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Melatonin and angiogenesis potential in stem cells

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Abstract

Ischemic diseases, especially coronary artery diseases and myocardial infarction, are the leading cause of human death in the clinical setting. Unfortunately, most of the available clinical interventions can partially restore the function of ischemic myocardium, resulting in the progression of chronic heart failure.The induction of vascular tissue formation, hereafter known as angiogenesis, can provide blood perfusion and prevent the expansion of ischemia-related pathologies. In recent years, the discovery and advent of multiple stem cells into human regenerative medicine have led to the alleviation of certain end-stage pathological conditions via direct differentiation into the mature and functional cells or secretion of various cytokines and angiogenesis factors in a paracrine manner. Melatonin (mel) is a natural molecule with direct and indirect pleiotropic actions on different biological phenomena. This neurohormone is primarily known for its antioxidant, tumoricidal, and anti-inflammatory actions in several pathological conditions. Whether and how mel regulates the angiogenesis behavior of stem cells is currently under debate. Here, we collected and evaluated recent data related to the angiogenic properties of mel on stem cells. Data from the present article may help us in the development of new therapeutic regimes in patients with ischemic conditions.

Keywords Melatonin, Stem cells, Neovascularization, Paracrine communication, Cell differentiation

Introduction

In recent decades, the risk of cardiovascular diseases (cvds) has increased in developing and industrialized societies due to intensive lifestyle changes [1]. Cvds encompass a group of heterogeneous pathological conditions influencing both heart tissue and the vascular system [2]. Among cvd patients, coronary artery diseases (cad) and subsequent endothelial cell (ec) injuries are the most prevalent conditions, leading to prominent myocardial infarction (mi) and, thereby, heart failure [3]. Data have shown that the gradual narrowing or sudden occlusion of the coronary artery can interrupt the blood flow into the myocardium [4]. The reduction of cardiac tissue o_2 levels and nutrients leads to oxidative and bioenergetic stress in cardiomyocytes. These features can lead to concurrent necrotic changes and aberrant myocardial remodeling [5]. It is believed that the increase of blood perfusion via the stimulation

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of angiogenesis/vasculogenesis is a strategic approach to reduce the sequelae and post-complications of acute ischemic conditions [6]. Angiogenesis is the formation of de novo vascular units from the pre-existing vasculature in response to hypoxia and the increase of proangiogenesis factors. The term vasculogenesis is related to the direct participation of vascular progenitor cells, such as endothelial progenitor cells (epcs), in the generation of new blood vessels. It is thought that both phenomena commonly occur in various pathological conditions [7]. In the clinical setting, coronary artery bypass graft (cabg) surgery and antithrombotic therapy are conventional therapeutic approaches in mi patients [8]. Despite the advantages of gabg methods and anti-coagulant administration, the individuals are prone to fibrillation, bleeding complications, and thromboembolism [8]. Because of these complications, clinicians and researchers have made attempts to increase the efficiency of therapeutic approaches or find new modalities to circumvent the limitations in clinical settings.

The advent of stem cells, progenitors, and their secretome to human medicine has led to significant advances in the alleviation of various pathologies [9, 10]. Stem cells have been applied via different routes in mi patients and experimentally induced mi animal models [11]. Based on the previously published data, harsh microenvironments, including hypoxic conditions and a lack of nutrient supply, can contribute to the death of transplanted stem cells at the site of injury [12]. Meanwhile, mechanical stress during the direct administration of stem cells into ischemic sites can make these cells vulnerable to numerous insulting conditions [13]. Therefore, pre-treatment and/or co-administration of stem cells or other cells with protective agents may increase the regenerative outcomes within the ischemic myocardium.

Melatonin (mel) is a lipophilic molecule with pleiotropic effects and has been studied in terms of its actions on angiogenesis and vascularization [14, 15]. With its uncommon mechanistic role, numerous signaling pathways are influenced by this hormone. Emerging data have indicated that mel exhibits both pro- and anti-angiogenesis properties in the context of cvds [16]. The increase of angiogenic properties of stem cells, either in a juxtacrine or paracrine manner, along with direct orientation toward ecs, can improve the healing of the myocardium [13]. To date, there are only a few reports related to the pro- and anti-angiogenesis properties of mel on various stem cell lineages. Herein, we try to highlight the possible role of mel in the angiogenic potential of stem cells under ischemic conditions (Fig. 1).

Mel biogenesis and its role in biological systems

Chemically, mel is n-acetyl-5-methoxytryptamine, which was initially detected in bovine pineal tissue [17]. The evidence is that mel evolved about 2.5 to 2.0 billion years ago in bacteria to eliminate the free reactive oxygen species (ros) [18]. In eukaryotes, mel is produced by mitochondria, perhaps in every cell [19]. The production by the pineal gland and systemic levels of mel depends on the circadian cycle [20]. In addition to the rhythm-regulating properties of mel, this molecule possesses potent anti-ros activity in biological systems [21]. The pineal gland only produces an estimated 5% of total body mel, while the mitochondria of other cells generate the bulk of the melatonin in animals [22–30]

The amino acid tryptophan is the precursor of mel. To this end, circulating, tryptophan is internalized into the pinealocyte parenchyma within the pineal gland and chemically modified to 5-hydroxytryptophan (serotonin) by the activity of tryptophan hydroxylase. In the next step, amino acid decarboxylase converts serotonin to 5-hydroxytryptamine, also known as serotonin, and the addition of the acetyl group leads to the production of n-acetylserotonin, which further converts into mel by the enzymatic activity of acetylserotonin o-methyltransferase (Fig. 2) [31].

The inherent lipophilic entity of mel leads to rapid blood and cerebrospinal fluid (csf) distribution, and about 70% of the total circulating mel can be transferred by albumin to reach different tissues [32]. The levels of mel are controlled by the direct activity of the above-mentioned enzymes in response to circadian rhythm and collaboration with hypothalamic suprachiasmatic nuclei [33, 34]. The importance of mel in different organs relates to pleiotropic properties such as ros scavenging, anti-aging effects, and inhibition of pathological processes [35]. Notably, mel has multiple biological actions, including inhibition of tumor cell growth [36], wound healing [37], improving metabolic disorders [38], inhibition of parasitic, bacterial, and viral infections [39], and promotion of immune cell function [40]. Due to the multifaceted activity of mel and its active role in numerous physiological and pathological conditions, some of its underlying mechanisms remain to be fully identified.

Besides, it was suggested that mel may have the potential to modulate several pro-angiogenesis factors such as epidermal growth factor [egf], platelet-derived growth factors [pdef], transforming growth factor beta-1 [tgf-β1], insulin-like growth factor-1 [igf-1], vascular endothelial growth factor [vegf], hepatocyte growth factor [hgf], and other factors [41]. Considering the critical role of angiogenic responses in various physiopathological conditions, here we addressed the potential function

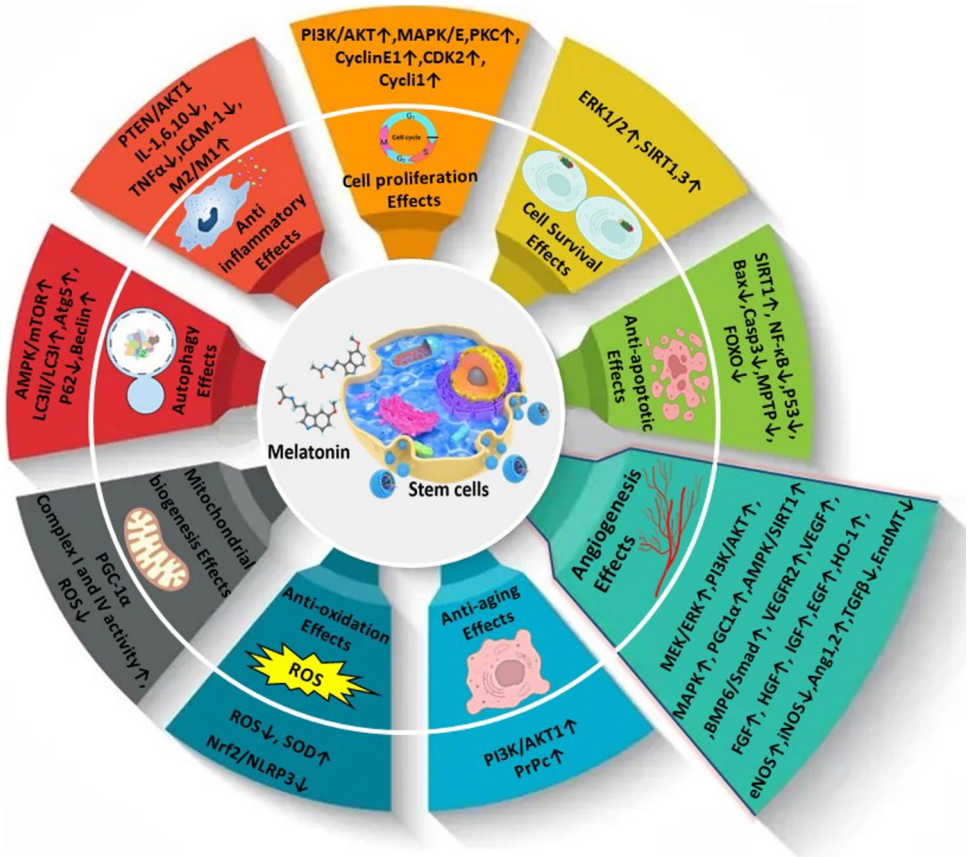

Fig. 1 Schematic illustration related to pleotropic effects of mel in stem cells. Designed by powerpoint software

of mel on the pro- and anti-angiogenesis properties of stem cells.

Angiogenesis and vasculogenesis

The regulation of angiogenesis/vasculogenesis is a critical step in a variety of different biological processes such as growth, development, tumor expansion, and the healing process [42]. Both angiogenesis and vasculogenesis are controlled by means of intricate mechanisms involving multiple cells, various cytokines, and growth factors [43, 44]. Understanding the molecular mechanisms and various cells involved in the vascularization process could help us achieve better regenerative outcomes [42].

Angiogenesis (neo-vascularization) is the common means of blood vessel formation and encompasses several consequential steps involving the generation of new blood vessels by the activity of mature ecs (Fig. 3). In response to hypoxia and ischemia, quiescent ecs are activated, proliferate, migrate, and undergo morphological change to generate nascent vessels [45, 46]. Certain signaling pathways and biomolecules are directly engaged in the process of angiogenesis. For instance, vegf/vegfr and angiopoietins (angs)/tie-2 axes, along with fgf/fgfr signaling pathways, are actively involved in the angiogenic response [43, 47]. The direct attachment of vegf to vegfr-1 and −2 on the ec surface triggers proliferation, migration, and phenotypic acquisition [48]. Co-activation of fgf/fgfr signaling pathway along with vegf/vegfr axis intensity ec proliferation, and tubulogenesis activity [49]. Ang-1 and −2 can bind to tie-2 on the ec surface to control cell-to-cell connection and blood vessel maturation, in which ang-1 stabilizes the nascent vascular tissue structure by recalling pericytes while ang-2 promotes vascular tissue remodeling and sprouting [50].

Vasculogenesis is also involved in the generation of new vascular units with significant participation of progenitors, and stem cells such as vegfr-2^+/tie-2^+/sca-1^+/$cd34^+$/$cd133^+$ epcs (Fig. 3) [7]. Vasculogenesis is the dominant form of blood vessel formation during the embryonic step when it forms the primary vascular plexus, and in adults, vasculogenesis, along with angiogenesis, can help to supply blood into the hypoxic sites [7]. Upon the activation of vasculogenesis, bone marrow epcs are attracted to the hypoxic sites and can promote blood vessel formation via the secretion of different cytokines, thereby promoting maturation into functional ecs [51].

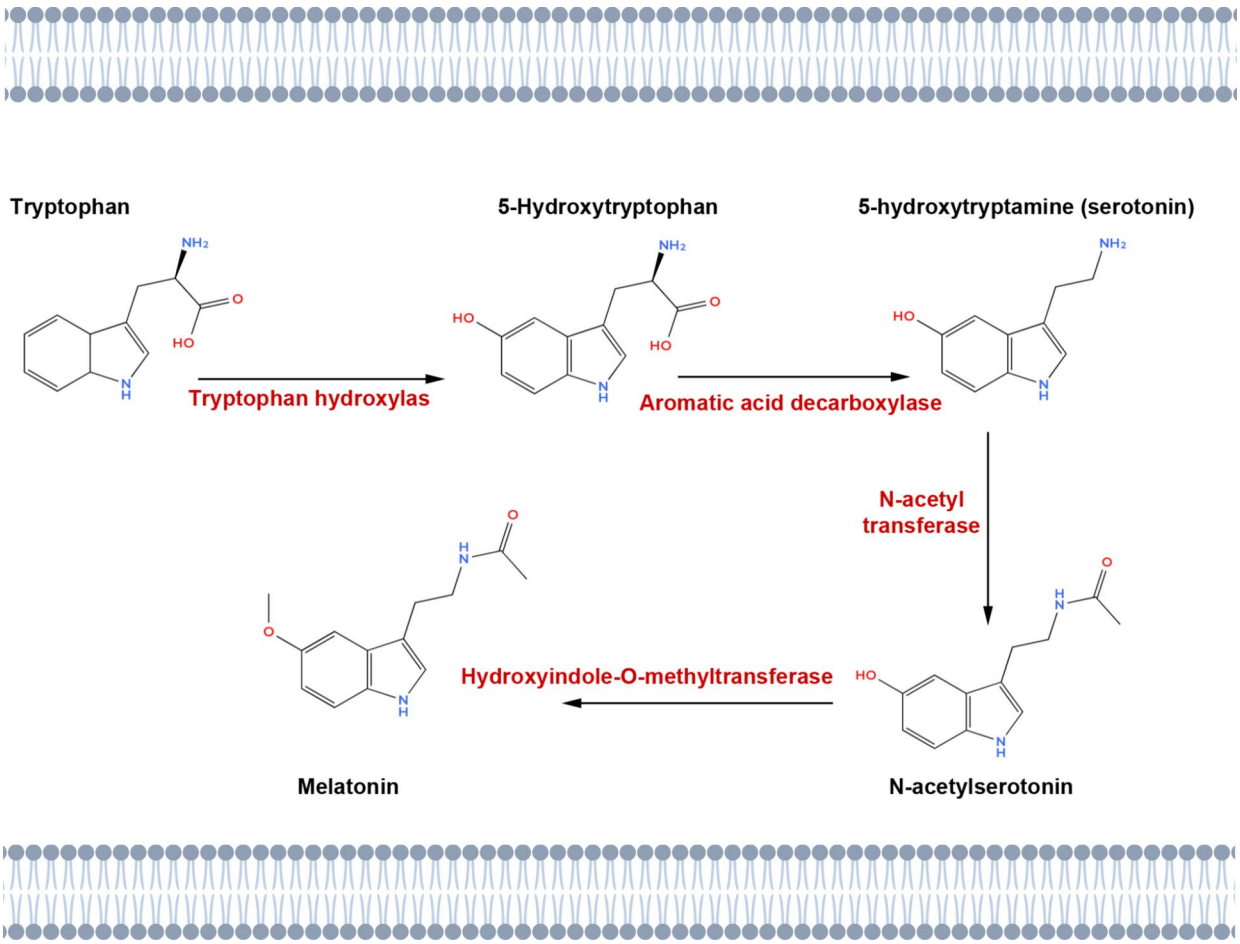

Fig. 2 The schematic illustration of mel biogenesis in pinealocytes within the brain pineal gland. Created by biorender's web-based software

Upon reaching the site of injury, epcs lose their stemness (cd133↓, cd34$^{\pm}$) and exhibit ec-related markers such as vwf, ve-cadherin, endothelial nitric synthetase (enos), and cd31 [7]. Like angiogenesis, several cytokines such as vegf, notch, sdf-1α/cxcr4, along with other factors, regulate the process of vasculogenesis by epcs [52–54]. Following the formation of the nascent vascular tubes, other cells, such as pericytes, wrap the ecs at the abluminal surface of the vascular wall [55].

Angiogenesis properties of stem cells

Following the tissue regeneration, new vascular units are generated to scavenge the dead cells and provide essential compounds such as oxygen and nutrients required for cell proliferation, growth, and functional phenotype acquisition [56]. The advent of stem cell therapy in the clinical setting has opened an avenue for enhancing blood perfusion in several pathological conditions [57]. Despite the angiogenic properties of stem cells and secretome, it requires significant time to achieve complete regenerative outcomes in ischemic conditions [58].

Of the different stem cell types, epcs, mesenchymal stem cells (mscs), and pluripotent stem cell-derived ecs have been extensively used for the promotion of vascularization in different pathological conditions [59]. As mentioned, epcs can regulate the process of vascularization directly and indirectly via differentiation into mature ecs or the release of several proangiogenesis factors [60]. However, due to the sacristy of epcs in the systemic circulation and issues related to their expansion, the application of epcs as common stem cell sources for ischemic conditions is limited [61]. Using some strategies, such as the culture of epcs in a serum-free medium enriched with growth factors, can increase the proliferation potential of these cells while preserving their stemness features (cd34↑) and angiogenesis potential (*vegf*↑, *igf-1*↑, and *mmp-9*↑) [62, 63]. Also, epcs can control the process of vascularization via the release of angiogenesis factors, *i.e.*, vegf, inside nano-sized extracellular vesicles (evs), namely exosomes (exos), and microvesicles (mvs) [64]. In response to the gradient density of vegf and other cytokines, epcs

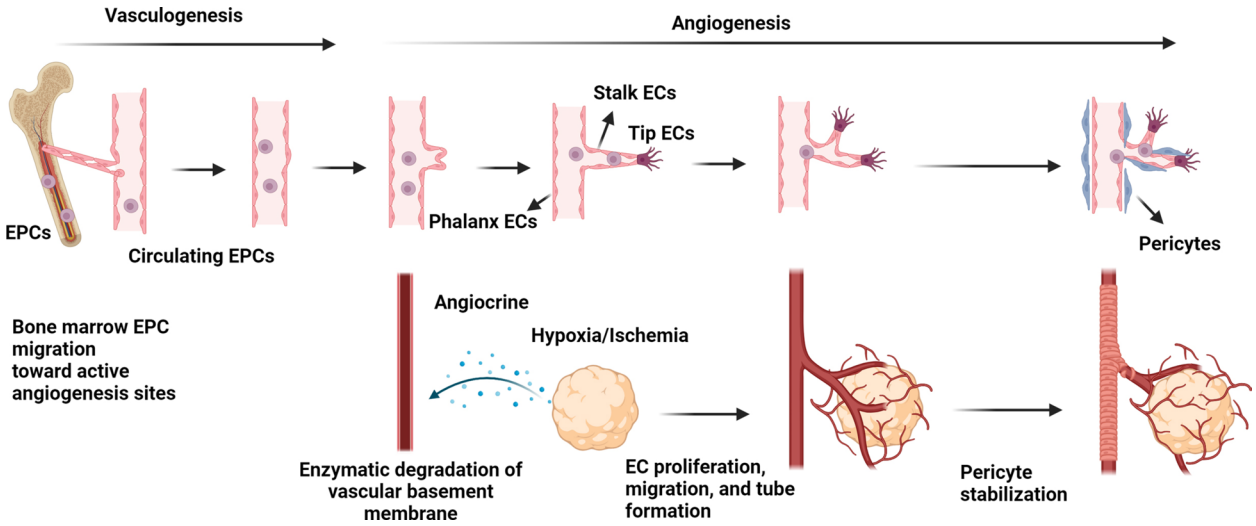

Fig. 3 Mechanism of angiogenesis versus vasculogenesis. In response to hypoxic/ischemic conditions, the release of proangiogenesis factors activates the mature ecs in the close blood vessels (angiogenesis). The pioneer ecs, also known as tip cells, migrate in a cytokine gradient density toward the ischemic/hypoxic zone. The lumen formation and proliferation of stalk and phalanx ecs can extend the developing blood vessels toward the target zone. The addition of pericytes to the abluminal surface of de novo vessels stabilizes the integrity of the vascular wall. It is also possible that the activated bone marrow epcs migrate toward the ischemic/hypoxic zone and are involved in the development of new vascular structure in a paracrine and/or direct orientation toward mature ecs (vasculogenesis) [7]. Reproduced with the permission of the publisher. 2024. Cell proliferation

migrate toward the ischemic area to foster the formation of new vessels [65].

Like epcs, mscs with spindle-shaped morphology exhibit angiogenic behavior with the potential to morph into ecs [66, 67]. These cells also release an array of angiogenesis factors after direct injection/transplantation into the target sites, resulting in the promotion of ec function, tubulogenesis capacity, and regulation of immune cell function [59, 68]. It should also be kept in mind that mscs can exert pro- and/or anti-angiogenesis properties in a context-dependent manner. Thus, the administration of mscs for the alleviation of ischemic conditions should be done cautiously [68]. Previously, it was shown that adipose tissue-derived mscs (ad-mscs) can produce angiocrine factors [69]. Data have confirmed that ad-mscs can stimulate the expression of cxcr-4, il-1α, il-6, vegfa, stat3, and il-8/cxcl8 in human umbilical vein ecs (huvecs) with active participation of recruited neutrophils and macrophages [70]. Stem cells, especially mscs and epcs, are biologically armed to control the process of vascularization under physiological and pathological conditions.

Effect of mel on the angiogenic properties of stem cells

Although stem cells offer a promising therapeutic avenue in the regeneration of ischemic microenvironments, their limited survival rate and retention time after transplantation are problematic issues [71]. Harsh ischemic niches can directly damage mscs via the induction of apoptotic changes, in which about 80% of transplanted mscs die within a few days after administration [72]. Mel easily interacts with various stem cell types with the potential to alter proliferation rate, stemness features, self-renewal properties, and commitment toward target cell lineages [71]. Based on the published data, mel has the potential to influence both paracrine and differentiation properties of stem cells in the context of angiogenesis (Table 1).

Inflammatory response, along with oxidative and nitrosative stresses, can directly influence the viability of mscs within the ischemic site. Thus, mel can protect the transplanted mscs by scavenging the free radicals such as ros and nitric oxide (no) metabolites [73–75]. Tang et al. found that treatment of rat mscs with mel can reduce oxidative stress induced by h_2o_2 under in vitro conditions. Of note, mel has the potential to increase the viability of oxygen-glucose-deprived rat mscs and close it to near-to-normal conditions. At least part of the activity of mel on mscs is orchestrated via the activation of membrane-bound mel receptors 1 (mt1) and 2 (mt2) (Fig. 4) [76]. In support of this, the protective effects of mel on mscs were blunted in the presence of mel receptors' antagonist luzindole [72]. Aierken et al. found that the expressions of mt1 and mt2 are stimulated in human umbilical cord mscs exposed to the mel treatment via the activation of the pi3k/akt signaling pathway [77]. Data have shown that mel-treated rat mscs produce catalase, superoxide

Table 1 Some previous studies related to the angiogenesis properties of mel on stem cells

Stem cells	Source of cells	Treatment protocol	Duration	Animal model	Route of administration	Type of injury	Outcomes	References
bmmscs	rat	24 h pretreatment with 5 µm mel	2 months	rat	intraparenchymal	iri	b-fgf↑, hgf↑, $vegf^{um}$, $igf1^{um}$, egf^{um}, $g\text{-}csf^{um}$	[76]
bmmscs	rat	24-h pretreatment with 5 µm mel	14 days	rat	striatum injection	mcao	vegf ↑, p-erk1/2 ↑, cd31↑, apoptosis↓	[72]
ucmscs	human	7-day pretreatment with 10 µm mel	4 weeks	mouse	tail vein injection	t2dm	activating pi3k/akt pathway, mt1↑, mt2↑, pdk1↑, pcna↑, ki67↑, sod↑, h_2o_2↓, bcl2↑, insulin resistance↓, bax↓, capase3↓, glut4↑	[77]
ucmscs	human	10 mg/kg mel	8 weeks	rat	intraperitoneal	pni	sni ↓, sfi↑, bdnf↑, mda↓, tac↑, ncv↑, emg↑	[84]
admscs	human	12 h-pretreatment with 1 µm mel	28 days	mouse	intramuscularly	hli	pgc-1α↑, cyclin e↑, cdk2↑, cyclin d1↑, cdk4↑, vegf↑, fgf↑, hgf↑, cd31↑, α-sma↑	[85]
admscs	mice	20 mg/kg/day mel for 28 days, and 5 µm mel for the in vitro study	28 days	mouse	intraperitoneally	ihd	enhancing sirt1 signaling, bcl2↑, ac-foxo1↓, ac-p53↓, ac-nf-κb↓, bax↓, tnf-a↓, il-6↓, mda ↓, il-10↑, vegf↑, bfgf↑, cd31↑, α-sma↑ (apoptosis↓, inflammation↓, oxidative stress↓, survival↑)	[81]
epcs	human	10 mg/kg mel injection per day from 2 weeks before surgery until sacrifice at 4 weeks after surgery, and 100 µm mel for the in vitro study	4 weeks	mouse	intraperitoneal	dii	h_2o_2↓, enos↑, ampk↑, ho-1↑, migration↑, senescence↓, $sca\text{-}1^+/flk\text{-}1^+$cell↑, cd31↑	[99]
epcs	mice	1 h-pretreatment with 5 µm mel	48 h	mouse	renal injection	iaki	annexin v^+/pi^+ cells↓, vegf↑, igf-1↑, hgf↑	[100]
epcs	mice	4 h-pretreatment with 50 µm mel	21 days	mouse	intraperitoneal	diabetic wound healing	activating ampk/mtor pathway, bcl2↑, bax↓, caspase-9↓, cytochrome c↓, lc3-ii/lc3-i ratio↑, p62↓, lamp2↑, $pink1^{ns}$, $parkin^{ns}$, α-sma↑	[101]
bmmscs	rat	24 h-pretreatment with 5 µm mel, and the media was collected to isolate exos	4 weeks	rat	renal injection	riri	bun↓, creatinine↓, mda↓, hif1α↓, nox2↓, ho1↑, sod↑, cat↑, gpx↑, caspase 3↓, parp1↓, bax↓, mpo↓, icam1↓, il1b↓, nfkb↓, il10↑, bfgf↑, hgf↑, sox9↑, vegf↑	[94]
bmscs	human	48-h pretreatment with 1 µm mel, and the media was collected to isolate exos	14 days	rat	subcutaneous	diabetic	il-1β↓, tnf-α↓, il-1β↓, nf-α ↓, inos↓, il-10↑, arg-1↑, pten↑, akt↓, m2 polarization/m1 polarization↑	[92]
bmmscs	rat	10 and 50 mg/kg/day mel daily for 4 weeks in an in vivo study, and 100 nm mel for in vitro experiments	4 weeks	rat	intraperitoneally	ovx	alp↑, ocn↑, runx2↑, vegf↑, ang-2↑, cd31↑, bmd↑, tb.n↑, bv/tv↑	[106]
npmscs	rat	24-h pretreatment with 1 µm mel two weeks after the puncture, the mel treatment group received 100 ng/kg/day of mel	5 weeks	rat	intraperitoneal	ivdd	activating pi3k/akt pathway, p53↓, p21↓, senescence↓, annexin v^+/pi^+ cells, apoptosis↓, caspase 3↓, bax↓, bcl2↑, collagen type ii↑, aggrecan↑, mmp-13↓, ros↓	[107]
hspcs	human	0.01 m mel	7 days	in vitro	-	oxidative stress	c-myc↓, p16↑, p19↑, p21 ↑, p53↑, tert↓, telomerase activity↓, mtor↓, no↓, cat↑	[108]

Table 1 (continued)

Stem cells	Source of cells	Treatment protocol	Duration	Animal model	Route of administration	Type of injury	Outcomes	References
bmmscs	rat	24-h pretreatment with 5 µm mel	2 weeks	rat	intraperitoneal	tidm	neuroligin 1↑, sortilin ↑, bdnf↑, inos↓, tlr2↓, tnf-α↓, gap43↓ (improvement compared to the diabetic group, but not compared to the control group)	[109]
bmmscs	rat	24 h-pretreatment with 100 µm mel	21 days	rat	topically	wound model	gsh↑, mda↓, no↓, protein carbonyls↓, il-1β↓, tnf-α↓, nf-κb↓, tgf-β ↑, α-sma↑	[110]
nscs	mice	30 min-pretreatment with 40 µm mel	–	in vitro		tocp-induced cytotoxicity	p-erk1/2 ↑, lc3-ii/lc3-i ratio↓, autophagosomes↓, cd31↑,	[111]
bmmscs	rat	10 nm mel	10 days	rat	subcutaneous	bone defect	alp↑, runx2↑, ocn↑, stemness↑, bmd↑, bv/tv↑, ros↓, sod↑, p53↓, nanog↑	[112]
bmmscs	rat	24 h-pretreatment with 5 µm mel	12 weeks	rat	intraperitoneal	hcc	alt↓, ast↓, alp↓, afp ↓, ggt↓, p53↓, caspase 9↓, caspase 3 ↓, pcna↓, il6↓, gfβ1↓(inflammation↓), carcinogenicity↓	[113]
bmmscs	mice	0.30 mg/g/day	2 weeks	mouse	intraperitoneal	liver fibrosis	bilirubin↓, alt↓, bax↓, bcl-xl↑, alb↑	[114]
nscs	mice	5–7 days per treatment with 10 nm physiological dose and 25 µm pharmacological dose of mel		mouse	striatum injection for parkinson's disease model hippocampus injection for alzheimer's disease model	nds	physiological dose causes nsc differentiation, mitochondrial mass↑, mtdna↑, coq9↑, mitochondrial complexes↑, ocr↑, src↑, atp synthesis↑, aβ plaques↓	[115]
ucmscs	human	48 h per treatment with 10 µm mel	4 weeks	rat	intrauterine injection	iua	endometrium thickness↑, cd34↑, vimentin↑, pcna↑, α-sma↑, oct-4↑, sox2↑, m2 macrophage marker (cd163) ↑, m1 macrophage marker (cd86) ↓, il-1β↓, tnf-α↓, and inos↓, survival↑, m2 polarization/m1 polarization↑, collagen deposition↓, fibrosis↓	[116]

bmmscs: bone marrow mesenchymal stem cells; **um**: unmodified; **iri**: renal ischemia–reperfusion injury; **mcao**: middle cerebral artery occlusion; **ucmsc**: umbilical cord mesenchymal stem cell; **t2dm**: type ii diabetes mellitus; **pcna**: proliferating cell nuclear antigen; **pni**: peripheral nerve injury; **sni**: sciatic nerve injury; **sfi**: sciatic function index; **bdnf**: brain derived neurotrophic factor; **mda**: malondialdehyde; **tac**: total antioxidant capacity; **ncv**: nerve conduction velocity; **emg**: electromyography; **admscs**: adipose-derived mesenchymal stem cells; **α-sma**: alpha small muscle antigen; **hli**: hind limb ischemia; **pgc-1α**: peroxisome proliferator activated receptor gamma coactivator-1 alpha; **fgf**: fibroblast growth factor; **hgf**: hepatocyte growth factor; **ihd**: ischemic heart disease; **epcs**: endothelial progenitor cells; exosomes: **exos**; **dii**: diabetic ischemic injury;**ho-1**: heme-oxygenase 1; **sca-1**: stem cell antigen 1; **flk-1**: fetal liver kinase 1; **iaki**: acute ischemic kidney injury; **ns**: non-significant; **riri**: renal ischemia–reperfusion injury; **inos**: inducible nitric oxide synthase; **tnf-α**: tumor necrosis; **bun**: blood urea nitrogen; **cat**: catalase; **gpx**: glutathione peroxidase; **mpo**: myeloperoxidase; **arg1**: arginase 1; **siop**: steroid-induced osteoporosis; **ovx**: ovariectomized; **bmd**: bone mineral density; **tb.n**: trabecular number; **bv/tv**: trabecular bone volume; **npmscs**: nucleus pulposus-derived mesenchymal stem cells; **ivdd**: intervertebral disc degeneration; **hspcs**: hematopoietic stem/progenitor cells; **tert**: telomerase reverse transcriptase; **tidm**: type i diabetes mellitus; **tlr2**: toll-like receptor 2; **gap43**: growth associated protein 43; gsh: glutathione; **tgf-β**: transforming growth factor β; **nscs**: neural stem cells; **tocp**: tri-ortho-cresyl phosphate; **alp**: alkaline phosphatase; hcc: hepatocellular carcinoma; **alt**: alanine transaminase; **ast**: aspartate transaminase; **alp**: alkaline phosphatase; **ggt**: gamma-glutamyl transpeptidase; **alb**: albumin; **nds**: neurodegenerative diseases; **ocr**: oxygen consumption rate; **iua**: intrauterine adhesions

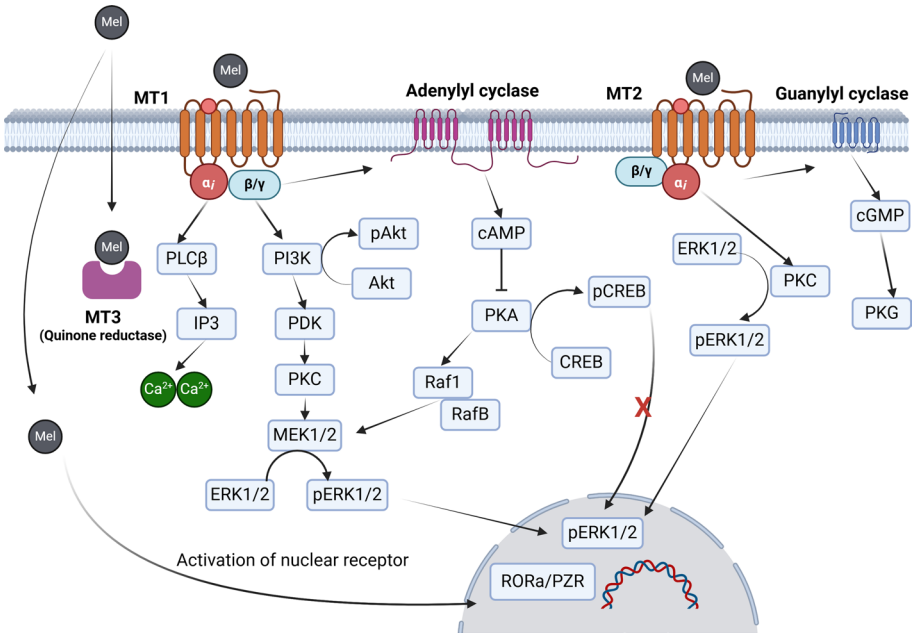

Fig. 4 Mechanisms of action of mel. This hormone exerts its effects by engaging membrane receptors mt1 and mt2. These receptors belong to the g-protein-coupled receptor superfamily. Along with these receptors, mel can activate cytosolic enzyme, namely quinone reductase 2 (qr2; also known as mt3), and nuclear receptors rzr/ror. The attachment of mel to mt1 and mt2 recruits several intracellular effectors such as pkc, plcβ, and pka. In the presence of mel, gαi activation of mt1 can contribute to the stimulation of plcβ, while the promotion of gβ/γ is followed by the stimulation of pkc and erk pathways. The mt1 receptor also functions via membrane adenyl cyclase, which inhibits creb phosphorylation by activating camp and pkc. Mel promotes conformational changes in mt2 and thereby activates the αi subunit. Along with these changes, pkg is triggered via guanylate cyclase. Also, mt2 can engage pkc and erk1/2 complexes. Created by biorender's web-based software

dismutase (sod), bfgf, and hgf compared to the non-treated control [76]. The incubation of human epcs with mel-treated mscs led to enhanced tubulogenesis properties in vitro as well [76].

It has been thought that mel can alleviate the pathological conditions within the cardiac tissue mostly via the neutralization of free radicals and stimulation of antioxidant systems [78]. Mel could protect transplanted mscs from the direct detrimental effects of ros and enhance the therapeutic potency for mi [79]. This neurohormone can enhance the angiogenic activity of ad-mscs by activating akt signaling, suppressing the caspase cascade, inhibiting ros formation, and inducing antioxidant enzymes such as sod-1 and catalase [78]. In vivo studies have shown that mel pre-treatment promoted the retention time and survival of transplanted ad-mscs in the rat model of mi by the regulation of paracrine activity, and release of proangiogenic and mitogenic factors like igf-1, bfgf, hgf, and egf [80]. It has also been indicated that mel can boost angiogenesis in injured myocardium via the regulation of the sirt signaling pathway (sirt1 and 3), leading to improved mitochondrial activity, autophagic response, and inhibition of apoptosis and inflammation [78]. Besides, mel induces sirt1 inside ad-mscs, leading to the increase of α-sma$^+$ vascular cells and induction of arteriogenesis in infarcted myocardium [81]. It has been thought that the promotion of angiogenesis a few hours after mi can reduce cardiomyocyte injury and aberrant myocardial remodeling [78]. To increase and prolong the stability and regenerative properties of ad-mscs in the target tissues, poly(lactide-co-glycolide)-monomethoxy-poly (polyethylene glycol nanoparticle loaded with mel was used. This strategy can help the transplanted cells survive the harsh niche. In 2018, ma et al. found that the encapsulated mel inhibits the formation of the p53-cyclophilin d complex, and mitochondrial dysfunction in response to hypoxia/reoxygenation injury [82]. In addition to exogenously administered stem cells, mel accelerates the healing of injured myocardium via the protection of local c-kit$^+$ cardiac progenitor cells against the oxidative stress by concomitant reduction of mir-98 and increase of stat3 in mi mice [83].

Mias and co-workers found higher pro-angiogenesis properties of mel-treated mscs in rats with renal ischemia–reperfusion injury, coinciding with the increase of cd31$^+$, and vwf$^+$ ecs and α-sma$^+$ pericytes [76]. Treatment with mscs not only increased the survival rate (~threefold) in the rat model of stroke via the stimulation of the erk1/2 signaling pathway but also promoted the formation of de novo cd31$^+$ vascular units. Along

with these changes, the expression of vegf transcription is induced in gfap$^+$ astrocytes [72]. These data confirmed that mel improves the survival, angiogenesis behavior, and neurogenic activity of mscs with simultaneous alteration of glial cell function [84]. Mel promotes the angiogenic behavior of mscs via many underlying mechanisms. For example, lee and co-workers proved that incubation of ad-mscs with mel increased proliferator-activated receptor gamma coactivator-1 alpha (pgc-1α), leading to stimulation of proliferation (cyclin e↑, cdk2↑, cyclin d1↑, and cdk4↑) coincided with the production of angiogenesis factors such as vegf, fgf, and hgf, and migration rate in vitro. Under such conditions, the mitochondrial activity (complex i and iv) is also enhanced [85].

The administration of mel-treated mscs in mice with ischemic hind limbs led to the reduction of fibrotic area and an increase of capillaries (cd31↑), and arterioles (α-sma↑) (Fig. 5) [85]. Pgc-1α influences angiogenic behavior differently. For instance, pgc-1α induces the production of no by enos under ischemic conditions [86]. Irrespective of mscs, the activation of pgc-1α in other cell lineages, such as multiple myeloma rpmi-8226 cells, can increase the expression of vegf and glut-4 [87], indicating the critical role of pgc-1α in the control of angiogenesis in multiple cell types, especially in mscs. Notably, the induction of vegf under hypoxic conditions is related to the activation of pgc-1α. Rahimifardin and co-workers confirmed the concomitant induction of vegf, pgc-1α, ampk, and estrogen-related receptor 1 alpha (err1α) in cardiac tissue of hypoxic rats exposed to aerobic training over 3 weeks [88].

Mel also upregulates the expression of sirt1, leading to postponing senile changes in mscs and enhanced survival rate, while the induction of sirt3 by mel also improves the differentiation capacity, and delays senescence via induction of antioxidant system activity [89]. Inhibition of sirt1 by sirtinol impaired hif-1α-induced tubulogenesis activity of human mscs after being exposed to 1% o_2 for 24 h, with simultaneous reduction of glut1 and vegf [90]. More interestingly, mscs can modulate the process of angiogenesis during pathological conditions in a paracrine manner via the secretion and release of exosomal sirt3, improving the tubulogenesis, migration, and antioxidative activity of hyperglycemic huvecs in vitro [91]. Along with these changes, the levels of pro-inflammatory cytokines such as il-1, il-6, tnf-α, mcp-1, vcam-1, and icam-1 were also diminished. The injection of msc exos in diabetic mice with a full-thickness cutaneous tissue injury led to accelerated wound healing, an increase in angiogenesis (cd34$^+$ cells), and re-epithelialization [91]. Han and co-workers reported that the cytoprotective effects of mel on mouse ad-mscs depend on the activation of the sirt-1 signaling pathway [81]. Based on the data, the synergistic properties of mel and ad-mscs led to a reduction of fibrosis in infarcted mice, via the increase of cardiac vegf and bfgf levels, coinciding with the significant increase of cd31$^+$ and α-sma$^+$ vascular units [81]. The regulation of target factors such as foxos, nf-κb, p53, pgc1-α, and autophagy-related genes (atgs), sirt1 exerts several cytoprotective effects on transplanted stem cells, leading to enhanced regenerative outcomes [81]. considering the data collectively, pre-treatment or co-administration of mscs with mel can improve the angiogenesis potential in part by the modulation of sirt proteins.

In recent years, the effects of mel on the paracrine activity of mscs via the production and release of evs have been at the center of debate. Mel-pretreated bone marrow mscs (bmscs) induce m1–m2 polarization of macrophages via the upregulation of pten, inhibition of akt phosphorylation, and suppression of immune cell response. As a result, m2 macrophages release several angiogenesis factors such as vegf, fgf, and egf, which are important in the healing process. Exos released from mel-treated mscs can regulate the inflammation and accelerate the regeneration of wounds (angiogenesis↑ and collagen synthesis↑) under diabetic conditions in diabetic rats [92]. Besides, mel-treated mscs produce evs with similar effects in spinal cord injury (sci) animal models. These evs stimulate microglia/macrophages to m2-like polarization and functional motor recovery via the delivery of ubiquitin-specific protease 29, leading to nrf2 ubiquitination [93]. Mel-treated msc exos exert therapeutic properties against renal ischemia–reperfusion injury via the local increase of bfgf, hgf, sox9, and vegf [94]. In hepatic injuries, mel-treated ad-msc evs alleviate the pathological conditions via the reduction of systemic aspartate aminotransferase and direct hepatocyte injury [95]. Such effects have been documented in several fibrotic diseases, including kidney fibrosis. Yea et al. found that mel-treated ad-mscs exos exhibit prominent anti-inflammatory and anti-fibrotic effects in chronic kidney disease. Mel preconditioning stimulates the mscs to produce exos with certain rna types with angiogenesis potential. Besides, mel can increase the exosomal levels of mir-29b-3p, mir-7a-3p, let-7b-5p, let-7c-3p, mir-153-3p, mir-26a-2-3p, and mir-846-5p. These microrna are recognized for their anti-inflammatory and anti-fibrotic properties, by regulation of certain genes involved in ecm production, fibrogenesis, and inflammatory cytokine release [96]. Yeo et al. found that mel-treated mscs release exos with the potential to improve mitochondrial function, proliferation, and upregulation of angiogenesis factors in chronic kidney disease. Under such conditions, the increase of prpc levels and activity of mir-4516 can delay the senile changes within the injured renal tissue [97]. In another study, it was found

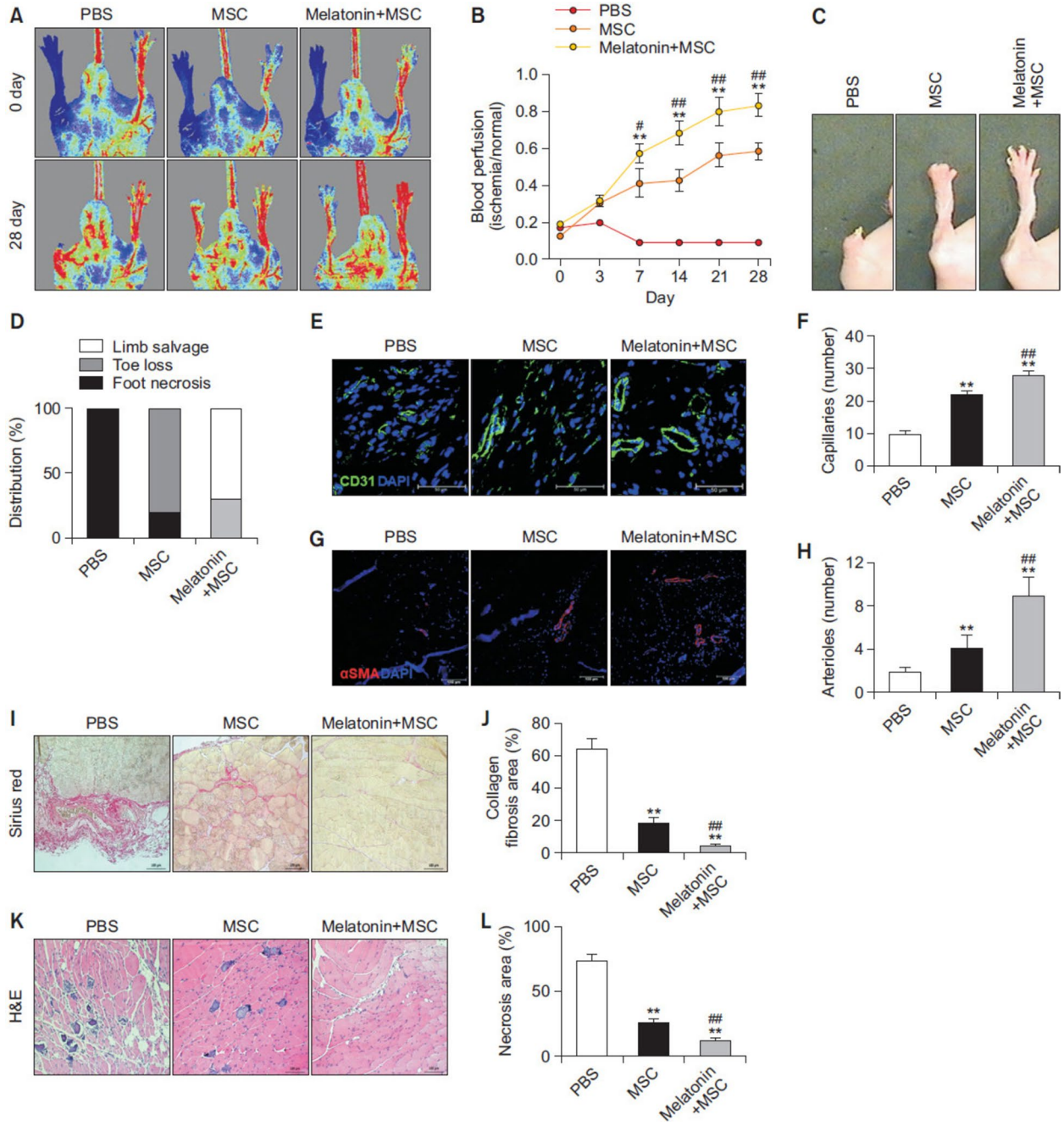

Fig. 5 Study of tissue regeneration in mice with hindlimb ischemia (**a**-**l**). Measuring blood perfusion using laser doppler imaging in mice with hindlimb ischemia that received phosphate-buffered saline (pbs), mscs, and mel-pretreated mscs (**a**, **b**). Data indicated that blood perfusion was significantly stimulated in mice that received mel-treated mscs compared to mscs and pbs groups after 28 days (**b**: $^{**}p<0.01$ vs. pbs; $^{\#}p<0.05$, $^{\#\#}p<0.01$ vs. mscs). Gross view of ischemic hindlimb in terms of toe loss, foot necrosis, and limb salvage 28 days after injection of mscs, and/or mel-treated mscs (**c**). The foot loss is reduced in ischemic mice treated with mscs and mel-treated mscs. Distribution of different parameters after 28 days (**d**). Immunofluorescence staining indicated enhanced microvascular intensity in the ischemic area with green-color cd31 capillaries and red-colored α-sma arterioles (**e**–**g**; scale bar: 50 μm). Panels **f** and **h** indicated capillaries and arterioles in different experimental groups after 28 days post-transplantation ($^{**}p<0.01$ vs. pbs; $^{\#\#}p<0.01$ vs. mscs). Measuring the fibrotic changes and collagen fibers using sirius red staining in the ischemic area after 28 days (**i**; scale bar: 100 μm). Data showed that the levels and density of collagen fibers were reduced in the presence of mscs, especially mel-treated mscs. fibrosis was quantified as % of sirius red-stained collagen area (**j**; $^{**}p<0.01$ vs. pbs; $^{\#\#}p<0.01$ vs. mscs). **h** & **e** staining was performed to monitor tissue necrotic changes in the ischemic limb after 28 days (**k**; scale bar: 100 μm). the necrotic area was quantified as the % of necrosis (**l**; $^{**}p<0.01$ vs. pbs; $^{\#\#}p<0.01$ vs. mscs). along with the reduction of fibrotic changes, the necrosis was also diminished in the ischemic mice after receiving mel-mscs. One-way anova and tukey's post hoc test (mean ± sem). phosphate-buffered saline *pbs*; [85]. Reproduced with the permission of the publisher. 2019. Biomolecules & therapeutics

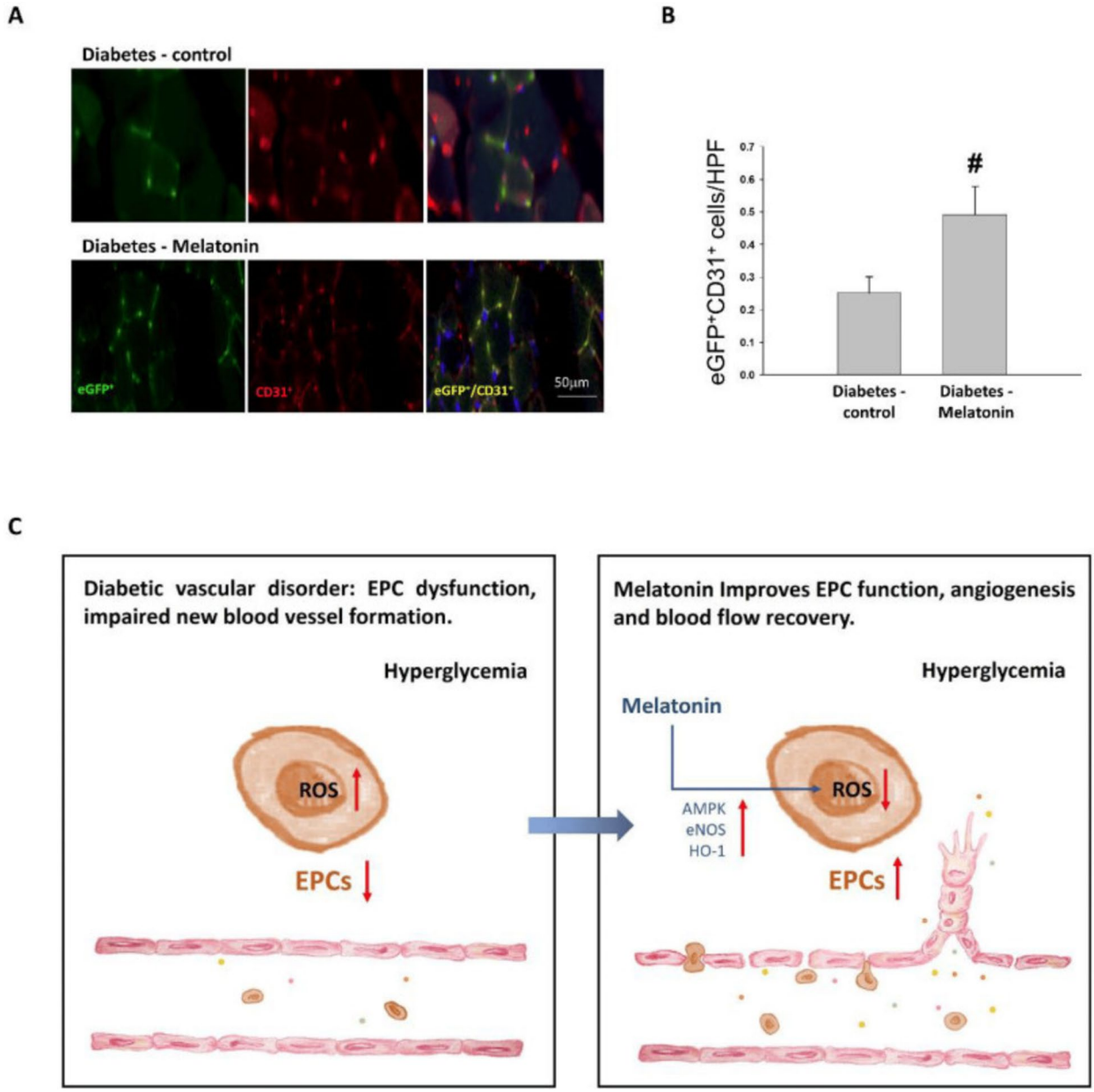

Fig. 6 Monitoring the angiogenesis properties of mel in lethally irradiated diabetic wild-type mice with ischemic hindlimb that received bone marrow transplantation from transgenic egfp$^+$ mice (**a**, **b**). Simultaneous expression of egfp and cd31 at the site of ischemia indicated the successful migration and maturation of donor bone marrow epcs in the presence of mel (**a**; scale bar: 50 μm). Data revealed a statistically significant difference in the number of recruited egfp$^+$/cd31$^+$ cells/hpf in diabetic mice with hindlimb ischemia that received mel compared to matched control mice (**b**; $^{\#}p < 0.05$ vs. diabetes). It was suggested that mel can reduce the abnormal epc function and stimulate blood perfusion via the up-regulation of enos, ampk, and ho-1, and reduction of oxidative stress (**c**). student's t-test. Wild-type mice = 21, diabetes-control, n = 27, and diabetes + melatonin treatment = 24). *egfp* enhanced green fluorescent protein. [99]. Reproduced with the permission of the publisher. 2022. International journal of molecular sciences

that mel-pretreated ad-mscs upregulate mir-145-5p to control the tgf-β2/smad3 signaling axis and inhibit corpus cavernosum fibrosis in the rat model of cavernous nerve injury [98].

As with mscs, the angiogenesis properties of mel have been proven on epcs in in vitro and in vivo conditions. Kuo and colleagues found that mel treatment (100 μm) can alleviate the detrimental effects of hyperglycemic conditions (25 mm glucose) on human epcs via the

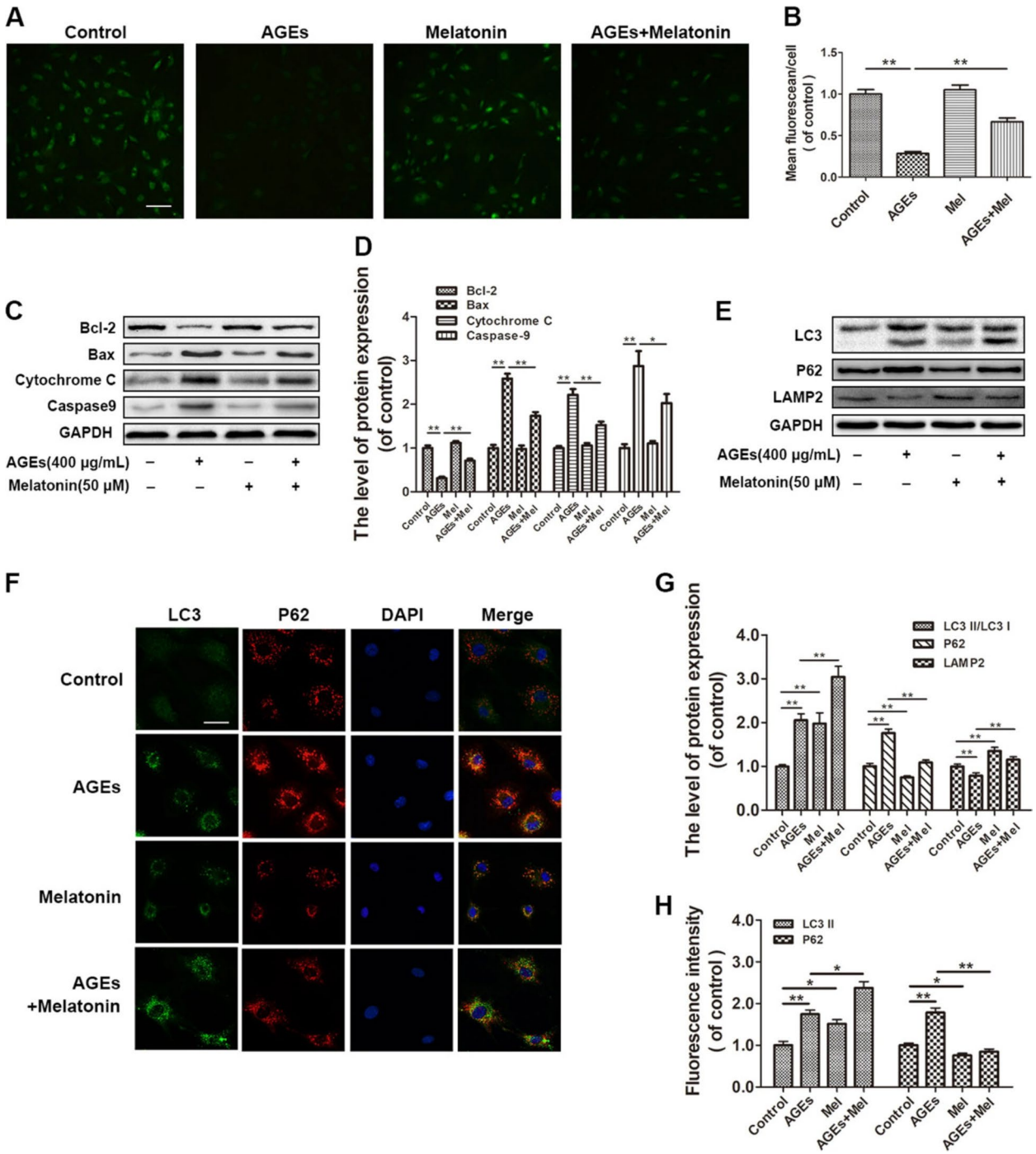

Fig. 7 Monitoring the cytoprotective impact of mel on mouse epcs (**a**–**h**). Pre-treated epcs with 50 μm mel for 2 h were incubated with 400 μg/ml ages for 24 h. Ages can affect the mitochondrial integrity via the alteration of mitochondrial permeability transition pore (mptp) opening, indicated by the reduction of green-fluorescent calcein-am and cobalt (**a, b**; scale bar, 50 μm). Pre-treatment with mel can reduce mptp opening in epcs and close it to near control levels. Mel can prevent the apoptotic changes in age-treated epcs via the reduction of bax, cytochrome c, and caspase-9, and the increase of bcl-2 (**c** and **d**). Monitoring the autophagy response in age-incubated mouse epcs (**e**–**h**). Western blotting showed that mel can reverse the detrimental effects of ages on autophagy effectors (lc3↑, p62↓, and lamp2↑) in mouse epcs (**e** and **g**). Immunofluorescence images indicated the reduction of red-colored p62, and an increase of green-colored lc3 punctata inside epcs in mel-treated epcs incubated with ages, indicating the activation and completion of autophagy response (**f** and **h**: scale bar: 25 μm). One-way anova followed by tukey's test (mean ± sem). n = 3. $^{**}p < 0.01$ or $^{*}p < 0.05$. [101]. Reproduced with the permission of the publisher. 2018. Experimental & molecular medicine

phosphorylation of enos, ampk, and an increase of heme oxygenase-1 [99]. The administration of mel in diabetic mice with hind limb ischemia also restored the mobilization properties of epcs to the site of injury, similar to the control groups. To be specific, the histological examination revealed the existence of $egfp^+$ epcs with concomitant cd31 expression within the ischemic regions, indicating the protective effects of mel on epcs'dynamic growth, migration, and maturation under diabetes-induced ischemia conditions (Fig. 6) [99].

Patashan et al. observed that mel improves the renoprotective properties of early-growth epcs [100]. The systemic injection of 0.5×10^6 epcs pre-treated with 5 µm mel can reduce acute renal ischemia complications (creatinine↓) compared to the ischemic mice that received non-treated epcs [100]. These effects were reduced in the presence of luzindole, indicating the cytoprotective activity of mel on epcs via surface mt1 and mt2 receptors [100]. Data indicated that treatment of epcs with mel can blunt the apoptotic effects of tgf-β and increase the angiocrine capacity of epcs (vegf↑) without any significant differences in the levels of ang-2, fgf-2, sdf-1α, hgf, and scf [100]. These data indicate that, similar to mscs, co-administration of epcs with mel or injection of mel pre-treated epcs can improve the angiogenesis behavior and reduce the apoptotic changes, leading to cell resistance against the harsh microenvironments.

The activation of autophagy in mel-treated epcs is another possible mechanism that helps these cells promote the vascularization process under pathological conditions. Jin et al. showed that mel improves the autophagic flux (lc3-ii/lc3-i ratio↑ and p62↓) of mouse epcs in response to advanced glycation end product (age) treatment (Fig. 7). Treatment with mel led to increased autophagic activity via ampk/mtor signaling pathway (p-ampk/ampk↑, p-mtor/mtor↑, p-p70s6k/p70s6k↑, and p-4ebp1/4ebp1↑), leading to enhanced in vitro tubulogenesis and angiogenesis (α-sma^+ arterioles) capacity in mice with diabetic wounds (Fig. 8) [101].

It seems that the stimulatory/inhibitory effects of mel on epcs are context-dependent. For example, lin and co-workers found that mel has the potential to inhibit pathological angiogenesis in terms of senile macular degeneration in mice with a corneal alkali burn model [102]. Mel at a dose of 60 mg/kg can exert cizumab-like activity on the angiogenesis potential with concomitantly reduced swelling rate and migration of $cd31^+$, $cd34^+$, and $cd133^+$ epcs in the corneal epithelial layer during 7 days (Fig. 9) [102]. Similar to these data, the recruitment of cd31, cd34, and cd133 cells was reduced in a matrigel plug containing 100 ng/ml vegf, and different doses of mel, ranging from 0.1 to 1 mm, in the chorioallantoic membrane assay. It seems that the opposite effects of mel on the mobility, recruitment, and angiogenesis capacity of epcs are dose-dependent, in which the higher mel levels can directly inhibit angiogenesis [102].

The molecular processes that may explain the anti-angiogenic effect of mel were identified in chronic obstructive pulmonary disease (copd) rats that received simultaneously 4×10^6 bm-mscs via intratracheal route and 30 mg/kg mel daily for 30 days [103]. Irrespective of improvements in pulmonary function parameters, data indicated the down-regulation of both hif-1α and reduction of vegf peptide in lungs in copd rats that received mel plus mscs. Along with these changes, $cd31^+$ capillaries were reduced in inflamed lungs, indicating the inhibition of local angiogenesis [103]. It is assumed that the major reason for these effects is related to the antioxidant and anti-inflammatory properties of mel. On the other hand, it is also possible that the decline in oxidant and inflammatory cytokines allows transplanted mscs to trans-differentiate into mature resident cells such as pneumocytes, resulting in the restoration of air-blood barrier function [104]. Mel has the potential to inhibit the translocation of hif-1α to the nucleus, leading to down-regulation of vegf and lack of hif-1α/phospho-stat3/cbp/p300 complex [105].

Conclusions

In vitro and in vivo experiments have revealed the cytoprotective and detrimental effects of mel on different cell types. It seems that the impact of mel on stem cell bioactivity is multifaceted and is achieved via engaging various mechanisms. Both pro-angiogenesis and anti-angiogenesis properties can be determined in mel-treated stem cells in a context- and dose-dependent manner. Along with the stimulation of angiogenesis properties, mel can also protect the stem cells against the harsh microenvironments after transplantation. In physiological doses of mel, the stimulation of membrane-bound receptors and shared signaling pathways can control the bioactivity of stem cells, while in pharmacological concentrations, mel can enter the host cells in a receptor-independent manner, and thus other intracellular mechanisms are activated. Both pro-angiogenesis and anti-angiogenesis properties have been documented in terms of mel on epcs under pathological and physiological conditions.

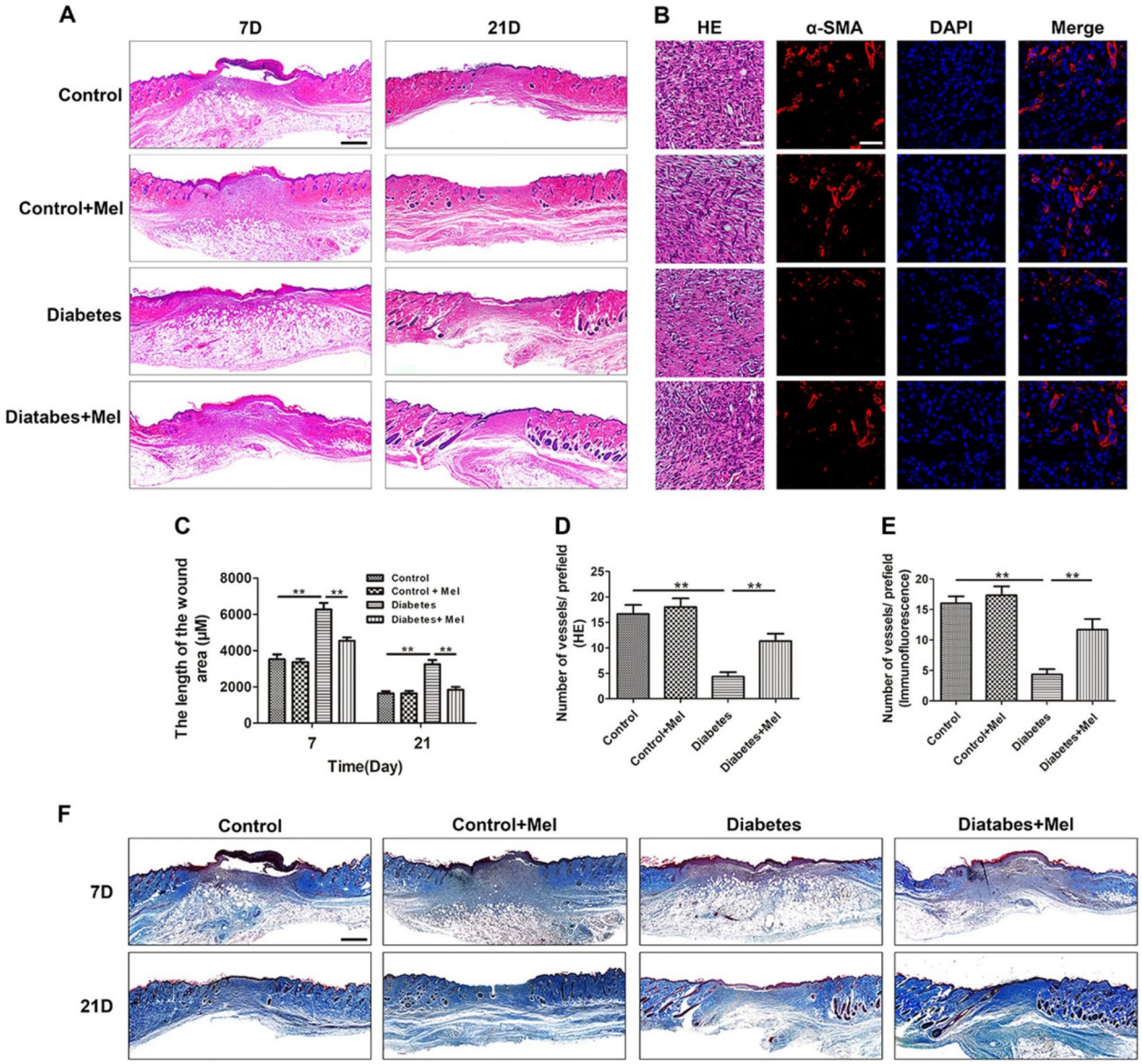

Fig. 8 Monitoring the healing process of cutaneous tissue wounds in diabetic mice on days 7 and 21 using h & e staining (**a**: scale bar: 1000 μm). Images revealed the reduction of wound area in diabetic mice that received mel. High-magnified images and immunofluorescence staining confirmed the increase of α-sma^{+} arterioles in the wound area after 7 days (**b, c**; scale bar: 1000 μm). Measuring the wound length in different experimental groups after 7 and 21 days (**d**). The number of vessels and α-sma^{+} arterioles were counted in h & e and immunofluorescent images, respectively, 7 days after diabetes mellitus induction (**e** and **f**; scale bar: 100 μm). Masson's trichrome staining was done to monitor the distribution of collagen fibers at the site of cutaneous tissue injury on days 7 and 21 (**f**; scale bar: 1000 μm). The levels of collagen fibers were higher in diabetic mice that received mel compared to matched diabetic controls. One-way anova followed by tukey's test (mean ± sem). $n = 24$. $^{**}p < 0.01$. [101]. Reproduced with the permission of the publisher. 2018. Experimental & molecular medicine

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Fig. 9 The inhibitory effect of mel on angiogenesis in a mouse model of corneal alkali burn (**a**–**e**). The angiogenesis levels in normal and alkali-burned corneas (**a**). stereomicroscopy indicated that the angiogenesis intensity was diminished in mel-treated mice in a dose-dependent manner (20 mg/kg or 60 mg/kg) compared to other groups that received pbs or 5 mg/μl bevacizumab ($n = 6$). Corneal stromal thickness was evaluated by h & e staining 7 days after alkali burn injury (**b** and **c**). Mel can diminish the swelling of the cornea in a dose-dependent manner. Immunofluorescence staining revealed that mel blunted the angiogenesis behavior by reduction of mature cd31^{+} ecs, and cd34^{+}, or cd133 + epcs at the site of injury (**d** and **e**). $n = 6$; one-way anova. $^{*}p < 0.05$ vs. uninjured corneas; and $\#p < 0.05$ vs. damaged corneas. [102]. Reproduced with the permission of the publisher. 2023. Cells

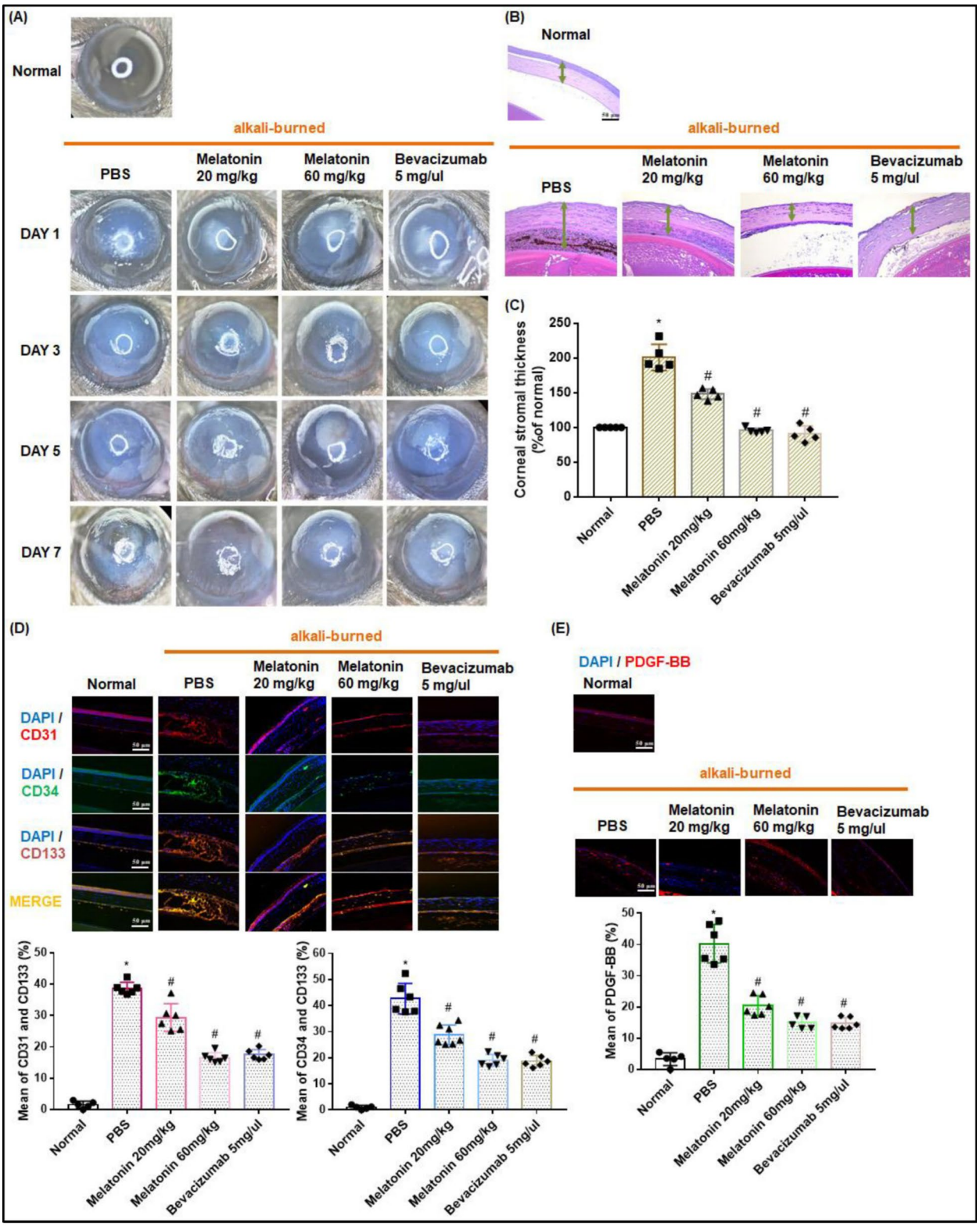

Fig. 9 (See legend on previous page.)

The apparent conflicting findings may relate to the dose and exposure duration in different situations. Future studies should focus on the determination of the dual effects of mel on angiogenesis outcomes under various pathological conditions.

Abbreviations

Ad-mscs	Adipose tissue-derived mscs
Angs	Angiopoietins
Atgs	Autophagy-related genes
Bfgf	Basic fibroblast growth factor
Bmscs	Bone marrow mscs
Cvds	Cardiovascular diseases
Csf	Cerebrospinal fluid
Copd	Chronic obstruction pulmonary disease
Cabg	Coronary artery bypass graft
Cad	Coronary artery diseases
Ec	Endothelial cell
Enos	Endothelial nitric synthetase
Epcs	Endothelial progenitor cells
Egf	Epidermal growth factor
Err1α	Estrogen-related receptor 1 alpha
Exos	Exosomes
Evs	Extracellular vesicles
Hgf	Hepatocyte growth factor
Huvecs	Human umbilical vein ecs
Igf-1	Insulin-like growth factor-1
Mt	Mel receptor
Mel	Melatonin
Mscs	Mesenchymal stem cells
Mptp	Mitochondrial permeability transition pore
Mi	Myocardial infarction
No	Nitric oxide
Prpc	Proliferator-activated receptor gamma coactivator-1 alpha
Pgc-1α	Cellular prion protein
Ros	Reactive oxygen species
Sci	Spinal cord injury
Sod-1	Superoxide dismutase-1
Vegf	Vascular endothelial growth factor

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Author contributions
S.r. literature search, drafting of the manuscript; s.a.c.: literature search, drafting of the manuscript; g.r.: literature search, drafting of the manuscript; r.r.: conceptualization; resources, funding acquisition, supervision; a.r.: conceptualization; r.j.r.: final edition of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability
No new data were generated or analyzed in the current article.

Declarations

Ethics approval and consent to participate
No human and/or animal samples were used in the current manuscript. The study was registered as titled "pro-angiogenesis/anti-angiogenesis capacity of melatonin on stem cells under ischemic conditions." to the research ethics committees of the vice-chancellor in research affairs, tabriz university of medical sciences.

Consent for publication
Not applicable.

Competing interests
None declared.

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