Journal of Diabetes and Its Complications xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.jdcjournal.com

Mitochondrial dysfunctions, endothelial progenitor cells and diabetic retinopathy☆

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ARTICLE INFO

Article history:
Received 26 March 2018
Received in revised form 18 June 2018
Accepted 28 June 2018
Available online xxxx

Keywords:
Diabetic retinopathy
Endothelial progenitor cell
Mitochondrial dysfunction
Stem cell fate
EPC therapy

ABSTRACT

Aim: Diabetic retinopathy (DR) is the leading cause of vision loss in the working age population. Endothelial progenitor cells (EPC) play a vital role in vascular damage repair. This article will review recent progress regarding mitochondrial and EPC dysfunction associated with DR.
Results: EPCs represent a limited population of adult stem cells possessing vasculogenic potential postnatally; their number and function are changed in DR. Among all the function changes, mitochondrial dysfunction plays an important role in the dysregulation of EPCs, as mitochondria regulate energy balance, and cell fate determination.
Conclusions: Although the mechanism for the role of mitochondria dysregulation in EPC function remains elusive, mitochondria of EPCs represent a promising target for the treatment of the vasculopathy presented within DR.

1. Introduction

According to a 2017 report by the International Diabetic Federation, the world wide prevalence of diabetes mellitus is 1 in 11 adults (425 million), representing one of the most common causes of mortality and morbidity including visual and labor incapacity in adults aged 20–74.[1]

Diabetic retinopathy (DR) refers to a diabetic complication affecting the retina.[2] The major retinal pathologies in this condition associated with severe vision loss include: diabetic macular edema (DME) and retinal neovascularization. Both of these vision-threatening complications are associated with retinal vascular dysfunction. Although early diagnosis and appropriate treatments may reduce vision loss in some patients, DR is a major threat to both patient vision and quality of life.

DR is now more accurately defined as a neurovascular disorder rather than a microvascular disease. However, vascular changes are still the primary pathology observed in DR.[2] Chronic hyperglycemia and other risk factors (e.g. hypertension) are believed to initiate a cascade of biochemical and physiological changes that ultimately lead to microvascular damage and retinal dysfunction. Mature vascular endothelial cells (EC) have a limited proliferative capacity and potential to repair injured vessels. In 1997, Asahara et al.[3] discovered that a rare population of circulating cells, endothelial progenitor cells (EPCs), which express the hematopoietic progenitor marker CD34, can develop endothelial phenotypes in vitro when they are stimulated with angiogenic factors.

EPCs, as an adult stem cell population, have been the subject of intense scrutiny as mediators of endothelial repair. In diabetic conditions, both the function and number of EPCs are modulated, as reported by a series of clinical and animal studies (Table 1). In the present review, we will highlight some of the mitochondrial dysfunctions induced by diabetic conditions, which may affect EPC function and influence EPC-mediated endothelial repair. Some of the mechanisms are supported by indirect evidence currently, and we will discuss further studies which are required to substantiate mitochondrial function as a determinant of EPC function in vivo. We will also review potential treatment

Abbreviations: DR, diabetic retinopathy; EPC, endothelial progenitor cell; DME, diabetic macular edema; EC, endothelial cells; VTDR, vision-threatening diabetic retinopathy; PDR, proliferative diabetic retinopathy; NVI, neovascularization in the iris; IOP, intraocular pressure; CAC, circulating angiogenic cell; CFU-EC, colony forming unit endothelial cell; ECFC, endothelial colony forming cell; ASM, acid sphingomyelinase; EPOR, erythropoietin receptor; NPDR, non-proliferative diabetic retinopathy; CFU, colony-forming units; CPC, circulating progenitor cells; NGF, nerve growth factor; BNDF, brain-derived neurotrophic factor; MNC, mononuclear cell; HIF-1, hypoxia-inducible factor-1; ESC, embryonic stem cell; SSC, somatic stem cell; iPSC, induced pluripotent stem cell; SDF-1, stromal derived factor 1; AGE, advanced glycation end product; ROS, reactive oxygen species; SOD, manganese superoxide dismutase; UCP-1, uncoupling protein-1; MAPR, mitochondrial ATP production rate; mtDNA, mitochondrial DNA; ETC, respiratory electron transport chain.

☆ Conflict of interest disclosures: The authors declare no conflict of interest.

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https://doi.org/10.1016/j.jdiacomp.2018.06.015
1056-8727/

Table 1
Summary of studies regarding number and functional changes of EPCs in DR.

First author	EPC marker	Target	Main finding
Nermin Kady[27]	$CD34^+$	ASM	Circulating CD34+ angiogenic cells displayed higher ASM levels and dysfunction in diabetic patients
Bhatwadekar AD[7]	$CD34^+$	miR-92	miR-92 was reduced in DR patients; restore miR-92 enhanced the efficacy of CD34+ cells therapeutically
Garcia de la Torre N[28]	$CD45^{dim}CD34^+KDR^+$ or $CD45^{dim}CD34^+CD144^+$	Angiogenic microRNAs	Circulating EPCs were reduced, miR-126 and miR-221 expression were altered
Hu LM[29]	Erythropoietin receptor (EPOR)$^+CD34^+$ and $EPOR^+CD34^+VEGFR2^+$	Number and percentage of $EPOR^+$ circulating progenitor cells and EPCs	Decrease in NPDR patients, but rebound in PDR and PDR-nephropathy patients
Gianpaolo Zerbini[30]	$CD45^{dim}CD34^+VEGFR2^+$	Colony forming ability	EPCs carrying both endothelial and monocyte markers manifested abnormalities in type 1 diabetic patients with NPDR
Simon Brunner[31]	CPCs (CD34/CD133), EPCs (CD34/CD133/CD30), mature EPCs (CD34/CD133/CD309)	CPCs, EPCs, mature EPCs' number change	CPCs, EPCs, and mature EPCs declined in advanced stages of retinopathy
Liu X ET[32]	$CD34^+CD133^+$	EPC number and CFU ability, serum level of NGF and BDNF	Increased levels of circulating EPCs, which is correlated with the serum NGF and BDNF levels in DR patients
Balaiya S[8]	$CD34^+$	EPC function (migration, NO, paracrine secretory function)	Proangiogenic effects of retina cells contributed to $CD34^+$ cells in aberrant neovascularization
Rigato M[33]	$CD34^+$ CPCs or $CD133^+VEGFR2^+$ EPCs	Number of CPCs and EPCs	$CD34^+$cells predicted onset/progression of retinopathy in type 2 diabetes
Brunner S[34]	CPCs ($CD34^+CD133^+$), EPCs ($CD34^+CD133^+VEGFR2^+$), mature EPCs ($CD34^+CD133^+VEGFR2^+CD31^+$)	Number of EPCs	EPCs were decreased in NPDR, while mature EPCs increased in PDR in type 1 diabetes
Abu Ei-Asrar AM[35]	$CD133^+$	Immunohistochemistry of diabetic epi-retinal membranes	Bone marrow derived $CD133^+$ cells may have contributed to vasculogenesis in PDR
Abu Ei-Asrar AM[36]	SCF/c-kit	Immunohistochemistry of PDR	SCF/c-Kit signaling contributed to neovascularization in PDR
V. Asnaghi[37]	$CD31^+CD133^+$	CFU ability	EPC-CFU number increased in PDR patients
IG Lee[38]	$CD34^+$MNCs, and c-Kit^+ MNCs	Number of circulating $CD34^+$MNCs and c-Kit^+ MNCs	$CD34^+$MNCs, c-Kit^+ MNCs increased in the NPDR and PDR groups compared with the control group.

Abbreviations: ASM, acid sphingomyelinase; EPOR, erythropoietin receptor; NPDR, non-proliferative diabetic retinopathy; CFU, colony-forming units; CPC, circulating progenitor cells; NGF, nerve growth factor; BNDF, brain-derived neurotrophic factor; MNC, mononuclear cell.

strategies, including rescuing EPC function and increasing EPC number, which may improve endothelial repair. Although the exact mechanism responsible for EPC dysfunction in DR remains enigmatic, the role of hyperglycemia seems to be the major contributing factor. Increased blood glucose levels are thought to have a structural and physiological impact on retinal capillaries, leading to their functional and anatomical incompetence and vascular leakage. Eventually, the closure of retinal capillaries occurs, leading to local hypoxia. Hypoxia is a key regulator of ocular neovascularization via the induction of hypoxia-inducible factor-1 (HIF-1) signaling. Under hypoxic conditions, HIF-1α levels are elevated due to decreased HIF-1α degradation. Further increases in retinal ischemia trigger the production of vasoproliferative factors such as vascular endothelial growth factor (VEGF), stimulating vascularization. Neovascularization from vessel sprouting, and microvascular branching is referred to as angiogenesis. This expansion of the existing vasculature is widely accepted to contribute to adult neovascularization in response to ischemic insult and injury. However, the de novo formation of new vessels, not the progeny of an existing mature vessel, is known as vasculogenesis where the recruitment of EPCs is essential.[4] DR is a classic example of abnormal angiogenesis; series of growth factors, cytokines and growth hormones play a pathogenic role in this process.[5,6] Taking VEGF as an example, EPC can be recruited by VEGF, as they express angiogenic surface markers, including VEGF receptor 2 (VEGFR2) and can be found at sites of vessel damage and tissue ischemia promoting vascular healing. EC migration and proliferation, acting in conjugation with EPC homing, plays an invaluable role in rectifying the pathology of DR. EPCs have been shown, however, to have impaired vasculogenic ability under diabetic conditions, leaving the vascular repair processes incomplete.[7,8] Incomplete vascular repair can result in the blood retinal barrier (BRB) breakdown, contributing to the diabetic macular edema. The current clinical therapeutic options for DR focus exclusively on controlling retinal neovascularization and vascular leakage. As a direct regulator of vascular integrity, EPCs represent a promising target in restoring vessel integrity.[9,10]

A number of studies support that long-term diabetic damage to the cellular and extracellular components of the bone marrow leads to a rapid decline in the bone marrow-hematopoietic stem/progenitor cell (HS/PC) compartment, which ultimately influences vascular integrity and repair, in diabetes caused by multiple pathological factors such as hyperglycemia, hypoxia, followed by ineffective vascular repair (Fig. 1).

2. Pathology of diabetic retinopathy

Diabetic macular edema (DME), a microvascular complication of diabetes, is the most common cause of vision loss in diabetic patients. As shown by population-based studies, the prevalence of DME is between 4.2% and 7.9% in type 1 diabetes[11,12] and between 1.4% and 12.8% in type 2 diabetes.[12,13] DME is commonly defined by hard exudates in the presence of microaneurysms and dot-blot hemorrhages within a one-disc diameter of the foveal center. This presentation is characteristic of a breakdown of the blood-retina barrier, causing intracellular and extracellular accumulation of fluid and lipid exudates, leading to retinal thickening, disturbing the architecture of the macular area and resulting in blurred vison (Fig. 2B).

Proliferative diabetic retinopathy (PDR) is another complication with deleterious impacts on visual quality and is hallmarked by retinal neovascularization (Fig. 2C). Based on global prevalence research including 22,896 diabetic individuals from 35 studies (1980–2008), the prevalence of PDR was found to be 6.96%.[14] The abnormal induction of vessel growth in this disease may cause vascular leakage, and the formation of fibrous tissue (Fig. 2C). The most severe complication of PDR is neovascular glaucoma, severe retinal ischemia-induced the development of new blood vessels on the surface of the iris, or neovascularization in the iris (NVI). NVI is uniquely challenging to the treatment

Please cite this article as: Shao Y, et al. Mitochondrial dysfunctions, endothelial progenitor cells and diabetic retinopathy. (2018), https://doi.org/10.1016/j.jdiacomp.2018.06.015