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Journal of Endocrinology, Diabetes & Obesity

Editorial

Mechanisms of Impaired Angiogenesis in Diabetes Mellitus: do Methylglyoxal and Autophagy Play a Role?

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Submitted: 24 July 2013

Accepted: 05 August 2013

Published: 07 August 2013

Impaired physiological angiogenesis in diabetes leads to delayed wound healing, exacerbated peripheral limb ischemia, and even cardiac mortality due to lack of collateral vessel development [1]. Left untreated, patients with severe limb ischemia may develop multiple organ dysfunctions and die [2]. poorly wound healing from the lower extremities can escalate into severe infections and diabetic ulcers, which are the cause of 86,000 lower limb amputations in the US per year [3]. Preventing such vascular complications requires physiological angiogenesis [4]. However, effective therapies to restore angiogenesis are elusive because it remains incompletely understood how diabetes impairs angiogenesis. Mechanisms by which diabetes impairs angiogenesis are complex, because angiogenesis itself, the formation of new blood vessels out of preexisting capillaries, is a process involving endothelial cell proliferation, matrix degradation, migration, tube formation, and vessel maturation [4]. Multiple mechanisms have been proposed for impaired angiogenesis in diabetes. Oxidative stress/reactive oxygen species (ROS) has been implicated in the pathogenesis of major diabetic complications [5-8]. Although ROS has been regarded as independent risk factors for cardiovascular disease including diabetes, the failure to demonstrate clinical benefit necessitates further studies to determine the role of ROS in these diseases [6,7]. Endothelial derangements and loss of endothelium-derived nitric oxide bioactivity have been shown to be important [9], although the cause and effect has yet to be confirmed in diabetic angiogenesis impairment. Micro RNA alterations have been identified to contribute to delayed angiogenesis [10], although mechanism underlying its regulation is unknown [11]. Growth factors deficiency has long been thought as the mechanism underlying delayed angiogenesis in diabetes, however, growth factors therapy in diabetic complications such as wound healing generates modest efficacy [3], indicating impaired signaling of the growth factor. Recently, it is found that O-GlcNAc modification mediated-Akt inhibition reduces angiogenesis [12], however, the dependency of Akt-pathway is lost pending serum presence, and it is yet to establish what serum factor contributes to the observations [13]. Nevertheless, these data imply that other factors essential in the angiogenic pathway are involved. Indeed, the alterations of vascular endothelial growth factor receptor (VEGFR) 1 have been shown to contribute to the impaired angiogenesis after hindlimb ischemia in a type 2 diabetic mouse model [14]. A recent study suggested that impaired angiogenesis is attributable to endothelial VEGFR2 but not VEGFR1 reduction by methylglyoxal (MGO) [15].

MGO is the major source of intracellular advanced glycation end-products (AGEs) [16]. As a highly reactive α-oxoaldehyde being formed primarily from the intermediates of glycolysis in cells [17], MGO is increased by elevated glucose concentration in diabetes [18]. MGO has been implicated in the pathogenesis of major diabetic complications [19-28] and yet the underlying mechanism remains elusive [29,30]. MGO-induced glycation of low density lipoprotein increases atherosclerosis, [31] whereas MGO modification of a sodium channel causes hyperalgesia in diabetic neuropathy [32]. MGO has also been implicated in diabetic retinal neuropathy [33] and nephropathy [34]. Consistent with the finding that high glucose increases MGO production in cell culture [35], hyperglycemia enhances MGO generation in diabetic patients [8]. MGO restriction has been demonstrated to improve angiogenesis and wound healing in diabetic animal model [36] and in MGO-impaired gastric ulcer healing. [37] MGO can be detoxified efficiently by Glyoxalase (Glo) 1 [38]. While overexpression of Glo1 inhibits AGEs formation in cultured endothelial cells [39], and in diabetic animals, [40] Glo1 deficiency is associated with increased intracellular AGEs [41]. Moreover, it is reported that AGEs attenuate the angiogenic response *in vitro* [42]. In contrast, overexpression of Glo1 reverses high glucose-impaired angiogenesis in cultured endothelial cells [43], blockade of AGEs formation by aminoguanidine restores ischemia-induced angiogenesis in peripheral limbs of diabetic mice *in vivo* [44]. Given the implications of MGO in diabetic complications [18-45,47] and the crucial role of VEGFR2 in endothelial angiogenesis [48-52], we identified a mechanism involving autophagy by which MGO reduced both VEGFR2 and angiogenesis [15], a finding in line with the clinical observations in patients with diabetes [53,54].

Autophagy is a lysosomal degradation pathway essential for

survival, differentiation, development, and homeostasis [55]. There are several forms of autophagy, each of which involves delivering intracellular cargo to lysosome for degradation [56]. Thus autophagy refers to a regulated catabolic cellular process for the lysosomal-dependent turnover of organelles and proteins [57]. Autophagy principally serves an adaptive role to protect organisms against diverse pathologies, including infections, cancer, aging, heart disease, and neurodegeneration, because autophagy is essential in several cellular functions such as cell proliferation and survival [58]. Intriguingly, several angiogenesis inhibitors employed in anti-angiogenesis therapy induce autophagy activation [59,60], linking autophagy initiation to angiogenesis suppression [61]. Consistently, suppression of autophagy apparently promotes angiogenesis [61]. Indeed, mice deficient in the autophagic protein Beclin-1 display a pro-angiogenic phenotype associated with hypoxia [62]. However, the role of autophagy in diabetes appears to be complicated [60-63,64]. For example, although basal autophagy is required to maintain islet homeostasis and its deficiency reduce islet viability, diabetes may induce compensatory autophagy as found in diabetic mice [65]and patients of diabetes [66], Furthermore, defective hepatic autophagy due to Atg7 reduction causes insulin resistance [67], on the contrary, Atg7 deficiency in skeletal muscle leads to protection from insulin resistance [68]. The apparent "paradox" suggests that the pathophysiological role of autophagy in diabetes may depend on the affected tissues/cells [69], the external stressors or inducers of autophagy [70], and the involved components of the autophagy machinery [71]. As such, further studies are required to fully understand the authentic role of autophagy in the pathogenesis of diabetes and its complications [72]. Given the fact that autophagy could be either protective from or causative to cell death, dysregulation of autophagy either by suppression or activation could affect angiogenesis depending conditions [73]. Indeed, suppression of starvation-induced autophagy in cultured endothelial cells in vitro blocked endothelial angiogenesis [74] however, mice deficient in the autophagic protein Beclin 1/Atg6 display a pro-angiogenic phenotype associated with hypoxia [62]. Consistent with the finding in mice, ceramide-initiated autophagy has been associated with a dose dependent inhibition of angiogenesis, [61] whereas suppression of indoxyl sulfate-induced autophagy by statin restores angiogenesis in a renal ischemia model [75], suggesting that autophagy initiation may block physiological angiogenesis. In line with this, an autophagy-mediated reduction of both VEGFR2 and angiogenesis has been demonstrated through pharmaceutical and genetic approaches [15]. Other angiogenic factors than VEGFR2 could be affected in similar fashion which merit further studies. It should be noted that depending on ligand or stimuli, VEGFR2 has been shown to be internalized by endocytosis induced by VEGF [76], affected by Golgi [77], or degraded by proteasome mediated by Nedd4 [78] or β-Trcp1 [79]. Provided the emerging implications for MGO modification in diabetic complications [32,80,81], it is important to know whether MGO selectively modifies a proteolytic systems to alter angiogenesis. To this end, a causative role of MGO and/or autophagy also needs to be established. Collectively, identification of the mechanism by which diabetes impairs physiological angiogenesis not only enhance our understanding toward angiogenesis but also help to develop therapeutic strategy for severe and costly diabetic vascular complications.

ACKNOWLEDGMENTS

Jian Xu is supported by an NIH Grant from the COBRE Program of the National Center for Research Resources (P20 RR 024215-05) and of the National Institute of General Medical Sciences (9P20GM104934-06, Project 2), a National Scientist Development Grant (10SDG2600164) from the American Heart Association, a Junior Faculty Award (1-12-JF-58) from the American Diabetes Association, and a Research Award (HR11-200) from the Oklahoma Center for Advancement of Science and Technology.

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Cite this article

Xu J (2013) Mechanisms of Impaired Angiogenesis in Diabetes Mellitus: do Methylglyoxal and Autophagy Play a Role? J Endocrinol Diabetes Obes 1(1): 1003.