beta_1$ signaling is regulated by VEGF-A and FGF-2 levels in the conditioned medium [4]. The adhesion receptor α_2 subunit is diversely regulated by VEGF-A and FGF-2 production, VEGF-A increasing and FGF-2 decreasing. Thus, during healing signaling events they induce EC migration and capillary formation from the surrounding vasculature [4].

The character of EC preferring smooth and hydrophilic surfaces seems to be based on their *in vivo* function, as they spread on and attach to the smooth structures of vascular vessels. Relatively smooth hydrophilic Ti implant surfaces, resembling biological structures or the physiological environment of blood vessels, may promote neovascularization in the wound healing phase after implantation [7]. The functional differentiation such as cell cluster and nodules formation of both EC and osteoblasts were enhanced on hydrophilic Ti surfaces with high surface energy [7]. The mRNA expression levels of well-known EC markers and essential angiogenic factors von Willebrand factor (vWF), Thrombomodulin (TM), and endothelial cell protein C receptor (EPCR) were elevated on hydrophilic surfaces (modA and modSLA) compared with hydrophobic surfaces (A and SLA) [7]. The expression of angiogenic factors and adhesion molecules by human umbilical vein endothelial cells

(HUVEC) and osteogenetic factors by osteoblasts is promoted mainly by surfaces with high wettability and energy [7]. The mechanisms could be due to the enhancement of protein adsorption by hydrophilic surfaces, which promote initial attachment, and may trigger various intracellular signaling pathways [7]. This assumption is supported by a recent finding that the modification of Ti surfaces from hydrophobic to hydrophilic state resulted in a substantial increase in fibronectin levels [9].

Hydrophilicity of different Ti surfaces influenced HUVEC proliferation grown in co-culture with osteoblasts, while surface roughness effect was of less significant. It was confirmed that the expression levels of angiogenesis-related proteins including TM, vWF, EPCR, and E-selectin were highest on hydrophobic smooth surfaces compared to other surfaces [5]. This was in contrast to the observation in the mono-culture study, in which the highest expression of angiogenesis related genes was observed on hydrophilic rough surface [7]. Thus, in the co-culture study both proliferation and differentiation of cells were inconsistent with those of the mono-culture study. These studies implied that the EC behavior on different Ti surfaces might be affected by cell-cell interactions in the co-culture studies [5].

Endothelial progenitor cells (EPC) are able to promote neovascularization under hypoxic conditions in adult humans, and secrete the most amount of VEGF on modSLA [17–20]. EPC affect neovascularization by secreting paracrine factors (cytokines, growth factors) like VEGF and by forming a primary cell network through differentiation into EC or perivascular supporting cells [18, 21]. Rougher titanium surfaces promoted an undifferentiated plump phenotype with low proliferation rate and endothelial nitric oxide (NO) synthase and/or inducible NO synthase activities [20]. However, they showed higher rate of VEGF-A secretion.

The ability of polymer coatings to entrap and release biologically active molecules involved in angiogenesis may result in a further improvement in Ti implant surface bioactivity. To improve angiogenesis in addition to bone mineralization, the ability of coatings to entrap and release recombinant human VEGF (rhVEGF) was evaluated [22]. The rhVEGF-loaded coatings were compatible with immobilized and soluble rhVEGF. The amount of rhVEGF released ($0.6\text{--}1\text{ ng mL}^{-1}$) was comparable with values reported in the literature as effective doses [23], and thus, able to stimulate cell proliferation without inducing pathological reactions.

Titanium dioxide (TiO_2) nanoparticles are known to induce apoptosis and neural toxicity, produce oxidative stress, and inflammatory responses in human bronchial EC [24–26]. TiO_2 nanoparticles also induce oxidative DNA damage and apoptosis in HepG2 cells through a mitochondria-mediated pathway [25]. Well-prepared and characterized TiO_2 nanoparticles in aqueous solution do not induce any definite genetic, cellular, and histologic toxicity. Surprisingly, they exert anti-angiogenic effect on retinal neovascularization. The anti-angiogenic effect of TiO_2 nanoparticles arises from their inhibition of angiogenic processes and not from their toxicity. Furthermore, the suppression of VEGF receptor-2 (VEGFR2) and mitogen activated protein kinase (MAPK) pathways by TiO_2 nanoparticles were declared [27]. A schematic presentation is shown in Figure 1. Proper preparation and establishment of an adequate concentration range for TiO_2 nanoparticles is essential for

maintenance of its biological effects and minimized toxicity, especially through local administration.

TiO₂ nanoparticles suppressed retinal neovascularization, demonstrated by the decreased number of vascular lumens at presumptive therapeutic concentrations. TiO₂ nanoparticles effectively suppressed VEGF-induced tube formation and migration of human retinal microvascular EC, demonstrating inhibitory effects of nanoparticles on angiogenesis processes. The treatment with metal nano particles, including TiO₂ nanoparticles, inhibited the phosphorylation of VEGFR2 and further activation of extracellular signal regulated kinase (ERK1/2) or phosphatidylinositol 3-kinase (PI3K)/Akt pathway [27–30]. However, the activation status of Akt was not affected by the treatment with TiO₂ nanoparticles [27]. These results demonstrated that TiO₂ nanoparticles exert their anti-angiogenic effects by suppressing the VEGF/VEGFR2/MAPK pathway independent of PI3K/Akt pathway [27].

Lithium (Li)

Sixteen related articles were found, among them 8 articles satisfied the inclusion criteria and were selected for review [$\alpha = 9 - \beta = 1$]. Dairy products (0.50 mg Li/Kg food), grains, vegetables (0.5–3.4 mg Li/Kg food), and meat (0.012 mg Li/Kg food) are major dietary sources of Li [31]. Water is too, with wide variations according to region-Depending on dose. Trace amounts of Li are considered essential, acting as neuroregulator (Biol Trace Elem Res. 1992 Aug;34(2):161-76). Lithium is considered as a therapeutic agent, which can affect various cellular processes [32–34]. The central nervous system is the first organ affected by Li toxicity [35], and Li is used for manic depression treatment. Lithium is also frequently used to activate the Wnt/ β -catenin and inhibit glycogen synthase kinase (GSK)-3 β signaling pathways [36]. GSK-3 β is required for nuclear factor- κ B (NF- κ B) suppression, tumor necrosis factor (TNF)-induced activation of I κ B α , kinase, c-Jun-N-terminal kinase, p44/p42 MAPK, and Akt activation [37]. Thus, NF- κ B-regulated gene products such as cyclooxygenase (COX)-2, cyclin D1, matrix metalloproteinase (MMP)-9, survivin, inhibitor-of-apoptosis protein 1 (IAP 1), IAP 2, Bcl-xL, Bfl-1/A1, and TNF receptor-associated factor 1 are increased upon exposure to Li[37].

Lithium treatment of EC significantly increased PAI-1 and MMP-1 levels, while it delicately increased interleukin 8 (IL-8) and Wnt/ β -catenin levels [38, 39]. Among various MMPs, Li specifically affected MMP-1 expression, while it increased MMP-2, decreased MMP-14 levels, and the MMP-3 level was unchanged [39]. The MMP-1 expression was significantly increased in a dose- and time- dependent manner after Li treatment [39]. The induction of the MMPs by Li- and/or basal form are dependent upon the levels of the tumor suppressor and cell senescence inducer p53 [39]. Both up and down regulation of cell proliferation and cell senescence by GSK-3 β inhibition have also been claimed [40, 41]. Similarly, the β -catenin stabilization was shown to induce proliferation of undifferentiated cells and tumorigenesis [42].

Chronic and delayed injections of Li improved blood oxygen level and functional cerebral blood volume, which is in agreement with enhanced neurovascular remodeling and angiogenesis. The expression of pro-angiogenic factors, MMP-9 and VEGF, were induced by Li in a GSK-3 β -dependent manner [43]. The treatment of cultured rat brain EC with Li was

also found to increase the protein levels of VEGF through a mechanism engaging the PI3K and GSK-3 β signaling pathways (Fig. 1) [44].

Lithium can directly affect vascularization and can disturb embryonic vascular development [45, 46]. LiCl inhibited normal vascular development and expansion of the area vasculosa in the majority of explants [45]. Klug et al. [47] demonstrated that in vitro exposure of rat embryos yolk sac vessels to Li, led to vascular stasis and did not experience confluence. In addition, considerable vascular widening were seen in the embryo cranial region. Lithium was also showed to have a concentration-dependent effect on early vascular development in the chick embryo area vasculosa. Blood islands continued to form but new vessels succeeding organization were either entirely inhibited or abnormal vascular patterns engendered in embryos treated with Li [45]. Vasculogenesis, but not angiogenesis, is affected by Li, which supports the hypothesis that vasculogenesis and angiogenesis are regulated by different molecular processes [48].

Cerium (Ce)

Seven related articles were found, among them five articles met the inclusion criteria, and were selected for review [$\alpha = 6 - \beta = 1$]. Cerium, especially during long-term exposure, can cause lung embolisms and threat the liver. The therapeutic applications of Cerium oxide, a rare earth metal, have gained attention recently because it can be synthesized into nanoparticles. The potential to act as a regenerative free radical scavenger to protect biological, chemical, and radiological insults that induce free radicals production, without cytotoxicity are the most valuable properties of Ce nanoparticles (nanoceria) [49–55]. The Ce atom valence structure integrated with the intrinsic crystal lattice structure is considered as the main characteristics of cerium to show such an antioxidant property. When the engineered nanoceria enter the cells, its unique structure inhibit cell senescence and decreases toxic insults [56] through preventing reactive oxygen species (ROS) accumulation [49]. Nanoceria have been reported to either promote [57, 58], or attenuate angiogenesis [59].

Nanoceria at high concentration were able to attenuate EC proliferation and this effect was enhanced when heparin functionalized nanoceria were used, while no effects were noted at low concentrations [60]. The proliferation of HUVEC was reduced by nanoceria at concentrations greater than 8.6 mg/mL [61]. Therefore, heparin-nanoceria and nanoceria may be practical therapeutic agents for controlling angiogenesis related to tumor growth and metastasis by inhibiting EC growth [60].

The expression of several key growth factors, inflammatory cytokines, and angiogenic factors define the protective effect of nanoceria in a mouse model of neovascularization-associated with oxidative stress [62]. Inhibiting and scavenging ROS, as well as other inflammatory mediators in biological systems, nanoceria may decrease the damage to cellular components [63, 64]. A significant and differential modulation of multiple growth factor genes and cytokine after nanoceria treatment were also declared [62]. Nanoceria prevented VEGF expression and vascular lesion development in the retina photoreceptor cell layer [62, 65], while it did not significantly affect VEGFb and VEGFc levels [62]. Most of the genes in FGF family including FGF 1, 2, 3, 5, 7, 9, 11, 21, and 22 are over-expressed in

the retina of Vldlr knockout mice compared to wild type mice, and nanoceria significantly inhibited their expression [62]. After nanoceria injection the highest up-regulated genes were FGF-7 and FGF-2, and the most down-regulated gene was FGF-9 [62]. Therefore, nanoceria has the ability to target signaling pathways other than VEGF that have been implicated in both normal retinal vasculogenesis and pathologic neovascularization [62]. Furthermore, nanoceria injection down-regulated the predicted kinase signaling pathways including MAPK and Akt [62].

Ovarian cancer cells treatment with nanoceria in both in vivo and in vitro conditions had shown the potential to inhibit proliferation and induce apoptosis of EC, suppress tumor growth and metastasis, and as a consequence lessened the microvessel density [59]. Furthermore, phosphorylation of VEGFR2 and VEGF mediated downstream signaling were also attenuated. More importantly, nanoceria as anti-angiogenic agent targeted vascular EC in vivo and suppressed tumor growth [59].

Moderate intracellular levels of ROS have been shown to lead to angiogenesis [66], while high concentrations are toxic to the cells [67]. ROS have been shown to induce gene expression of angiogenic growth factors, including FGF-2 and VEGF, and their receptors through NF- κ B [68, 69]. Heparanase expression is increased by ROS [70], which leads to release of bound growth factors as well as their increased expression, which in turn can induce angiogenesis [71]. The heparin functionalized nanoceria provide a more potent ROS scavenger than nanoceria alone [72]. In addition, in endometriosis mice treated with nanoceria the levels of oxidative stress, angiogenesis, and microvessel density were effectively reduced [73].

The solubility, size, shape (i.e. nanorods, particles, stars), and composition influences the surface reactivity, oxygen storage, and ease of oxygen extraction. In addition, transportation from the surface of the nanoceria/biological interface was investigated to test the pro-angiogenic properties of nanoceria [57]. Different shapes of nanoceria, except ceria nanorods, did not show cytotoxicity towards HUVEC, and induced cell proliferation at optimum concentration (1 μ M) to trigger angiogenesis. However, exposure to ceria nanorods led to a slight reduction in cell proliferation [57]. The addition of nanoceria to cells resulted in a remarkable concentration dependent induction of tube formation (up to 1 μ M), while nano silisium oxide with similar size did not show any effect on tube formation [57]. Only nanoceria sized <15 nm showed the potential to induce tube formation. Exposing HUVEC to cerium oxide particles >15 nm in size did not result in tube formation. Interestingly, micron size particles inhibited tube formation, though inhibition was not statistically significant. It is well known that the catalytically active surface area of nanoparticles decreases with increase in particle size, and therefore, it is not surprising that nanoparticles >15 nm did not influence tube formation [57]. It was also claimed that tube induction was not influenced when cells treated with the original nanoceria or surface charged altered nanoceria, both positive and negative charge [57].

The analysis of the reactivity maps of a model nanoceria, resulted from atomistic computer simulation, revealed that oxygen vacancy formation in the vicinity of surface Ce⁺³ is easier, and therefore more reactive towards participating in a catalytic reaction, compared with

unreduced areas of the nanoparticle. This finding helps explain why nanoceria with a high $\text{Ce}^{+3}/\text{Ce}^{+4}$ ratio promotes angiogenesis [57].

Nanoceria induces EC proliferation as well as vascular sprouting [57]. A significant increase in VEGF level in culture medium in nanoceria treated cells was observed with a maximum of VEGF when cells were exposed to a concentration of 1 μM nanoceria positive surface charge had more impact rather than negative charge. Nanoceria activated hypoxia-inducible factor (HIF)-1 α by modulation of intracellular oxygen levels. Exposure to nanoceria did not induce angiogenesis by triggering higher levels of ROS. HIF-1 α stabilization and translocation to the nucleus indicated that nanoceria induced angiogenesis by regulating HIF-1 α [57]. In contrast to aforementioned findings, it was declared that EC treatment with nanoceria inhibited MMP2 activation, VEGF induced proliferation, and capillary tube formation [59]. Both effects of nanoceria on angiogenesis are schematically presented in Figure 1.

Arsenic (As)

Ninety three related articles were found, among them 21 articles matched the inclusion criteria and were selected for review [$\alpha = 26 - \beta = 8$]. Arsenic is a well-recognized human carcinogen which causes major health concerns while the exact mechanism has not been elucidated [74, 75]. The primary routes of arsenic entry into the body are via ingestion and inhalation. Epidemiological and experimental studies have shown that chronic arsenic exposure through contaminated drinking water increases the risk of skin, lung, bladder, liver, and prostate cancer [76–78]. It has been shown that ever smokers with high arsenic exposure had significantly increased risks of bladder cancer and upper urinary tract urothelial carcinomas [79].

Arsenic has the dual effects on vascular cells and tumor angiogenesis, at low doses (5–500 ppb *in vivo* 0.1–5.0 μM in cell culture) promotes and at high dose inhibits [80–85]. High environmental levels of arsenic (10–100 ppm) in drinking water accelerate atherosclerosis [86], and promotes liver vascular channel formation in rodent models [87, 88]. Concentrations of arsenic above 5 μM are toxic to confluent EC, and limit tube formation in culture [84]. However, low and high doses of arsenic trioxide were synergistic with FGF-2 in increasing vessel density in the Matrigel assay [83].

Treatment of EC and smooth muscle cells with arsenic stimulates NOX enzyme-mediated ROS generation [89–91]. To elicit phenotypic change and signal transduction, arsenic selectively acts on the sphingosine-1-phosphate type 1 receptor (S1P1), which activates vascular cell NOX enzymes. S1P1 is crucial for arsenic to stimulate primary steps in angiogenesis, microvascular cells migration, and tube formation through engagement of the signaling pathways that impact EC phenotypical and morphological changes [92].

In addition to regulating motility, increasing tumor cell migration and invasion, of mammary tumor epithelial cells, arsenic also promotes tumor angiogenesis [93]. It was initially reported by Zhao et al. [94] that a 18-week exposure to arsenite (0.125–0.5 μM) induced malignant transformation of the rat liver epithelial TRL 1215 cells, accompanied by a dramatic morphological change of cells, from epithelioid to fibroblast-like. Arsenic exposure

triggered EMT through increasing the expression of EMT-inducing transcription factors, zinc finger E-box-binding homeobox 1 (ZEB1) and ZEB2, and depleting the expression of EMT-repressing miRNA-200s [95]. Recently, other independent studies also showed that a 15-week arsenite (1 μ M) exposure resulted in malignant transformation of human bronchial epithelial cells and keratinocytes, accompanied by EMT [96]. While it was previously reported that treatment of HUVEC with acute short term arsenic exposure stimulated angiogenesis [97, 98], the exact mechanism has not been clearly defined.

The effect of arsenic-transformed human bronchial epithelial cells that underwent EMT during angiogenesis and the underlying mechanism was also investigated. Tube formation in the absence of arsenic was significantly increased in the conditioned medium from arsenic-transformed cells [99]. Moreover, subcutaneous vaccination of arsenic-transformed cells in mouse xenograft tumor tissues resulted in promotion of angiogenesis. Arsenic-transformed cells stabilized miRNA-200b expression, which in turn resulted in MET inhibited angiogenesis [99]. Further mechanistic studies revealed that EMT in arsenic-transformed cells promotes angiogenesis through activation of β -catenin-VEGF pathway [99]. These findings provide additional novel evidence suggesting that EMT plays an important role in arsenic carcinogenesis by promoting angiogenesis.

Arsenic exposure also induced the suppression of miR-199a expression, which led to inhibition of HIF-1 α , induction of angiogenesis and tumor growth [100]. In the context of arsenic-induced transformation, miR-199a showed strong anti-angiogenic properties not only by directly targeting HIF-1 α but also another pro-angiogenic factor COX-2, which highlights the important role of miR-199a in angiogenesis [100]. Tumor vessels are leaky, immature, or morphologically abnormal because of the absence or incomplete basement membrane and mural cells (pericytes and smooth muscle cells). The baseline of HIF-1 α expression, which is oxygen independent, was dramatically up-regulated in arsenic-transformed cells [100]. The activation of mitogen-activated protein kinase, thymoma viral oncogene, mechanistic target of rapamycin (serine/threonine kinase), and ribosomal protein S6 kinase, polypeptide 1 (*p70S6K1*) genes might be the underlying mechanism [100, 101]. Oxidative stress was reported as a mediator of arsenic-induced cell transformation and carcinogenesis [101, 102]. In addition, ROS can activate HIF-1 α and COX-2 in various contexts [103].

Arsenic induces VEGF expression in human prostate cancer cells and tumor angiogenesis [104]. VEGF expression through induction of heme oxygenase-1 gene expression was induced in human microvascular EC after acute arsenic treatment [98]. Sodium arsenite treatment also showed angiogenesis enhancement in the chick chorioallantoic membrane model [105]. MAPK and PI3K/AKT signaling pathways were suggested as possible regulators of VEGF, COX-2, and HIF-1 α expressions induced by arsenite [106].

Arsenic advanced ROS production in a dose-dependent manner, the dependency of angiogenesis enhancement by arsenic to ROS production initiated from the evidence that ROS suppression by catalase prevented the induction of angiogenesis by arsenic [97]. Arsenic promoted angiogenesis through ERK1/2 and AKT activation, and their inhibition led to inhibition of angiogenesis modulated by arsenic [97]. The arsenic pro-angiogenesis

impact is launched at the plasma membrane involving integrin $\alpha_v\beta_3$, including ERK1/2 pathway activation and selenium-derived compounds significantly reversed the process [105]. Thus, arsenic-modulation of angiogenesis is related to AKT and ERK pathways [97, 107]. Indeed, inhibition of ROS generation blocked HIF-1 and VEGF induction, AKT and ERK1/2 activation, and angiogenesis in response to arsenic treatment [97]. The effect of arsenic on angiogenesis is schematically presented in Figure 2.

The As_2O_3 is active against angiogenesis *in vivo* and *in vitro* [108]. The mechanisms that mediate As_2O_3 anti-angiogenic activity include inhibition of VEGF protein expression but not VEGF mRNA expression, COX-2, MMP-2, and MMP-9 in dose- and time- dependent manners [108, 109]. The effect of As_2O_3 is on VEGF expression at the threshold level rather than the mRNA level. As_2O_3 decreased microvessel density in a dose-dependent manner, along with tumor growth inhibition [108]. As_2O_3 inhibits the angiogenic potential in Hepatocellular carcinoma cell. As_2O_3 attenuated the angiogenic ability through miR-491-mediated inhibition of TGF- β /SMAD3/NF- κ B signaling pathway in MHCC97H and MHCC97L cells [110]. *In vivo*, the expression of HIF-1 α , VEGF-A, delta like ligand 4, VEGFR-2, and Notch-1 were significantly inhibited by As_2O_3 [111]. As_2O_3 acts as a potential chemopreventive agent when used alone or in combination with other current anticancer drugs [110]. The use of selenium-derived compounds along with arsenic trioxide might lead to improved efficacy and safety of the use of arsenic alone.

Mercury (Hg)

Six related articles were found, among them 2 articles satisfied the inclusion criteria, and were selected for review [$\alpha = 2 - \beta = 0$]. The most common mercury exposure sources are dental amalgam and fish consumption. Mercury effect on arterial vessel walls include decreased NO and NO synthase expression [112], increased free radicals generation, and increased reactivity to vasoconstrictors, resulting in accelerated development of atherosclerosis and arterial hypertension [113].

Methylmercury (MeHg) is a known neurotoxicant even at low levels of exposure. Mammalian cells nucleic acid synthesis, protein synthesis, growth, and mitochondrial respiration were disturbed [114, 115]. MeHg might damage cell migration and tube formation activities in a dose- and time- dependent manner, resulting in morphological damage, viable cell number suppression, and the inhibition of wound repair [116, 117]. MeHg intoxication induces swelling of mitochondria, reduced cytoplasmic density, and dilatation of rough endoplasmic reticulum in cerebral blood vessel EC [118]. In dose- and time- dependent fashion, MeHg significantly activated both PLD (formation of [^{32}P]-phosphatidylbutanol) and PLA2 (release of [3H]arachidonic acid). The COX- and lipxygenase-catalyzed eicosanoids formations were promoted in EC exposed to MeHg. The MeHg-treated embryos cerebellar vessels compared with untreated ones revealed endothelial barrier devices poor differentiation, immature morphology, and high permeability to the exogenous protein horseradish peroxidase [119]. Increased carotid intima-media thickness and blood pressure were significantly linked with mercury exposure, which in turn support the notion that increased MeHg exposure promotes the development of cardiovascular disease [120, 121]. However, the underlying cellular mechanisms remain undetermined.

In mice treated with HgCl_2 , another mercury component, the conductance and resistance vasculature wall thickness and size of smooth muscle cells nucleus were decreased, while the number of smooth muscle cells were increased. Superoxide anion production NOX-1, COX-2, and the EC- and Mn-superoxide dismutases were increased in vascular smooth muscle cells exposed to HgCl_2 . It also promoted ERK1/2 and p38 MAPK activation. Vascular smooth muscle cells proliferation and size changed when exposed to mercury (long time- low dose) as a result of inflammatory proteins activation (nicotinamide adenine dinucleotide phosphate-oxidase and COX-2) through MAPK signaling pathways [120]. At nanomolar concentrations HgCl_2 increased the vasoconstrictor response to phenylephrine by reducing NO bioavailability and increasing the involvement of ROS and constrictor prostanoids [122–124]. Mercury mediated enhanced cell size and proliferation variations were normalized through suppression of HgCl_2 -induced NOX-1 and COX-2 expression by ERK1/2 and p38 signaling pathways blockade [120]. Selenium by forming a seleno-mercury complex, which is less toxic antagonizes mercury adverse effects [125, 126].

Vanadium and Niobium (Va and Nb)

Four related articles were found, among them 3 articles satisfied the inclusion criteria and were selected for review [$\alpha = 3 - \beta = 0$]. The major exposure route of vanadium (mainly in the form of VO_2C (vanadyl, V(IV)) or HVO_4^{2-} (vanadate, V(V)) is ingestion [127]. Vanadate can scavenge free radicals [128], and in the diabetic heart vanadate administration is associated with a decrease in oxidative damage [129]. An interesting property of vanadate is its ability to inhibit the activity of PTPases and thereby cause a net increase in the level of protein tyrosine phosphorylation [130, 131].

Vanadium treatment inhibited cell proliferation with a predominance of early apoptosis over late apoptosis [132], and induce cytotoxic effects by DNA interaction [133, 134]. Interleukin adhesion molecule-1, vascular cell adhesion protein-1, and especially platelet EC adhesion molecule-1 expressions were enhanced through V_2O_5 exposure, which indicated a clear pro-inflammatory phenotype [132]. It was strongly suggested that V-induced ROS enhanced formation also participated in EC damage [132, 135].

Nitrate secretion was also augmented in V_2O_5 -treated HUVEC, thus suggesting that nitric oxide production was enhanced, possibly owing to an increase in endothelial NO synthase activity. Such an enhanced activity has been observed for HUVEC treated with vanadium sulfate [136], in osteoblast-like cells treated with vanadate [137], and ovariectomized female rats treated with bis(1-oxy-2-pyridinethiolato) oxovanadium [138].

The study which relate organic form of vanadium and angiogenesis, declared that local administration of vanadyl acetylacetonate enhanced femur fracture healing in a nondiabetic BB Wistar rat model, suggesting that local administration of vanadyl acetylacetonate is a potential therapeutic strategy for fracture healing [139]. These results revealed that new blood vessels and VEGF levels were remarkably increased in the fracture callus [139]. Although it was found that VEGF expression in mouse epidermal cells after exposure to vanadium (IV and V) was significantly increased [140], no other studies have investigated the effects of vanadium on blood vessel formation [139].

In our search for article, there was no article relating Nb and angiogenesis. Nb is used in implants with Ti and Va, thus following comparison were made between Va and Nb. Niobium had less inhibitory effect than vanadium on human osteoblasts, fibroblasts, and lymphocytes proliferation and viability [141]. The degradation products of Ti-6Al-4V may induce adverse biological effects rather than Ti-6Al-7Nb. Ti-6Al-4V activates monocytes and induces the release of the inflammatory mediator prostaglandin E2, IL-1, TNF- α , and IL-6 to a greater extent than Ti-6Al-7Nb [142]. In an in vivo study Ti-6Al-7Nb and cpTi induced slightly less inflammation than Ti-6Al-4V while both showed slight increase of microvascular permeability [143]. It was also declared that Ti- 6Al-4V particles implanted into the murine air pouch-model caused a reactive membrane inflammation, probably mediated by IL-6 [144]. This discrepancy may result from the fact that niobium is less toxic to cells than vanadium, as has been recently verified using cell proliferation and viability tests [141].

Lead (Pb)

Six related articles were found when the key word “Lead in Angiogenesis was searched. Among them 3 articles fitted the inclusion criteria and were selected for review [$\alpha = 3 - \beta = 0$]. Unfortunately, in most cases “Lead was miss interpreted with its verb form meaning “Induction. Exposure to Pb and its chemicals can occur through inhalation, ingestion, and dermal contact. Lead was shown to be nongenotoxic by most in vitro assays [145, 146]. However, lead was indicated to be carcinogenic in animals. Rodents given a high dose of lead administration were reported to develop cancers [146]. The mechanism of lead-induced carcinogenesis is also unclear, but it was suggested to be related to the ability of lead to inhibit DNA synthesis or repair, as well as to induce oxidative damage [146, 147]. The majority of published articles focused on the inflammatory reaction of Pb in vivo and in vitro, and indicated that lead is capable of inducing inflammatory reactions in various cell types [148–151].

Epidemiological studies have revealed that workers exposed to Pb had higher levels of inflammatory cytokines such as TNF- α and IL-10 than those who were not exposed [152]. The cellular inflammatory response (increased IL-8 level) to Pb plays an important role in the progression of cancer [153]. Kitadai et al. [154] showed that IL-8 mRNA levels were directly correlated with tumor vascularity and disease progression in gastric carcinoma. IL-8 was indicated to promote tumor angiogenesis and invasion via inducing angiogenesis and the epithelial-mesenchymal transition of multiple human carcinoma cells [155, 156]. Chronic exposure to low doses of Pb, even at very low levels (0.1 μ M), may induce local IL-8 production [153, 157]. The transcription factor AP-1 is necessary, whereas NF- κ B is not crucial for Pb-induced IL-8 activation [153]. The Pb induced IL-8 gene expression occurs through a MAPK pathway (Figure 1). Phosphorylation of ERK1/2 and activation of c-Jun are key elements in transducing Pb signals to activate the IL-8 gene. Epidermal growth factor receptor also participates in Pb-induced IL-8 gene expression. Lead regulates cPLA2/COX-2 expression and prostaglandin E2 secretion mainly through epidermal growth factor receptor phosphorylation that is mediated through ERK1/2 pathways in vascular smooth muscle cells [158].

Conclusions

- Ti surface cellular responses with different topographies and hydrophilicities are necessary because different results have been reported.
- TiO₂ nanoparticles effectively suppressed VEGF-induced tube formation and migration of human retinal microvascular EC, demonstrating inhibitory effects of nanoparticles on angiogenesis processes. The anti-angiogenic effect of TiO₂ nanoparticles comes from the inhibition of angiogenic processes, and not from cytotoxicity.
- Li in a GSK-3-dependent manner induced the expression of two pro-angiogenic factors expression, MMP-9 and VEGF.
- Li affects vasculogenesis but not angiogenesis, supporting the hypothesis that vasculogenesis and angiogenesis are regulated by different molecular processes
- Heparin-nanoceria and nanoceria may be practical therapeutic agents for controlling angiogenesis related tumor growth and metastasis by inhibiting EC growth.
- Nanoceria different shapes, except ceria nanorods, did not show cytotoxicity towards HUVEC, and induced cell proliferation. While, only nanoceria sized <15 nm showed the potential to induce tube formation.
- Arsenic has the dual effects on vascular cells and tumor angiogenesis, at low dose promotes, while at high dose inhibits angiogenesis.
- As₂O₃ acts as anti-angiogenic factor through inhibition of VEGF protein, COX-2, MMP-2, and MMP-9 expression in dose- and time-dependent manner.
- MeHg affects cell migration and tube formation activities of EC in a dose- and time-dependent manner,
- Vanadium treatment inhibited cell proliferation and induced cytotoxic effects by DNA interaction.
- Lead exposure induced IL-8 production, promotes tumor angiogenesis and invasion via inducing angiogenesis.

Abbreviations

As	Arsenic
FGF-2	Basic fibroblast growth factor
BMP-2	Bone morphogenetic protein-2
Ce	Cerium
COX	Cyclooxygenase

EC	Endothelial cells
EPCR	Endothelial cell protein C receptor
EPCs	Endothelial progenitor cells
EMT	Epithelial to mesenchymal transition
ERK	Extracellular signal regulated kinase
HUVEC	Human umbilical vein endothelial cells
HIF	Hypoxia-inducible factor
IAP	Inhibitor-of-apoptosis protein
IL	Interleukin
GSK	Glycogen synthase kinase
Pb	Lead
Li	Lithium
MMP	Matrix metalloproteinase
Hg	Mercury
MeHg	Methylmercury
MAPK	Mitogen activated protein kinase
Nb	Niobium
NO	Nitric oxide
NF-κB	Nuclear factor- κ B
PI3K	Phosphatidylinositol 3-kinase
ROS	Reactive oxygen species
rhVEGF	Recombinant human VEGF
S1P1	Sphingosine-1-phosphate type 1 receptor
TM	Thrombomodulin
Ti	Titanium
TiO₂	Titanium dioxide
TGF	Transforming growth factor
TNF	Tumor necrosis factor
Va	Vanadium

VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
vWF	von Willebrand factor
ZEB	Zinc finger E-box-binding homeobox

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Fig. 1. Schematic presentation of the effect of lead, lithium, nanoceria, and titanium dioxide on cells and their consequences on angiogenesis.

Fig. 2.
Schematic presentation of the effect of Arsenic on cells and its consequence on angiogenesis.