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ABSTRACT

The angiogenesis process is a phenomenon in which numerous molecules participate in the stimulation of the new vessels' formation from pre-existing vessels. Angiogenesis is a crucial step in tissue regeneration and recovery of organ and tissue function. Muscle diseases affect millions of people worldwide overcome the ability of skeletal muscle to self-repair. Pro-angiogenic therapies are key in skeletal muscle regeneration where both myogenesis and angiogenesis occur. These therapies have been based on mesenchymal stem cells (MSCs), exosomes, microRNAs (miRs) and delivery of biological factors. The use of different calls of biomaterials is another approach, including ceramics, composites, and polymers. Natural polymers are use due its bioactivity and biocompatibility in addition to its use as scaffolds and in drug delivery systems. One of these polymers is the natural rubber latex (NRL) which is biocompatible, bioactive, versatile, low-costing, and capable of promoting tissue regeneration and angiogenesis. In this review, the advances in the field of pro-angiogenic therapies are discussed.

1. Introduction

Angiogenesis is a phenomenon in which numerous molecules participate stimulating the formation of new vessels [1]. Angiogenesis consists of sequential steps, *viz*, vascular destabilization, angiogenic sprouting, migration, proliferation, and differentiation of endothelial

Abbreviations: AMPK, Adenosine monophosphate-activated protein kinase; Ang1, Angiopoietin-1; angiomiRs, Pro-angiogenic miRs; APLN, Apelin; bFGF, Basic fibroblast growth factor; CLI, Critical limb ischemia; ECs, Endothelial cells; EPCs, Endothelial progenitor cells; eNOS, Endothelial nitric oxide synthase; GDMy, Gestational diabetic myopathy; HGF, Hepatocyte growth factor; HUVECs, Human umbilical vein endothelial cells; IGF-1, Insulin-like growth factor 1; MSCs, Mesenchymal stem cells; MiRs, MicroRNAs; NRL, Natural rubber latex; OSM, Oncostatin; PDGF, Platelet-derived growth factor; POSTN, Periostin; SHH, Sonic hedgehog; TGF, Transforming growth factor; VEGF, Vascular endothelial growth factor.

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cells (ECs) [2,3], lumen formation, and vascular stabilization [4,5]. Moreover, the process encompasses the growth and regression of capillary blood vessels and is regulated at molecular and genetic levels [6].

The formation of new blood vessels from pre-existing vessels occurs under physiological and pathological conditions [1]. Angiogenesis is related to the progression of some diseases [7] such as cancer [8–10] Several studies show that the activation and improvement of angiogenic processes is an efficient therapeutic approach [11–13] . New methodologies for the stimulation of angiogenesis have been applied in regenerative medicine aiming at regeneration and recovery of the tissue and organ function [14–22]. Therefore, several benefits in the treatment of pathologies [23] is obtained by stimulation of angiogenesis such as in patients with cardiovascular diseases [24–26], limb ischemia [14,23,27,28] chronic wound healing [15,16,29] among others pathological conditions. On the other hand, inhibition of angiogenesis is a suitable approach for cancer therapies[5,30] implying the inhibition of disease progression [31,32], and metastasis [33–35].

This review summarizes relevant aspects of angiogenesis in physiological and pathological conditions focusing on the benefits of pro-angiogenic therapies in skeletal muscle regeneration (Fig. 1).

2. Angiogenesis and pathological implications

Angiogenesis is essential for an adequate tissue repair involving the expansion and remodelling of tissues in physiological processes such as wound healing, ovulation and embryonic development, and in pathologies such as cancer, atherosclerosis, and chronic inflammation [3,36]. The sequence of steps undertaken in the angiogenesis process requires different mediators including the vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) stimulating ECs proliferation and migration. Also, matrix metalloproteinases, especially matrix metalloproteinases 1 and 2, mediate degradation of the capillary wall and the extracellular matrix components urokinase and integrins favouring ECs migration towards the extracellular matrix [37]. Angiopoietin-1 (Ang1) promotes the reorganization of the ECs in stable tubules with a central lumen, and platelet-derived growth factor (PDGF) action results in formation of a vascular network with the newly formed tubules [38,39].

A fine balance between pro-angiogenic and anti-angiogenic factors allows a balanced progression of the vascular system. When this balance is broken, angiogenesis is altered leading to pathological states

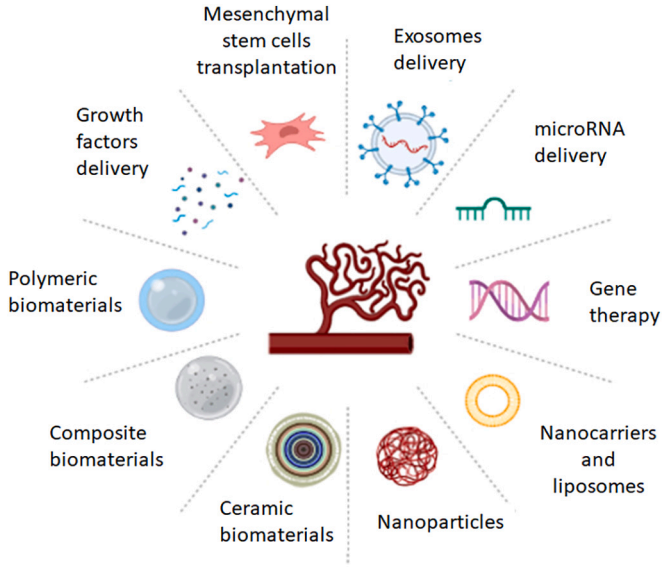

Fig. 1. Diversity of therapies with a pro-angiogenic approach.

including inflammation, tumour, and restenosis [40–42] . Tumours and metastases depend on a regular blood supply and the balance between pro-angiogenic and anti-angiogenic factors shifted in favour of increased angiogenesis in this disease. Increased angiogenesis allows a rapid tumour growth and cancer progression [34]. In tumours, the endothelial cells become more accessible to angiogenic inducers due to hypoxia and VEGF-mediated up-regulation and synthetized by angiotensin II [43,44], a phenomenon that results in a stronger angiogenic response [41]. Thus, pathological conditions leads to unregulated synthesis and release of angiogenic growth factors and modulation of vascular support cells [3] promoting a 'pathological angiogenesis'. In this context the inhibition of angiogenesis is a promising strategy to treat diseases with pathological angiogenesis [45]. Moreover, pro-angiogenic therapies may become crucial in tissue regeneration to rescue the organ and tissue function.

2.1. *Angiogenesis in skeletal muscle regeneration*

Angiogenesis and vascularization are determinant in tissue regeneration allowing blood supply to support tissue function by avoiding hypoxia, reduced metabolic nutrients supply, accumulation of waste products, and interruption of biochemical signalling mechanism [46,47]. The skeletal muscle is considered an organ highly adaptable largely depending on the microcirculation homeostasis [48]. Also, it is an organ that can be experimentally manipulated to study physiological regulation of angiogenesis [49]. Since the recovery from skeletal muscle injury is often incomplete because of the fibrosis formation and inadequate myofiber regeneration angiogenesis is a prerequisite for large tissue reconstitution and crucial for efficient skeletal muscle regeneration [50–54].

During muscle regeneration both myogenesis and angiogenesis occur and ECs and myogenic precursor cells interact to expand and differentiate [51]. Evidence *in vitro* and *in vivo* showed that these cells interact coupling myogenesis and angiogenesis in the skeletal muscle regeneration [55]. A proper coupling of these mechanisms result in higher muscle blood flow, increased capillary wall tension, and mechanical stress leading to increased sarcomere length [56]. Molecular profile of ECs and satellite cells from regenerating skeletal muscle allowed the identification of three effectors, *viz*, apelin (APLN), oncostatin M (OSM), and periostin (POSTN). These effectors stimulate the coupling of myogenesis/angiogenesis necessary for muscle regeneration [55]. Also, APLN, POSTN, and OSM show differential profile expression during muscle regeneration in 3D cultures with a peak of expression on day 2 for APLN and OSM and day 4–8 for POSTN [55]. Thus, a temporality in the effect of these molecules in skeletal muscle regeneration is likely.

APLN acts through its receptor APJ, a G protein-coupled receptor whose activation results in activation of angiogenesis [57]. APLN also acts as chemoattractant facilitating its own pro-angiogenic effects [58]. The involvement of APLN in angiogenesis and its epistatic relationship with VEGF-factor A signalling has been established in a series of *in vivo* assays [58–60] . APLN acts in a paracrine manner modulating the early vessel development, primarily inducing the growth of intersomitic blood vessels shaping the primitive vascular plexus [61,62]. Subsequently, during vessel sprouting, APLN expression is confined to endothelial tip cells, whereas APJ receptor is found in stalk cells which control vessel orientation and maturation [60,63].

OSM, a member of the gp130/interleukin 6 cytokine family, exerts pleiotropic effects through its receptor OSMR and has been reported to stimulate angiogenesis by upregulating VEGF, bFGF and angiotensin II [64,65]. OSM treatment has a potential to preserve the cardiac function in the infarct border zone of an ischemic myocardium through apoptosis and fibrosis inhibition, and angiogenesis stimulation via upregulating VEGF and bFGF [64]. In this context increased expression of POSTN, a 90-kDa secretory protein, has been correlated with angiogenesis in the development of keloids [66], tumour angiogenesis, and progression in oesophageal squamous cell carcinoma [67] and osteosarcoma [68].

Also, high expression of POSTN correlated with VEGF expression and microvessel density [68]. In pancreatic cancer, POSTN was identified as a promoter of angiogenesis and metastases upregulating the extracellular signal-regulated kinase/VEGF signalling pathway [69].

Muscular injuries associate with damage to the vascular network which causes the depletion of satellite cells affecting the ECs and the entire vascular network [70]. A functional dependency and crosstalk between pro-myogenic, pro-angiogenic, and pro-neurogenic growth factors is shown to play a role in skeletal muscle regeneration [71-73] . In this context the muscle regeneration is impacted by macrophages which orchestrate myogenesis/angiogenesis by coupling requiring OSM release [55]. Although skeletal muscle has a high potential for self-repair in acute injuries though mononucleated (myocytes), multipotent satellite cells found in mature skeletal muscle fibbers between the sarcolemma and the basement membrane [74], most cases of myopathic diseases or severe muscle injuries outweigh this muscle's ability [75].

It has been reported that specific subsets of periendothelial cells exhibit potent myogenic properties, while other subsets maintain the quiescence of satellite cells [76]. Interestingly, ECs stimulate the growth of myogenic progenitor cells, which exhibit angiogenic-like properties [77,78]. Several growth factors are involved in this ECs-myogenic progenitor cells interaction, including VEGF, insulin-like growth factor 1 (IGF-1) the PDGF-factor BB homodimer, hepatocyte growth factor (HGF) and bFGF [79,80]. Also, β-catenin is an angiogenesis modulator and can promote myocyte regeneration by enhancing ECs and skeletal myocytes proliferation and survival. The mechanisms include β-catenin–induced VEGF expression and angiogenic progenitor cell mobilization and muscle progenitor cell activation [81].

Interestingly, the hedgehog family member sonic hedgehog (SHH) is code by the *Shh* gene and acts as a morphogen-regulating silenced in postnatal life [82]. SHH is *de novo* expressed after injury and during regeneration of adult skeletal muscle [83,84]. Expression of SHH resulted in up-regulation of its receptor patched forming patched-SHH complexes targeting *Ptc1* gene which code for protein phosphatase 2C homolog 1, a metal-dependent protein phosphatase linked to cell growth and cellular stress signalling in injured and regenerating muscles [85]. Inhibition of SHH function resulted in lower up-regulation of angiogenic factors such as VEGF and stromal-derived factor 1α, decreased muscle blood flow, and reduced capillary density after injury [83]. These findings address the role of SHH on angiogenesis and skeletal muscle

Table 1
Clinical trials using pro-angiogenic therapeutic approaches to treating critical limb ischemia and associated diseases.

Present status	Condition	Therapy type	Type of intervention	Administration	Phase	Reference
Suspended	CLI	ACPs	Drug	Intramuscular injection	2	[339]
Completed	CLI	Platelet lysate	Biological	Intramuscular injection	1,2	[340]
Completed	CLI, PAD	ACPs, VesCell™	Biological	ACPs intramuscular injection	1	[341]
Unknown	CLI	BMMSCs and BMMNCs	Biological	Intramuscular injection	2	[342]
Completed	CLI	ACPs	Biological	Intramuscular injection	2	[343]
Completed	CLI, diabetic foot	Autologous BMMNCs	Other	Intra-arterial infusion	1,2	[344]
Completed	CLI, diabetes mellitus	Autologous AMSCs	Drug	Intra-arterial administration through a selective cannulation	1,2	[345]
Completed	PAD, CLI, diabetic foot	Autologous BMMNCs	Biological	Intra-arterial administration through a selective cannulation	1,2	[346]
Recruiting	CLI	ACPs	Biological	Intramuscular injection	2	[347]
Unknown	CLI, PAD	RV-P1501	Biological	Injection	1,2	[348]
Completed	CLI	BMMNCs	Other	Intraarterial injection	2	[349]
Completed	CLI	BMAC	Biological	Transplantation	2	[350]
Completed	CLI, AOD, PVD, ischemia, ulcers	HGF	Genetic	Plasmid vector	2	[351]
Unknown	CLI	Calf compression	Device	Pneumatic calf compression	*N.a.*	[352]
Unknown	CLI	Autologous ADSVF Autologous SVF	Biological	Autologous SVF and ADSVF were intravenous and intramuscular infusion concomitantly	1,2	[353]
Unknown	CLI, diabetic foot	hUCMSCs	Biological	Intramuscular, intraarterial, and intravenous infusion	1,2	[354]
Unknown	CLI, PAD	Recombinant SeV-hFGF2/dF	Biological	Intramuscular injection	1	[355]
Unknown	CLI, T2DM	Autologous BMAC	Biological	Intramuscular, intraarterial, and intravenous infusion	2,3	[356]
Completed	CLI	Autologous BMMNCs	Other	Intramuscular injections	1,2	[357]
Completed	CLI, PAD	BALI	Biological	Implantation of BALI-harvested versus BMMNCs implantation	3	[358]
Terminated	CLI, PVD, PAD	cBMA	Device	cBMA intramuscular injection into the affected limb	*N.a.*	[359]
Active, *N.r.*	CLI, PVD, PAD	MultiGeneAngio	Biological	Intraarterial injection	1,2	[360]
Withdrawn	CLI	Stempeucel(R)	Biological	Intramuscular injection	2	[361]
Completed	CLI, Buerger's disease	Stempeucel	Biological	Intramuscular injection	2	[362]
Completed	CLI, PVD, PAD	ALDHbr	Procedure	ALDHbr versus BM-MNCs surgery	1,2	[363]
Unknown	CLI, Buerger's disease, ACO	BMMNCs	Procedure	Implantation	Unknown	[364]
Recruiting	CLI, PAD, T1DM	REX-001	Drug	Intraarterial infusion	3	[365]
Terminated	CLI, PAD, T1DM	REX-001	Drug	Intraarterial infusion	3	[366]
N.r.	CLI, PAD, CVD, VD	Allogeneic BMMSCs	Drug	Intramuscular injection	2,3	[367]
Unknown	CLI, foot ulcer, skin ulceration	Carbothera	Procedure	Bathing	*N.a.*	[368]
Completed	CLI	Autologous adult MSCs	Other	Intramuscular injection	1,2	[369]

ACO, arteriosclerosis obliterans; ACPs, autologous angiogenic cell precursors; ADSVF, adipose derived stromal vascular fraction; ALDHbr, autologous bone marrow derived aldehyde dehydrogenase-bright; AMSCs, adipose-derived MSCs; AOD, arterial occlusive disease; BALI, bone marrow autograft in limb ischemia; BMAC, bone-marrow aspiration concentrate; BMMNCs, bone-marrow mononuclear cells; BMMSCs, bone marrow-derived mesenchymal stem cells; Carbothera, CO_2-enriched (1000–1200 ppm) tap water; cBMA, concentrated bone marrow aspirate; CLI, critical limb ischemia; CVD, cardiovascular diseases; HGF, hepatocyte growth factor plasmid; huMSC, human umbilical cord mesenchymal stem cells; MSCs, mesenchymal stem cells; PAD, peripheral arterial disease; PVD, peripheral vascular disease; REX-001, novel autologous cell therapy; RV-P1501, gel-like hyaluronan combined with BMMNCs; SeV-hFGF2/dF, Sendai virus recombinant to express human basic fibroblast growth factor (hFGF2); Stempeucel(R), *ex vivo* cultured adult bone marrow derived allogeneic MSCs; SVF, stromal vascular fraction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; VD, vascular diseases; VesCell™, autologous adult stem cell therapy; *N.a.*, not applicable; *N.r.*, not recruiting.

regeneration processes. The combination of *Shh* transfer and bone marrow-derived endothelial progenitor cells (EPCs) promotes angiogenesis and muscle regeneration showing the potential beneficial effects of Shh + EPCs combination therapy in pro-angiogenic therapies [86].

Since angiogenesis is required for muscle regeneration and pro-angiogenic therapies, i.e. therapeutic angiogenesis, it is considered as a key phenomenon in clinical (Table 1) and preclinical studies. Ang1 effect on fiber regeneration, myogenesis, and angiogenesis has been assessed in a mice model of injured tibialis muscle. A single injection of adenoviral-delivered Ang1 into the tibialis muscle increased tibialis anterior muscle contractility, muscle fiber regeneration, and capillary density [87]. These findings suggested that Ang1 enhances skeletal muscle regeneration likely via induction of the myogenesis and angiogenesis program through regulatory mechanisms involved in coordinated gene expression in myogenic progenitor cells and ECs, respectively [87–89] . Interestingly, the basic helix-loop-helix transcription factors, such as MyoD, Myf5, MRF4, myogenin, and the cyclin-dependent kinase inhibitor p21 play key roles in the myogenic transcriptional program [90].

Other studies reported the effect of a sustained delivery of VEGF and IGF-1 in angiogenesis, muscle regeneration, and rescue of muscle function in hind limbs of ischemic rodents [79]. Delivery of VEGF alone led to neo-angiogenesis in ischemic limbs returning to normal tissue perfusion and protecting against hypoxia and tissue necrosis ending in improved muscle contractility. IGF-1 delivery increases muscle fiber regeneration and protected cells against apoptosis. Interestingly, combined delivery of VEGF and IGF-1 led to parallel angiogenesis, reinnervation, and myogenesis along with activation and proliferation of satellite cells, protection against apoptosis, silencing of inflammatory response, and formation of highly functional muscle tissue [79]. An efficient coordination between myogenesis and angiogenesis is suggestive of a proper regeneration of skeletal muscle, including an adequate regulation of signalling pathways and gene expression.

Also, the therapeutic potential of VEGF family members VEGF-factor A, VEGF-factor B, VEGF-factor C and VEGF-factor D, and a specific mutant of VEGF receptor-3 (VEGF-factor C156S) was evaluated in rabbit hind limb skeletal muscle [91]. Overexpression of the ligands of VEGF receptor-2, VEGF-factor A and VEGF-factor $D^{\Delta N\Delta C}$ induced angiogenesis and vascular permeability with a remarkable increase in microvessels and recruitment of pericytes suggesting the formation of arterioles or venules. Overexpression of VEGF-factor A caused a moderated increase in the capillary density and formation of glomeruloid bodies while there was a diffuse angiogenesis induced by overexpression of VEGF-$D^{\Delta N\Delta C}$ [91]. It is also reported that transplantation of human adipose derived stromal cells modified by the recombinant adeno-associated virus (rAAV) serotype 2 encoding human VEGF165, which substantially increases secretion of VEGF, has stronger therapeutic effects on ischemic skeletal muscle and may be a promising clinical treatment for therapeutic angiogenesis [92]. Another group showed that the delivery of mesenchymal stem cells including adipose derived stromal cells by subcutaneous transplant of cell sheets stimulates angiogenesis and protect the limbs tissue with ischemia including the skeletal muscle in mice [93].

Human trials on angiogenesis therapies designed to increase the VEGF level by injecting VEGF-factor A gene family using DNA plasmid or viral vectors or its proteins have failed, probably because of their short viability and systemic toxicity. Other assays show that PR1P, a 12-amino acids peptide whose sequence derives from one extracellular VEGF binding domain of the pro-angiogenic glycoprotein proemin-1, increased the angiogenesis due to potentiation of the endogenous VEGF activity [23]. It is interesting that the latter is an approach taking advantage of the endogenous tissue gradient concentrations of VEGF generated in the damaged tissues. This phenomenon improves the VEGF efficacy without altering the normal signalling associated to this growth factor elsewhere in the body avoiding systemic toxicity of VEGF as reported in other therapies [23].

The potential contribution of adult human CD133+ cells to skeletal muscle regeneration in an athymic mouse model was investigated [94]. CD133+ were locally transplanted into skeletal muscle lacerations. After treatment, histological and functional skeletal myogenesis was significantly observed in the CD133+ treated animals. The injected CD133+ cells differentiated into endothelial and myogenic lineages, a finding paralleled by the up and down expression of genes related to angiogenesis, fibrosis, and host myogenesis. As an example, up-regulation of Pax7 expression and down-regulation of TGF-β1 gene expression found in these animals. CD133+ cells enhanced histological and functional recovery from skeletal muscle injury [94].

Secreted factors from different CD4+ T cells (Th1, Th2, Th17, and Treg) were delivered from an injectable alginate biomaterial into a murine model of ischemia to assess their effects on vascularization and skeletal muscle regeneration [95]. The findings suggest that angiogenesis and myogenesis were increased in ischemic lesions by Th2 and Th17 cells action. Interestingly, these findings could be useful in the design of immunomodulatory biomaterials to treat ischemia altered skeletal muscle regeneration. Another study shows that angiogenesis induced by muscle-derived stem cell transplantation in the muscle healing process in mice was improved involving higher VEGF expression and consequent increased muscle regeneration and strength and decreased fibrosis [96]. The *in vivo* transplantation of muscle-derived stem cell transduced to overexpress VEGF in mdx mice, a model of muscular dystrophy, resulted in increased angiogenesis, endogenous muscle regeneration, and reduced muscle fibrosis with VEGF-induced skeletal muscle angiogenesis [97].

The prostacyclin agonist YS-1402 stimulates neovascularization and skeletal muscle regeneration in rats with critical limb ischemia (CLI) [98]. The effect of YS-1402 was an increase in the tissue blood flow. These findings were complemented by detection of arterioles showing CD31+/α-smooth muscle actin+ and increased level of prostacyclin receptor, stromal cell-derived factor-1, hepatocyte growth factor, neural cell adhesion molecule, and higher myogenin and MyoD expression. Therefore, functional angiogenesis and skeletal muscle regeneration were promoted by YS-1402 in this animal model [98].

Another approach has been the use of adenoviral delivery of peroxisome proliferation activator receptor-γ coactivator-1α which increased angiogenesis in adult and elderly, and in diabetic mice [99]. Peroxisome proliferation activator receptor-γ coactivator-1α induced the secretion of phosphoprotein 1 and the recruitment of macrophages with a higher monocytes-secreted chemoattractant protein-1. The latter activated adjacent ECs, pericytes, and smooth muscle cells leading to improved blood flow in a hindlimb ischemia model of peripheral arterial disease [99]. The AMP-activated protein kinase activator 5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside (AICAR) increases the D-glucose uptake and reduces the reactive oxygen species generation in skeletal muscle [100]. Treatment of ischemic hind limbs in mice with AICAR accelerated the angiogenic repair in a VEGF-dependent AMP-activated protein kinase (AMPK) manner. Since AICAR also activates $p38^{mapk}$, an AMPK/$p38^{mapk}$ signalling cascade in response to VEGF in skeletal muscle promoting angiogenesis in ischemic injury is likely [101].

2.2. Angiogenesis in critical limb ischemia

CLI is the most severe manifestation of peripheral arterial disease characterized by ischemic non healing wounds, gangrene, tissue loss, or rest pain and is considered the ‘end stage’ of this artery disease [102,103]. CLI associates with poor prognosis with a 5-year mortality (~50% patients) and low quality of life compared with patients with advanced cancer [104,105,22] . Patients with CLI cannot receive revascularization therapy due to late diagnosis and accumulation of severe comorbidities [106,107]. Also, revascularization therapy is palliative and increase the abundance of sequelae, disabilities, and new hospitalizations [108,109]. However, patients with CLI might benefited from a pro-angiogenic treatment [106,107]. Pro-angiogenic therapeutic

approach is an important alternative for the treatment of CLI aiming at better perfusion in ischemic tissues, regardless of invasive surgeries for macrovascular manipulation [22,110]. These approaches are mainly focused on wound healing and tissue regeneration [14], avoiding amputations, improving quality of life and decreasing morbidity and mortality.

Through the knowledge gained about the complex processes involved in angiogenesis and the pioneer work of therapeutic angiogenesis by Judah Folkman (1974) [1,47], many pro-angiogenic therapeutic approaches have been applied in the CLI treatment. Currently, several clinical and preclinical studies have supported the safety and clinical potential of treating CLI through pro-angiogenic therapeutic interventions [111–117]. These pro-angiogenic interventions are based on the involvement of growth factors such as VEGF [117], cell-based strategies, exosomes, miRs, proteins and gene therapy [23,112,116,118,119]. According to www.clinicaltrials.gov website, 31 clinical trials for treating CLI based on pro-angiogenic therapies are registered of which 22 are cell-based therapy (Table 1).

The evaluation of the efficacy, tolerability, and safety of intramuscular injections of 'off the shelf' allogeneic placental derived mesenchymal like cell therapy (PLX-peripheral artery disease) for the CLI treatment is assayed in the Pacing, graded Activity, and Cognitive behaviour therapy —a randomised Evaluation trial parallel group phase III study (randomized, double blind, multicentre, placebo controlled, Clinicaltrials.gov: NCT03006770) [114]—. PLX- peripheral artery disease previously in two small, open label, phase I trials, showed pro-angiogenic, anti-inflammatory, regenerative properties which were favourable to one year amputation free survival showing trends in reduction of pain scores and increased tissue perfusion.

In a miR-based approach, the therapeutic potential of Ad.Luc-Decoy-15a/16 (fragment of firefly luciferase-decoy 15–16) in a mouse limb ischemia model was studied [107]. The results showed that local delivery of Ad.Luc-Decoy-15a/16 increased the level of tyrosine-protein kinase receptor Tie-2 precursor (angiopoietin 1 receptor) in ischemic skeletal muscle and improved post-mouse limb ischemia angiogenesis and perfusion recovery. The effects of Ad.Luc-Decoy-15a/16 reduced toe necrosis, providing new mechanistic evidence of therapeutic potential [107]. Thus, pro-angiogenic therapy has evolved increasing its potential use for the treatment of CLI with more effective and safe results. Also, the therapy broadens the perspectives of using pro-angiogenic therapeutic approaches for unmet clinical conditions bringing countless benefits to the field of regenerative medicine for regeneration and recovery of tissue and organ functions.

3. Mesenchymal Stem cells and angiogenesis

3.1. Cell-based therapy

Cell-based pro-angiogenic therapy shows promising results in clinical and pre-clinical trials in the treatment of several pathologies, such as CLI [111], cardiovascular diseases [120], peripheral artery disease [115], and wound healing [19]. Although it is of high potential the mechanisms of action remain largely unknown [111]. The MSCs privileged immunogenic activity in addition to the pro-angiogenic factors secreted by these cells [121]. MSCs are probably responsible for the effectiveness of the cell-based pro-angiogenic therapy [111,122–124]. Along the factors promoting angiogenesis that are involved in the therapy are VEGF [110], bFGF [125] and HGF [126] which are secreted by MSCs. The biological actions of these growth factors are enhanced due to the involvement of extracellular vesicles, including exosomes [127], which show high capacity of delivering its cargo of miRs, proteins, and others molecules targeting cells with a high angiogenic activity.

MSCs are adult stem cells capable of trans-differentiation in the presence of proper stimuli. Activation of MSCs leads to differentiation into ectodermal (neurons and skin) and endodermal (hepatocytes, lung, and intestinal cells) origin [128,130] or from the cell fusion process [131]. The most common source of MSCs are the bone marrow, umbilical cord blood, Wharton's jelly, cartilage, dental pulp, adipose tissue [19] and placenta [132]. The minimum criteria for characterization of MSCs are based on their adherence to plastic in culture, surface markers CD105, CD73, and CD90, and absence of markers of hematopoietic cells, monocytes, macrophages, or B cells and the capacity of the cells to differentiate in osteoblasts, adipocytes, and chondroblasts [128,133].

MSCs are of clinical interest due to their potential use in autologous transplantation [134]. These cells correspond to stem cells with almost no endogenous teratogenic potential risk [130] [135]. Also, MSCs shows ability to orientable differentiation [136] —a differential response to differentiation stimuli increasing the biosynthesis of specific factors ending in a better regenerative response— becoming a convenient cell source for tissue regeneration [137–140]. Although multiple coordinated mechanisms governing MSCs-based therapy is not fully elucidated, pre-clinical and clinical trials has shown evidence that MSCs promote tissue regeneration mainly through increased angiogenesis, synthesis and release of neurotrophic factors, inhibition of apoptosis, and modulation of the immune system [141–144].

The intra-arterial infusion of MSCs enhances microvascular regeneration by increasing the vasculogenesis and angiogenesis as well as cell survival [129,145] MSCs release a variety of angiogenic paracrine factors [146], including VEGF [147], HGF [147], brain-derived neurotrophic factor [148], glial-derived neurotrophic factor [149], fibroblast growth factor (FGF) [150], cytokines such as monocyte chemoattractant protein [150] and interleukin 6 [151], Ang1 [152], IGF-1 [153], transforming growth factor (TGF)-β [154] and stromal derived factor − 1 alfa [155].

Several pre-clinical and clinical trials consider the MSCs transplantation a safe pro-angiogenic recovery strategy [156–160]. There is evidence showing that systemic MSCs injection resulted in these cells become trapped in capillary beds in different tissues, especially in the lungs. Thus, local administration of MSCs is the preferred method of administration to avoid side effects including a higher thrombogenic risk [161–164]. Interestingly, cell migration [164], tumorigenic potential [165], and insufficient graft cell survival [166,167] remain unsolved problems in MSCs-based pro-angiogenic therapies. Another major issue in MSCs-based pro-angiogenic is that the new formed vessels are often immature [111,168]. Maturation of new formed vessels is critical for a good regenerative response as the must be fully functional to provide sufficient blood flow to meet the tissue's oxygen and metabolic demand [111,168]. Pre-clinical and clinical trials on MSCs–based pro-angiogenic therapies demonstrate great potential and beneficial pro-regenerative and anti-inflammatory action [169-172], although there are still lack of information about action mechanisms. Some studies support the possibility that the beneficial effects of this therapy are mediated by a paracrine action and activation of the acute immune response to cell delivery rather than *in situ* trans-differentiation [173,174].

3.2. Extracellular vesicles/exosomes

A factor involved in the MSCs beneficial effects is the capacity of these cells to release extracellular vesicles [175]. The extracellular vesicles, including exosomes, are actively released by the cells and are of interest for regenerative medicine and pro-angiogenic approaches [176-178]. Exosomes show a diameter ranging 50–150 nm, are of endosomal origin through the dripping of multiple vesicles in the late endosome (multivesicular body) [179–181], and are released by exocytosis [179,182]. Since exosomes are formed by a lipid bilayer that protects their cargo from enzymatic degradation, these vesicles are efficient in delivering proteins, messenger RNAs (mRNAs), miRs, and other cytosol components to the target cells. Exosomes of autologous or allogeneic origin show efficacy and safety in the treatment of pathological conditions expanding its use in regenerative medicine and in pro-angiogenic therapeutic approaches. Exosomes cargo carry pro-angiogenic miRs

which may amplify stem cells function explaining the angiogenic and therapeutic benefits associated with $CD34^+$ stem cell therapy [175]. Exosomes carry immunorelevant structures regulating the immune response, such as major histocompatibility complex (MHC) molecules, co-stimulatory molecules, heat shock proteins, and naive tumour antigens showing a considerable anti-tumour effect [183–186]. Also, exosomes can orchestrate vascular repair via miRs transfer [187,188]. MSCs-derived exosomes can activate signalling pathways critical for wound healing such as Akt, MAP kinases, and STAT3, and induce the expression of growth factors including HGF, IGF-1, nerve growth factor, and stromal cell-derived factor 1 [189,190].

MSCs-generated extracellular vesicles increase angiogenesis-associated tissue regeneration by delivering signalling molecules to activate ECs [191] via miRs (v.g. miR-126, miR-214, miR-296, miR-125a, miR-31, miR150) [192–197], proteins (v.g. VEGF, FGF-2, PDGF, IL-8, TGF-β1) [198–200], lipids (v.g. sphingosine-1-phosphate) [201], activation signalling pathways (v.g. PI3K, $p44/42^{mapk}$) [201,202], and transfer of transcription factors (v.g. signal transducer and activator of transcription 3 (STAT3) and STAT5 [203,204] MSCs-generated exosomes have a therapeutic effect comparable to a direct cell transplantation, actively acting in angiogenesis, inflammation, immunomodulation, cell proliferation and other processes for tissue repair [205]. Exosomes present unique advantages over cell therapies. For example, in stroke patients the exosomes cross the blood-brain barrier increasing their biodistribution preventing infarcts caused by vascular occlusion, thus, offering a ready-to-use approach for acute ischemic stroke [206]. Therefore, MSCs-generated exosomes may be new therapeutic effectors in regenerative medicine for neurological diseases [207,208]. The latter due to their reported actions in promoting functional recovery [209], providing long-term brain protection [210], acting in the grey matter repair and recovery, increasing neurogenesis and angiogenesis [211], white matter repair [212], and immunomodulation [210] in experimental stroke models [213]. MSCs-generated exosomes therapy benefits from the exosomes high viability [214] and because reduces the risk associated with live cell therapies such as ectopic tissue formation (i.e. tumorigenesis) and infusion toxicities due to cells lodging and cellular rejection or unwanted engraftment [215]. However, some gaps in this type of therapy still need to be resolved before its clinical implementation. For example, the ideal time, the most effective route, and the minimum effective administration dose for adequate treatment are key elements to resolve when treating patients [215]. Preclinical studies show strong evidence addressing the importance of the dose of exosomes used regarding neurological outcomes after cerebral ischemia [209,215].

3.3. miRs

The paracrine role of MSCs-generated exosomes in tissue regeneration results in promoting myogenesis and angiogenesis *in vitro*, and muscle regeneration *in vivo* in skeletal muscle injury models. This effective repair performance of exosomes is due to its rich cargo [216]. The exosome cargo also include small RNAs (including ~22 nucleotides miRs) and other small non-coding RNAs (including vaultRNA), and transfer RNAs [217]. miRs mediate post-transcriptional gene silencing by binding the 3′-untranslated region of target mRNAs [218]. Post-transcriptional regulation mediated by miRs result in the modulation of crucial cell phenomena including proliferation, division, and differentiation, neuronal asymmetry, metabolism, development, stem cell properties, protein secretion, apoptosis, and viral infection [219,220].

The miRs are involved in the regulation of angiogenesis. Recent reports show that miRs depletion suppresses tumour angiogenesis in human cancers [221,222]. These findings suggest a pivotal role played by miRs in angiogenesis in vascular function-dependent tumour growth. Thus, miRs are a major focus of interest aiming the identification of new pro-angiogenic therapeutic targets, mainly delivering and blocking tissue specific miRs rescuing its function [223-226]. Also, miRs can be either pro-angiogenic (angiomiRs) or antiangiogenic (antio-angiomiRs) [227,228]. AngiomiRs promote angiogenesis by targeting negative regulators in angiogenic signalling pathways, while anti-angiomiRs inhibit angiogenesis by targeting positive regulators of angiogenesis [229].

Many angiomiRs have been identified as good targets for pro-angiogenic therapy (Table 2). Vascular endothelium responds to angiogenic stimuli via miRs including miR-126, miR-221/222, miR-17-92 cluster, miR-93, let-7f, miR-27b, miR-214, and the enzymes Dicer and Drosha are prerequisite in miRs processing and show the essential role of these molecules in angiogenesis [228,230]. It is known that miR-126 play critical roles in promoting angiogenesis in response to VEGF and bFGF through the suppression of phosphoinositide-3-kinase regulatory subunit 2, increasing the action of Ang1 on neovessel stabilization and maturation [231,232], or repressing the sprouty-related protein-1 and inhibiting the actions of vascular cell adhesion molecule 1 [233] and PI3K/Akt [234,235]. Another example is miR-221 and miR-222 which regulate several essential physiological processes in the endothelium, such as differentiation, proliferation, and apoptosis [27,236]. These miRs target at least two important regulators of pro-angiogenic function of ECs, *viz*, c-kit and endothelial nitric oxide synthase (eNOS) [237]. However, high expression of miR-221 and miR-222 blocks angiogenesis

Table 2
microRNAs with pro-angiogenic activity and targets for new pro-angiogenic therapies.

microRNA	Target	Function	Reference
miRNA-126	SPRED-1, PIK3R2, VECAM-1	Activation of VEGF, Akt and enhances MAP kinase signalling, p85-β depressing	[231] [228]
miRNA-210	Ephrin-A3	Increased capillary-like formation and ECs chemotaxis	[370]
miRNA-10b, miRNA-9b	HOX pathway	Increased ECs proliferation, migration, tubule formation	[371]
Let-7b, Let-7f	Let-7b, TIMP, Let-7f, TSP-1	Regulation of sprout formation	[230]
miRNA-132	p120RasGAP	Increased ECs proliferation by p120RasGAP downregulation	[372]
miRNA-378	Sufu, Fus1	Increased ECs migration, tube formation, tumour angiogenesis	[373]
miRNA-17-92 cluster	TIMP1, TSR, VEGF	Increased ECs division and migration	[374]
miRNA-23, miRNA-27	Sprouty 2, Sema6a proteins	Inhibition of anti-angiogenic proteins	[375]
miRNA-296	VEGF, VEGFR2, DLL4, Notch1	Increased angiogenesis signalling and regulation	[376]
miRNA-106b-25 cluster	PTEN, Akt	Regulation of ANSCs, BMSTCs, ECs proliferation and differentiation	[377]
miRNA-21-5p	Spry1, MMP-13, VEGF, p-44/42^{mapk}	Regulation of angiogenesis	[378]
miRNA-135b	FIH-1	Increased endothelial tube formation via HIF-FIH signalling	[379]

Akt, protein kinase B; ANSCs, adult neural stem-cells; BMSTCs, bone marrow-derived stromal cells; DLL4, delta-like protein 4 precursor; ECs, endothelial cells; FIH-1, HIF-1 inhibiting factor; HIF, hypoxia-inducible factor; HOX, subset of homeobox genes; Let-7b, lethal-7 gene family; Let-7f, lethal-7 gene family; MAPK, mitogen-activated protein kinases; miRNAs, microRNAs; MMP-13, methyl metaloprotease 13; Notch1, neurogenic locus notch homolog protein 1; p-44/42^{mapk}, phosphorylated 44/42 kDa MAPK; p120RasGAP, Ras GTPase activating protein; p85, phosphatidylinositol 3-kinase regulatory subunit; PIK3R2, phosphoinositide-3-kinase regulatory subunit 2; PTEN, phosphatase and tensin homolog; Sema6a, semaphorin 6A; SPRED-1, sprouty related EVH1 domain containing 1; Spry1, Sprouty RTK Signaling Antagonist 1; Sufu, Negative Regulator Of Hedgehog Signaling; TIMP, metallopeptidase inhibitor; TIMP1, TIMP 1; TSP-1, thrombospondin 1; TSR, methyl-accepting chemotaxis protein I; VECAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2. Adapted from [220].

and ECs proliferation, and promotes proliferation in cancer cells by targeting the cell cycle inhibitor p27 [238]. The latter findings suggest that the regulation of proliferation by these miRs is cell-specific. On the other hand, miR-17–92 cluster participates in tumour-induced angiogenesis by regulating VEGF-induced ECs angiogenic function, also cooperatively regulate a large number of genes affecting ECs function [239]. MiR-93 was shown to activate ECs resulting in higher spreading, proliferation, migration, and tube formation. The pro-angiogenic activity of miR-93 was linked with the partial suppression of integrin-β8 expression in ECs [240]. The miR-let-7f and miR-27b promote angiogenesis by targeting antiangiogenic genes such as *THBS1*(coding for thrombospondin 1) [238]. In a mouse model of hindlimb ischemia, intramuscular injection of miR-let-7f mimic restored ischemia-induced neovascularization, a phenomenon paralleled by improved Doppler flow rates and capillary density in ischemic muscles in mice exposed to cigarette smoke [241]. MiR-27b promotes capillary sprouting and endothelial tip fate by suppressing the Notch ligand, delta-like ligand 4 and the negative regulator of branching, Sprouty-2 [242]. Also, miR-27b inhibits Sprouty-2 and repulsive signalling by semaphorin 6A [242,243]. Over expression of miR-214 decreased the release of pro-angiogenic growth factors, including VEGF, a phenomenon reversed when miR activity was inhibited; however, miR-214 silencing increased the secretion of pro-angiogenic growth factors [244]. The delivery of angiomiRs in pro-angiogenic therapies can be based on exosomes as reported to reverse the drug resistance in colorectal cancer [245]. Exosomes enriched in miR-214 promote ECs migration and angiogenesis *in vitro* and *in vivo*. The ataxia telangiectasia mutated —a serine/threonine kinase recruited to DNA double-strand breaks involved in the initiating cell cycle arrest and DNA repair— was repressed in cells receiving miR-214 resulting in blood vessel formation [194]. Also, the miR-based therapy using adenovirus-associated vector delivered miR-26a was shown to suppress liver cancer [246], lung carcinoma [247,248] and other type of cancers [249].

3.4. Biomaterials

Furthermore, several other ways to miRs delivery are reported including those based on biomaterials such as polymers [250], hydrogels [225], nanoparticles [251], and liposomes [252–254]. Also, *in vivo* attenuation of neuroinflammation was assayed using chitosan miR nanocarriers [255] and nanocarriers encapsulated into the injectable hydrogel matrix Gel@MSN/miR-21-5p enabling control on-demand of microRNA-21 delivery triggered by a local acidic microenvironment. The use of Gel@MSN/miR-21-5p resulted in a synergy of anti-inflammatory and pro-angiogenic effects effectively reducing the myocardial infarct size in pigs [225]. Alternatively, the delivery of miR-145 through gold-nanoparticles (Au-NPs) improved the tissue distribution and site-specific localization of this miRs. Also, Au-NPs delivering miR-145 restored its reduced level detected in prostate and breast cancer [256]. Nanoliposomes are likely internalized through the endocytic pathway in breast cancer cells [252,257]. Thus, nanoparticle delivery may be an efficient strategy for pro-angiogenic therapies but further studies in clinical trials are needed to address their potential side effects and effectiveness.

4. Angiogenesis promoting biomaterials

The term biomaterials was defined in 1986 as “nonviable material used in medical devices intended to interact with the biological system” [258]. Since its definition the field of biomaterials has evolved along with advances in technology and materials engineering [259]. Biomaterials are used for tissue engineering and regenerative medicine [260]. In the pro-angiogenic therapy, biomaterials induce the angiogenesis process and may be set up to deliver pro-angiogenic factors such as MSCs, exosomes, growth factors, and angiomiRs. There are several classes of biomaterials including ceramics [261], composites [262], metallic [263], and polymers [264]. The association of biological factors with bioactive biomaterials (smart biomaterials) are key strategies optimizing pro-angiogenic therapy with fewer adverse effects [265].

4.1. Ceramics, composites, and polymers pro-angiogenic biomaterials

Ceramics are inorganic compounds formed from metallic and non-metallic elements joined by ionic and covalent bonds. Bioactive ceramics such as hydroxyapatite, bioglasses, and glass-ceramics interact with the surrounding tissue stimulating angiogenesis [266,267]. The use of 45S5 Bioglass® has been successful meeting the challenges of *in vivo* administration of growth factors such as VEGF for angiogenesis therapy [268]. Surfaces coated with 45S5 Bioglass® stimulate the release of VEGF and bFGF enhancing angiogenesis [268]. Furthermore, in order to provide a structure that resists physiological stresses and also maximize osteogenic and angiogenic properties, the composition of bioactive glasses can be manipulated [269]. Furthermore, bioglasses showed the ability to stimulate fibroblasts to release VEGF, bFGF, epidermal growth factor, collagen I, and fibronectin enhancing angiogenesis [270].

Silicate bioceramics such as akermanite ($Ca_2MgSi_2O_7$) induces angiogenesis during bone regeneration by increasing the gene expression of pro-angiogenic cytokine receptors and up-regulating downstream signalling mechanisms [271,272]. A recent study showed that bone marrow stromal cells-generated exosomes after strontium-substituted calcium silicate (Sr-CS) promoted angiogenesis in human umbilical vein endothelial cells (HUVECs), a response attributed to the elevated exosomes cargo with the pro-angiogenic miR-146a and to inhibition of mothers against decapentaplegic homolog 4 and merlin proteins [273]. Studies in Zebrafish confirmed that bone marrow stromal cells-generated exosomes have pro-angiogenic ability contributing to an accelerated development of vascularization [273]. Porous calcium phosphate is a typical bone bioceramic which allows formation of functional capillary whose density depended on the pore size [274]. Also, the interconnected macropores (350–500 μm) in the ceramic scaffold led to uniform deposition of collagen allowing endothelialisation of microchannels, thus, demonstrating enhanced angiogenic sprouting and anastomosis [274,275].

Some pro-angiogenic microcarriers release silicate ions during dissolution or cellular degradation which ultimately influences angiogenesis and osteogenesis [275,276]. These biomaterials include silica-based bioactive glasses, akermanite, bredigite ($Ca_2Mg(SiO_4)_4$), monocalcium silicate ($CaSiO_3$), dicalcium silicate (Ca_2SiO_4), tricalcium silicate (Ca_3SiO_5), silicon-doped calcium phosphates, tricalcium phosphate, silica incorporated calcium phosphate cement (CPC), silicate-doped calcium carbonate ($CaCO_3$), silicon-incorporated glasses, and glass ceramics. To improve the pro-angiogenic potential, some composite materials [277,278] based on ceramics, metal and polymers have been developed. Composites are a class of materials consisting of a continuous phase (matrix) and a dispersed phase (reinforcement component or modifier) separated by interfaces, whose characteristics can incorporate combined properties of the individual constituents [279]. Recently, lanthanum-doped bioglasses/chitosan composite scaffolds, a hierarchically porous structures combining hollow cores and mesoporous shells, are available. This new composite biomaterial showed that the as-doped lanthanum oxide in the scaffolds stimulated migration and tube formation of HUVECs and also promoted vascularization *in vivo* [280]. Despite the positive effects on angiogenesis using foetal macrovascular endothelium as a model, it is still pending to see whether the properties of this biomaterial are resembled in human adult microvascular endothelium [281].

Polymer-ceramic composites have been an alternative in the construction of composite biomaterials with high pro-angiogenic activity since polymeric biomaterials [282]. Polymers are macromolecules of high molar mass formed by linking smaller repetitive units along a main chain. Polymers can be obtained from polymerization reactions or from living organisms, thus classifying them as synthetic and natural,

respectively [283,284]. One of these polymers is the synthetic poly(L-lactic acid), a polymer that have pro-angiogenic properties in HUVECs and stimulates the migration of vascular smooth muscle cells via a nuclear factor κB-dependent pathway [285,286]. Natural polymers or bio-derived materials have stood out in the construction of biomaterials for pro-angiogenic therapies, since they are biocompatible, show low side effects, are of wide availability, easy to handle, and are of low cost [287]. Natural polymer occur in nature and can be extracted using physical or chemical methods and present different physical and chemical characteristics [288]. These characteristics can be modified during the preparation of biomaterials reaching specific goals, such as sustained release of proteins, degradability, mechanical resistance, among others [289]. The combination of stromal derived factor-1 alpha with the natural polymer collagen-based scaffolds provides a suitable condition for assaying angiogenic response in wound closure [290]. Chitosan/gelatin hydrogel is another natural polymer that provides a suitable condition to adipose-derived stem cells encapsulation. The use of this approach increased the VEGF level and tube-like structures in SVEC4-10 ECs and the capillary density in chick embryo chorioallantoic membrane assay [291].

The natural polymer fibrin carriers pro- and anti-angiogenic proteins [292]. Thus, a cross-linked, slowly biodegradable fibrin/alginate scaffold with calcium phosphate was developed to improve the angiogenesis. This composite biomaterial showed pro-angiogenic potential leading to increased vascularisation in chorioallantoic membranes due the faster dissolution process making calcium ions available promoting angiogenesis [293]. Other studies show that a leukocyte- and platelet-rich fibrin biomaterial (platelet-rich fibrin) acts as binding site for platelets and growth factors. The platelet-rich fibrin increased the expression of VEGF and vessel-like structure formation of co-culture systems consisting of outgrowth ECs and primary osteoblasts [294]. Since this biomaterial is of ease autologous transplantation and easy obtainment and production it might be a natural polymer to consider when promoting angiogenesis and tissue regeneration [295].

Composites with natural polymers nano-sized (20–30 nm) bioglass (n-BG) (nominally 45S5 BIOGLASS) associated with bovine type I collagen/n-BG composites are also available. Addition of n-BG (10% wt) to collagen films induced early angiogenic response making selected collagen/n-BG composites a possibility for tissue engineering and regenerative medicine [296]. Porous β-calcium silicate (β-CS) with the *co*-polymer poly(D,L-lactide-glycolide) composite scaffolds are also available (240). Ionic extracts of β-CS/poly(D,L-lactide-glycolide) composites increased HUVECs proliferation associated with activation of the Akt pathway and eNOS, and higher NO level and VEGF release [297]. Another biomaterial is the collagen-chitosan-sodium hyaluronic composite —a natural biopolymer with biocompatibility, biodegradable, and non-toxic— which increases neovascularization in rabbit corneal stroma [298] and skin [299]. The increase in neovascularization was due to its ability in promoting greater ECs differentiation, enhancing vascular growth expression, and recruiting a greater number of vWFþ and CXCR4þ endothelial/angiogenic cells, enhancing VE-cadherin expression [300]. It is worth highlighting that a pre-screening study showed differences in the angiogenesis effect between composites biomaterials with natural polymers and polymers with high overall porosity showing a greater vascularisation compared to synthetic polymers [301].

Biomaterials has also been developed by combining stem cells and bioactive molecules to produce three-dimensional pro-angiogenic scaffolds. One example is the electrospun nanofibrous scaffolds which offers opportunities for pro-angiogenic approaches in tissue repair and regeneration [302,303]. In addition, they are efficient in drug delivery for pro-angiogenic factors [304]. Nanofibers made of natural and synthetic polymers are often used to incorporate bioactive components such as bioglasses and biomolecules such as VEGF, with pro-angiogenic activity. Alterations in the electrospun scaffold architecture modulates the response of mast cells promoting cell/scaffold regenerative interactions [305] affecting the VEGF release and angiogenesis. VEGF release is supported best by scaffolds with large fibers and pores [305,306]. The pore size throughout an implant can facilitate the transmural angiogenesis throughout the walls of the implant [307], large pores are less inflammatory and can promote wound healing/angiogenesis [305].

4.2. Natural rubber latex pro-angiogenic biomaterial

Natural polymers have several advantages compared with synthetic polymers, *viz*, biocompatibility, not toxic degradation products, bioactivity, good physical chemical characteristics, low cost, and handling versatility [308]. In this context, the use of natural rubber latex (NRL) as a pro-angiogenic biomaterial has shown promising in clinical and preclinical studies. NRL shows high angiogenic potential resulting in high capacity to regenerate damaged tissue [309–318]. NRL is the sap produced after injury from the bark of the rubber tree (*Hevea brasiliensis*), a native Brazilian plant found in the Amazon region [319]. NRL composition is characterized by a mix of colloidal rubber particles which is stabilized by a phospholipids and proteins layer (Fig. 2). Its composition is 40–45% weight of rubber (the common form of polyisoprene poly(cis-1,4-isoprene)), 4–5% weight of non-rubber (proteins, lipids, carbohydrates), and ~ 50% of water [320,321].

NRL has numerous characteristics that make it an excellent pro-angiogenic biomaterial such as high permeability, bioactivity, elasticity, biocompatibility, surface porosity, mechanical resistance, low cost, and abundance [308]. Also, its bioactivity is due to a wide composition of pro-angiogenic proteins found in the aqueous fraction of NRL released in a sustained manner due to the chains formed by polyisoprene after its polymerization. Thus, NRL is a polymer for the development of drug delivery [322–326]. Furthermore, NRL is also a scaffold for the use of MSCs in pro-angiogenic therapies due to its bioactivity, roughness and surface porosity, which can be modulated during the scaffold preparation [327] (Fig. 3). The latter are characteristics facilitating cell adhesion, proliferation, and viability [327]. Thus, the immobilized MSCs in NRL and the maintenance of these cells' viability are an alternative to overcome the challenges of MSCs therapy.

5. Biodevice development for muscle regeneration

Skeletal muscle diseases such as myopathies and other muscle injuries affect millions of people worldwide [328]. Therefore, it is urgent and essential to develop new, more effective and safer therapies to repair the structural and functional deficits of the affected skeletal muscle. Injured skeletal muscle repair is a process involving immune, muscle, perivascular, and neural cells [329]. The repair capacity of skeletal muscle regeneration therapies often results in structural and functional deficits due to the fibrosis formation [330]. Furthermore, an inappropriate recovery of skeletal muscle functionality can lead to debilitating problems and a decrease in patients' quality of life [331]. Currently the treatments to skeletal muscle regeneration are poorly addressed and are of low capacity to rescue the muscle structure and functionality. Thus, more effective approaches are urgently needed. There are new therapies focused on regeneration and engineering of the skeletal muscle based on

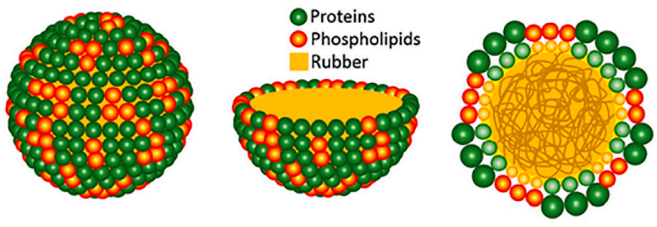

Fig. 2. Suggested schematic representation of a natural rubber latex particle showing the layers composed of proteins, phospholipids, and rubber. From [322],[338].

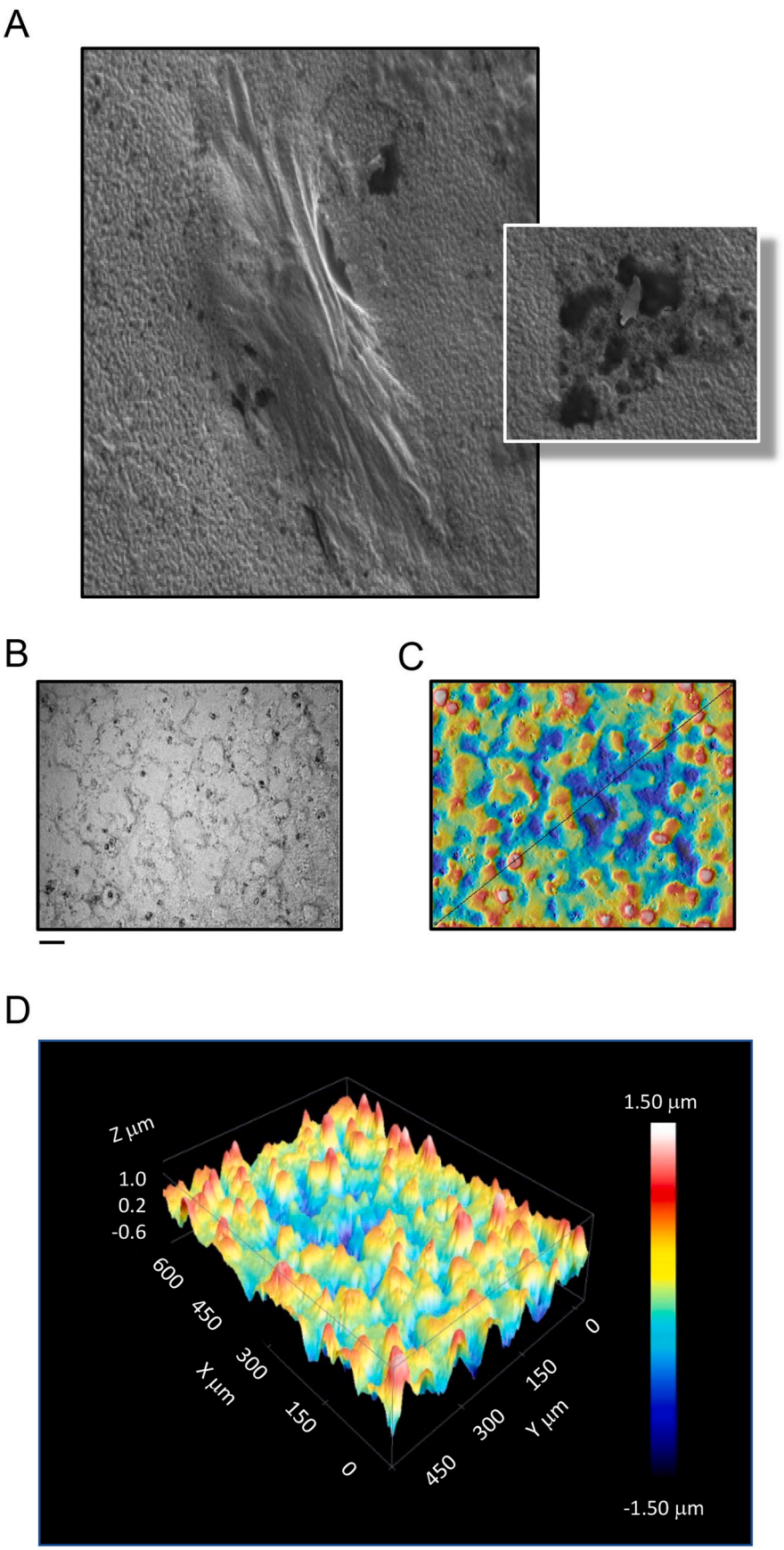

Fig. 3. Natural rubber latex scaffold. (A) Scanning electron microscopy showing the natural rubber latex porous surface (500×). The insert shows a greater magnification (1500×) of a superficial porous region from A. (B and C) 2D confocal images for the scaffold surface region of biomembranes. Bar in B is 50 µm. (D) 3D construction for the scaffold surface region of biomembranes showing the surface roughness (1.5 µm) from C.

the use of biomaterials, including natural polymers to produce scaffolds guiding infiltration, alignment, and cell differentiation [332–334].

Women with pregnancy complicated by gestational diabetes mellitus have high risk to develop the gestational diabetic myopathy (GDMy) characterized by pelvic floor skeletal muscle severe atrophy leading to urinary incontinence [335–337]. GDMy is a condition poorly addressed still waiting for an efficient therapy. Clinical interventions in patients with GDMy are only palliative, recurrent, and leading to an increase in the health public and social costs ending in a lower quality of life. Interestingly, a new biodevice for the regeneration of skeletal muscle was recently proposed for women with this complication [327] (patent number BR 102020 005536 4) (Fig. 4). The biodevice was designed using a porous NRL membrane coated with MSCs and it has being tested in an experimental model of GDMy in the post-partum. The design of the biodevice aimed to improve the pro-angiogenic capacity of the NRL and overcome the challenges of MSCs therapy. Preliminary results show that application of the biodevice promoted higher neovascularization, inflammation, and fibroblast reactivity in the rectus abdomis muscle skeletal muscle from GDMy rats compared with non GDMy rats. Thus, the biodevice may be an alternative for the recovering of the functionality of the rectus abdomis skeletal muscle by increasing neovascularization and fibroblast reactivity. Based on the versatility of NRL innovative designs are being developed based on this natural polymer aiming to improve its pro-angiogenic potential in sustained delivery capacity of bioactive molecules.

6. Conclusions and remarks

Angiogenesis is a fundamental step for regeneration and recovery of skeletal muscle function. Although the skeletal muscle has the capacity to regenerate itself, some diseases and injuries overcome this capacity leading to disabilities, physical limitations, and reduced quality of life, thus requiring clinical interventions. In recent years, many advances in pre-clinical and clinical trials suggest effectiveness of pro-angiogenic therapies in skeletal muscle recovery, including delivery of growth factors, MSCs therapy, gene therapy, delivery of exosomes, miRs, and the use of different classes of biomaterials. Although success has been achieved in the area, there are still several limitations and gaps in this field, including the clinical safety and effective application of these therapies. In this context, studies with innovative and bold approaches have been focused on improvement of the therapies based on MSCs and MSCs-derived exosomes, delivery systems for miRs, and suitable biomaterials. Clinical trials are being carried out and are at various stages, all focused in ensuring the safety of the clinical application and optimization of these pro-angiogenic approaches. A more effective and safer therapy may associate the bioactive pro-angiogenic and biocompatible characteristics of the NRL with the pro-angiogenic characteristics of MSCs. The latter might result in a biodevice overcoming the challenges of MSCs therapy, increasing the maintenance of live and immobilized cells in a bioactive scaffold to prevent its migration and loss of viability. Scientific and technological advances to engineering methodologies are fundamental in the development of more effective and safer pro-angiogenic therapies, even when enormous advances have been made in this area in the recent years.

Authors' contributions

General outline of the review: JFF, MVCR, LS. Collected literature: JFF, MVCR, LS, CE, SV, AMPB, RGO, EAFF, CFOG, JFA, RDH. Discussed and analysed the collected literature: JFF, MVCR, LS, CE, SV, AMPB, RGO, EAFF, CFOG, JFA, RDH. Wrote the manuscript: JFF, MVCR, LS.

Consent for publication

Not applicable

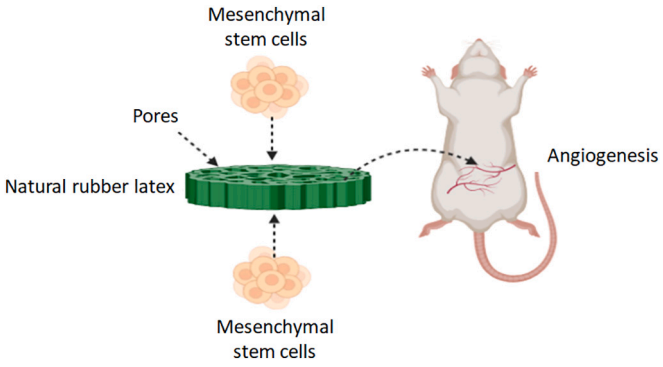

Fig. 4. Scheme of the biodevice design based on a porous natural rubber latex scaffold coated with mesenchymal stem cells. The biodevice was implanted in the rat rectus abdominis skeletal muscle where angiogenesis is achieved.

Declaration of Competing Interest

The authors declare no conflict of interest, financial or otherwise.

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