Ubiquitin - proteasome system in diabetic retinopathy (#67203)

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Ubiquitin - proteasome system in diabetic retinopathy

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The ubiquitin proteasome system (UPS) is the main protein quality control system responsible for recognition and degradation of damaged proteins. Accumulating evidence demonstrates the potential role of UPS in diabetes and its complications, including diabetic retinopathy (DR). In diabetes, the overall activity of the UPS is inhibited by the oxidative stress. However, several factors responsible for antioxidative response are selectively degraded by the UPS. Downregulation of some UPS components is associated with endoplasmic reticulum stress and over-activation of unfolded protein response eventually leading to retinal cell death. Increased proteasomal degradation of synaptophysin compromises synaptic activity and contributes to neurodegeneration, this happens due to upregulation of the angiotensin II receptors in diabetes. Downregulation of the UPS leads also to the rhodopsin degradation. Hypoxia-induced decrease of the UPS activity enhances the response via HIF1-alpha, leading to pathological angiogenesis. Both stimulators and inhibitors of the UPS activity and inhibitors of the UPS-mediated degradation of individual proteins are tested as remedies against the diabetic retinopathy. Currently, there is deficiency of literature reviews devoted to the role of UPS specifically in DR. A summary of recent findings in the field is needed to structure existing data and help to identify gaps in knowledge on UPS in DR. In this review, we briefly describe the physiologic regulation of UPS and overview the data on changes in UPS regulation in diabetes and DR.

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Keywords

ubiquitin- proteasome system, retinopathy, diabetes, diabetic eye disease

Running head

Ubiquitin - proteasome system in diabetic retinopathy

Abstract

The ubiquitin proteasome system (UPS) is the main protein quality control system responsible for recognition and degradation of damaged proteins. Accumulating evidence demonstrates the potential role of UPS in diabetes and its complications, including diabetic retinopathy (DR). In diabetes, the overall activity of the UPS is inhibited by the oxidative stress. However, several factors responsible for antioxidative response are selectively degraded by the UPS. Downregulation of some UPS components is associated with endoplasmic reticulum stress and over-activation of unfolded protein response eventually leading to retinal cell death. Increased proteasomal degradation of synaptophysin compromises synaptic activity and contributes to neurodegeneration, this happens due to upregulation of the angiotensin II receptors in diabetes. Dysregulation of the UPS leads also to the rhodopsin degradation. Hypoxia-induced decrease of the UPS activity enhances the response via HIF1-alpha, leading to pathological angiogenesis. Both stimulators and inhibitors of the UPS activity and inhibitors of the UPS-mediated degradation of individual proteins are tested as remedies against the ~~diabetic retinopathy~~ DR.

Currently, there is deficiency of literature reviews devoted to the role of UPS specifically in DR. A summary of recent findings in the field is needed to structure existing data and help to identify gaps in knowledge on UPS in DR.

In this review, we briefly describe the physiologic regulation of UPS and overview the data on changes in UPS regulation in diabetes and DR.

Introduction

The number of patients with diabetes mellitus is increasing steadily throughout the world. Diabetes is a chronic condition characterized by hyperglycemia. In the case of type 1 diabetes (T1D), which is an autoimmune disease, hyperglycemia results from autoimmune destruction of pancreatic beta cells. In type 2 diabetes (T2D) hyperglycemia develops due a combination of pancreatic beta cell dysfunction and insulin resistance [1]. Diabetes is associated with increased morbidity and mortality mainly due to development of neuro-vascular complications. Diabetic retinopathy (DR) is the most common complication of diabetes, being the most prevalent reason of blindness among working-age population in developed world [2,3]. DR is characterised by microangiopathy [4] and neurodegeneration [5,6]. Microangiopathy is staged clinically according to the proliferative status of the retinal vasculature [7,8]. At first, retinal endothelial cell dysfunction appears with loss of pericytes [9] and development of capillaries with enhanced permeability and leukocyte adhesion [10], which leads to vascular obliteration, retinal ischemia and the resulting neovascularization [5,10]. Diabetes - induced retinal vascular lesions may progress independently of the neural degeneration [5]. ~~Diabetic retinopathy~~ DR is also known as one of inflammatory retinal diseases, where inflammatory cytokines influence protein metabolism [11,12].

Despite constant improvement of understanding of the pathogenesis of ~~diabetic retinopathy~~, identification of *novel biomarkers* of DR is needed for improvement of patient risk stratification and development of novel prevention and therapeutic approaches.

The ubiquitin proteasome system (UPS) is the main protein quality control system responsible for recognition and degradation of damaged proteins. Accumulating

evidence demonstrates the potential role of UPS in diabetes and its complications [1,13,14]. However, there is deficiency of literature reviews devoted to the role of UPS specifically in DR. A summary of recent findings in the field is needed to structure existing data and help to identify gaps in knowledge on UPS in DR.

In this review, we briefly describe the physiologic regulation of UPS and overview the data on changes in UPS regulation in diabetes and diabetic retinopathy.

Survey methodology

check google scholar too

The literature search was conducted in the PubMed and Medline databases. Emphasis was placed on articles published since 2015, but earlier articles were also included. The following keywords were used: *proteasomes, ubiquitin-proteasome system, telomeres, retinopathy, diabetes, diabetic retinal disease, diabetic eye disease, diabetic macular edema*. We included original studies and reviews that contained information about UPS and telomere length in diabetic complications, with an emphasis on diabetic eye disease. Case reports were excluded. Of the studies retrieved by this method, we reviewed all publications in English and those having English abstracts. Other articles cited in the reference lists of identified publications were considered as a potential source of information.

Functioning

~~Functions~~ of the ubiquitin-proteasome system (UPS).

repetition

~~UPS is the main protein quality control system responsible for recognition and degradation of damaged proteins in the body~~. UPS is essential in regulating cell cycle (progression, proliferation, apoptosis), immune response, inflammatory response, endoplasmic reticulum - associated degradation of proteins and protein misfolding. Its deregulation leads to multiple disturbances in the normal cell functioning [24,25].

ubiquitinating

The UPS includes ubiquitin, ~~ubiquitin~~ enzymes, proteasome, its substrate proteins and deubiquitinases (DUBs). UPS – mediated protein degradation starts with ubiquitination

and continues with proteasomal degradation. During the ubiquitination process, ubiquitin proteins can be covalently coupled to a target protein by sequential actions of ubiquitination enzymes. These ubiquitination enzymes include ubiquitin activating enzyme (E1), ubiquitin conjugating enzyme (E2), and ubiquitin protein ligase (E3). To mark proteins for degradation, target proteins are covalently tagged with ubiquitin, a small protein with 76 amino acids [26]. Initially ubiquitin is activated by E1 ~~(ubiquitin activating enzyme)~~ in an ATP-dependent manner and then the activated monoubiquitin molecule is transferred to a cysteine residue of the E2 enzyme [24,27]. E2 ~~(ubiquitin conjugating or carrier enzyme)~~ receives ubiquitin from E1 and prepares it for conjugation [28]. E3 ~~(ubiquitin ligase)~~ identifies specific substrates and shifts ubiquitin from E2 to the lysine residue of a targeted protein, forming polyubiquitin chain which transfers the intended protein to the proteasome for degradation [24,27,29]. Eukaryotic cells contain more than 1,000 types of E3; different substrate proteins depend on the specific E3 [27,30,31]. The destiny of ubiquitinated substrate relies on the amount of ubiquitin added [29]. After polyubiquitination (i.e., four ubiquitins attached), substrate proteins are transferred to the 26S proteasome for breakdown. [28,32,33].

Proteasomes exist inside cells in multiple forms including proteasome complexes with different regulatory particles to carry out protein degradation. Eukaryotic cells have several types of constitutive proteasome complexes: 20S core proteasome [28,34–39], 19S proteasome [27,36,40], 26S proteasome [41–43]. ~~In addition, immunoproteasomes (i20S) are inducible form of “constitutive” 20S proteasome [38]. In nonimmune cells formation of immunoproteasome and 11S regulatory complex is induced by interferons~~,

TNF alpha and liposaccharides, oxidative stress as well as physiological causes, like environmental stress factors or aging. [43,45–48].

Immunoproteasome differs from constitutive proteasome – it has increased trypsin like and chymotrypsin like activities, but misses the caspase like activity, also there are differences in sets of antigenic peptides produced by proteasomes [44].

Nearly 100 deubiquitinases (DUBs) are expressed by human genome to regulate compensate the ubiquitination process [49]. DUBs can remove ubiquitin from substrates and deconstruct polyubiquitin chains, leading to protein stabilization [24]. DUBs usually have various substrates and are cell specific. The interaction between ubiquitination and deubiquitination appears to regulate equilibrium of proteasomal degradation, cell cycle progression, gene expression, apoptosis etc [50].

The UPS is also involved in the degradation of misfolded secretory proteins and most integral membrane proteins in the endoplasmic reticulum (ER) for proper folding through the protein quality control system - ERAD (Endoplasmic reticulum – associated protein degradation) pathway [28]. Proteins in the ERAD system are degraded in ER lumen and ER membrane in the cytoplasm [51]. E3 ligases of ERAD ubiquinate non-functional proteins, that are accumulated in the ER, for the proteasomal degradation, thereby protecting against ER stress -induced cell death [52,53]. Unfolded protein response (UPR) activates when misfolded proteins are accumulated into the ER [28]. Multiple pathologies and physiological states, like genetic mutations and oxidative stress, cause accumulation of misfolded proteins in ER and induce UPR activation. UPR has a protective function to restore ER homeostasis, but in prolonged stress situation UPR activation leads to ER induced cell death [28,54].

Derangements of ubiquitin - proteasome system in diabetes and diabetic retinopathy

Accumulating evidence demonstrates the potential role of UPS in diabetes [1,13,14]. The regulation of protein quality and its homeostasis in the retinal cells is essential for maintaining visual function. This regulation is mainly mediated by the UPS in the retina [12]. The summary of UPS involvement in the pathogenesis of DR is presented in Figure 1.

UPS in development of diabetes. Hyperglycemia may decrease proteasome activity in pancreatic beta cells thus contributing to their ER stress, dysfunction and apoptosis [1,34,54–56]. Long term activation of unfolded protein response (UPR) due to hyperglycemia contributes to development of insulin resistance as well [28,57,58]. Initially beta cells activate proinsulin synthesis to adapt to insulin resistance, but increased proinsulin concentration burden for ER does not allow proper proinsulin folding and trafficking [54,59]. ER stress triggers the UPR to remove misfolded proinsulin and to re-establish protein homeostasis. If protein misfolding persists, beta cells eventually die [60].

UPS is involved in the development of autoimmune diabetes [51,60,61]. In the presence of insulitis, proinflammatory cytokines interrupt homeostasis of ER, leading to ER stress [62], that activates ER sensors: inositol-requiring enzyme 1α (IRE1 alpha), PRKR-like ER kinase (PERK) and ATF6, and triggers the UPR [61]. It is considered that PERK pathway plays an important role in the pathogenesis of diabetes [63]. UPR predisposes to activation of chaperone protein synthesis, reducing protein translation into the ER to

166 restore ER homeostasis [28]. This adaptive phase is considered to initiate the
167 development of autoimmunity [61].
168 Nuclear Factor KappaB (NF-kB) transcription factors regulate expression of genes
169 involved in inflammation, immunity and beta cell development. NF-kB activation is
170 mediated through proteasomal degradation for transcriptional activation. [28]. Ubiquitin -
171 editing protein A20 (tumor necrosis factor alpha – induced protein 3, TNFAIP3) acts as
172 a negative – ubiquitin - dependent regulator of NF-kB [64] and is a potent anti -
173 inflammatory signalling molecule. There are indications on involvement of A20
174 dysfunction in autoimmune and inflammatory diseases, including diabetes [65]. Several
175 mutations in A20 have been recognized to be associated with T1D [66]. A20 protected
176 mice from streptozotocin-induced diabetes [67] possibly via impact on beta cell survival
177 pathways [65].
178 ***UPS-associated genetic factors, diabetes and ~~diabetic retinopathy~~.*** DR In humans,
format
179 polymorphisms in PSMA3, PSMA6 and PSMC6 proteasome genes have been found to
180 be associated with T1D in a cohort of Latvian patients. Moreover, correlations have
181 been revealed between some polymorphisms of proteasome genes and 42 T1D-
182 susceptible genes encoding proteins involved in innate and adaptive immunity, antiviral
183 response, insulin signalling, glucose-energy metabolism and other pathways implicated
184 in T1D pathogenesis [68]. Several SNPs and microsatellite alleles localized inside the
185 *PSMA6* proteasome gene and in its vicinity are associated with the risk of T2D [69,70].
186 Moreover, PSMD9 gene SNPs rs74421874, rs3825172 and rs14259 were reported in
DR
187 association with ~~diabetic retinopathy~~ in T2D and non-diabetic retinopathy in Italians [71],
188 as well as PSMD9 SNPs were linked with other microvascular T2D complications –

nephropathy [72], neuropathy [73] and late – onset T2D itself [74]. PSMD9 association is also observed with MODY3 [75].

Two PSMB8 SNPs, rs3763365 and rs9276810, were also identified as genetic risk factors for T1D development [76]. It is observed that PSMB8-B/B may be the protective genotype, but PSMB8-B/A could be susceptible genotype for T1D development in Asian population [77]. Other study concluded that allelic and dominant models of PSMB8 G37360T could be protective in T1D in Caucasian population, but dominant model of PSMB9 *CfoI* could be a risk factor for T1D in Asian population [78].

Genetic deletion of proteasome activator genes, PA28*α* and PA28*β* genes, protected the diabetic mice in the experimental STZ-induced diabetes model against renal injury and retinal microvascular injury and prolonged their survival compared with wild type STZ diabetic mice. The authors conclude that diabetic hyperglycemia promotes PA28-mediated alteration of proteasome activity in vulnerable perivascular cells resulting in microvascular injury and development of diabetic nephropathy and DR [86]. Thus decrease of the proteasome activity appears to be favourable in the above case.

UPS, diabetes - induced oxidative stress and ~~diabetic retinopathy~~ DR. Diabetes is a state of chronic hyperglycemia - induced oxidative stress [87]. 26S proteasomes are not very effective in degrading oxidised proteins, in contrast 20S proteasome - mediated degradation is more or less intact, even in the presence of high concentrations of H2O2 [88]. However, ~~hydrogen peroxide (~~H2O2~~)~~ interferes with proteasomal activity and increases the amount of ubiquitinated proteins [89]. Immunoproteasome is more resistant to reactive oxygen species (ROS) and degrades oxidised proteins more successfully than the ~~20~~26S proteasome [45]. In case of moderate oxidative stress

expand

immunoproteasomal activity can be increased to sustain protein homeostasis. Continuous oxidative stress elevates amount of damaged proteins and UPS impairment, that leads to their build - up in cells [89,90].

Oxidative stress plays an important role in the pathogenesis of ~~diabetic retinopathy~~ DR [10,91,92]. Levels of reactive oxygen and nitrogen species, including the highly reactive oxidant peroxynitrite are increased in diabetic retinas [93]. Fernandes et al. reported that increased oxidative stress in diabetic retinas led to inactivation of the 20S proteasome in Goto – Kakizaki rats with dyslipidaemia. They showed that oxidative stress induced the accumulation of ubiquitinated proteins and affected the chymotrypsin - like activity of the proteasome under the influence of chronic hyperglycemia. Application of atorvastatin had a local antioxidative effect and restored the ubiquitin – proteasome pathway in atherogenic diet - fed rats [10]. In this case decrease in proteasomal activity appears to be unfavourable.

Transcription factor NF-E2 related factor 2 (Nrf2) is one of the stress-response proteins for antioxidative defence of the cell [94]. Under unstressed conditions, Kelch-like ECH-associated protein 1-nuclear factor (Keap1) serves as an adaptor for ubiquitin E3 ligase and promotes proteasomal degradation of Nrf2. Nrf2 is stabilized when Keap1 is inactivated under oxidative/electrophilic stress conditions. Once activated, Nrf2 migrates into the nucleus and binds to the DNA at the location of the antioxidant response element (ARE) to control the expression of cytoprotective genes. In diabetes, however, Nrf2 binding to KEAP1 is increased, leading to its proteasomal degradation and decreased cell-stress response. In DR, epigenetic changes of Keap1 gene can lead to decreased Nrf2 expression, and impaired anti-oxidative response [95]. Also, Nrf2

function in diabetes is suppressed by stress response protein regulated in development and DNA damage 1 (REDD1). Specifically, REDD1 suppressed Nrf2 stability by promoting its proteasomal degradation independently of Nrf2's interaction with Keap1, preventing antioxidative response in retinal cells of diabetic mice [96]. Taken together, these findings suggest that targeting proteasomal degradation of Nrf2 is a promising approach in DR, as increased proteasomal degradation of Nrf2 seems to be nocive.

UPS and diabetes - induced ER stress. Downregulation of ERAD components was documented in experimental diabetes [97]. Shruthi et al. observed that there are changes in ERAD components in the cerebral cortex of animals with experimental diabetes. Upregulation of ERAD components (HRD1, Derlin1, and VCP) in early diabetes is observed and might represent a defensive mechanism against ER stress. However, continuing chronic hyperglycemia and oxidative stress leads to significant decrease of the mentioned ERAD components, further elevating ER stress [1].

ER stress is also involved in development of ~~diabetic retinopathy~~ DR [11,14], possibly because of reduced amounts of E1 and HRD1 (ER stress induced protein with ubiquitin – ligase - like activity), components of UPS. Treatment with a chemical chaperone 4-phenylbutyric acid (4-PBA) altered retinal cells, restored levels of deubiquitinases and improving ER stress – related cell death [14]. In cultured human retinal pericytes exposed to high glucose treatment, induction of ER stress was associated with upregulation of proteasome activator 11S REG (PA28 a/-β) [98–100].

UPS and neurodegeneration in ~~diabetic retinopathy~~ DR. Angiotensin II and its receptors angiotensin II type 1 receptor (AT1R) and type 2 receptor (AT2R) become upregulated in experimental diabetic eye disease [5,6]. Synaptophysin is a major synaptic vesicle

protein which is co-expressed with AT1R in the inner layers of the retina [101]. Synaptophysin levels are reduced in neurodegenerative diseases such as dementia, Parkinson's disease and Alzheimer's disease [102,103]. In the diabetic retina, angiotensin II and AT1R are upregulated together with AT1R's downstream extracellular signal - related protein kinase (ERK) activation [6], that induces synaptophysin degradation. Therefore, activation of the angiotensin II - AT1R - ERK pathway increases the ubiquitin-conjugated synaptophysin protein levels [6] leading to decreased synaptophysin levels in experimental ~~diabetic retinopathy~~ DR [5,12]. Increased proteasomal degradation of synaptophysin compromises synaptic activity, worsens neuronal cell survival and vision in diabetes. However, synaptophysin degradation can be inhibited by blocking AT1R signalling in vivo by angiotensin receptor blockers. Telmisartan and valsartan significantly reversed diabetes-induced changes in the electroretinogram, suggesting that suppression of diabetes - induced retinal dysfunction and synaptophysin degradation is a class effect for angiotensin receptor blockers [12]. Antioxidant lutein can also prevent ERK activation and the following reduction of synaptophysin in the diabetic retina [91].

Decreased levels of rhodopsin have been observed in rats with experimental diabetes and may be associated with vision impairment in early diabetes [104]. Degradation of rhodopsin, an essential protein for photoreceptor function, is mediated by the STAT3-dependent E3 ubiquitin ligase, Ubr1 [105], suggesting impairment of UPS regulation as one of the reasons for decrease of rhodopsin in diabetic retina.

Reduced protein expression of UPS components were observed in retinal ganglion and horizontal cells [14,106] possibly contributing to neurodegeneration in diabetic eye disease [91,107].

UPS, hypoxia and ~~diabetic retinopathy~~ DR. Diabetes is a state of chronic hypoxia, due to glycation of haemoglobin and increased oxidative stress [108]. Proteasome activity is impaired in response to hyperglycemia - associated hypoxia [99,109]. As a result, changes in degradation of proteins involved in anti - hypoxic defence might occur. A protein important for pathogenesis of DR is hypoxia - induced factor 1 alpha (HIF1-alpha). HIF-alpha undergoes hydroxylation by prolyl hydroxylase domain in a normoxic conditions, resulting in proteasomal degradation. Under hypoxia or prolyl hydroxylase domain inhibition, HIF1-alpha is not hydroxylated, but is stabilized in cytosol and forms a heterodimer with HIF1-beta. This heterodimer translocates into the nucleus, binds to the consensus enhancer through hypoxia -responsive elements and activates downstream genes such as GLUT1, erythropoietin, vascular endothelial growth factor (VEGF) [110] and angiopoietin 2 [111] involved in pathogenic angiogenesis in DR.

UPS in the adaptive mechanisms in ~~diabetic retinopathy~~ DR. Hyperglycemia is associated with increased ubiquitination and proteasomal degradation of some proteins, which might represent an adaptive mechanism [112,113]. In ~~diabetic retinopathy~~ DR in the setting of oxidative stress, subcellular redistribution of glucose transporter 1 (GLUT1) occurs [113], which is the main isoform of glucose transporters in retinal endothelial cells [114]. In conditions of increased oxidative stress, endothelial cells upregulate ubiquitin proteasome pathway with subsequent increases turnover of ubiquitin conjugates. GLUT1 seems to be mono- or diubiquitinated and accordingly targeted for

lysosomal degradation, decreasing glucose transport into retinal endothelial cells and thus the associated glycotoxicity [113].

UPS targeted therapies in diabetic microangiopathy. Proteasome inhibitors have entered clinical practice to treat malignancies, especially multiple myeloma. In addition, a variety of novel preparations targeting different components of UPS ~~system~~ are under development and testing in neurodegenerative disease nowadays [28]. As neurodegeneration is a crucial mechanism of diabetic eye disease, we are looking forward to preclinical studies also in DR. Current data on UPS - affecting treatments in diabetic microangiopathy are very limited. A compound under investigation Trichostatin A induced ubiquitination of p300 - histone acetyltransferase leading to reduced levels of NADPH oxidase 4 (Nox4), a mediator of angiogenesis, and inhibited angiogenesis in in vitro model [115]. There are slightly more data on UPS-affecting treatments in diabetic nephropathy. Proteasome inhibitor MG132 leads to inhibition of TGF-beta activation, affects Nrf2 pathway and antioxidative capacity, all involved in the pathogenesis of microvascular disease in diabetes [116–120]. Furthermore, inhibitors of heat shock protein 90 (Hsp90) which stabilises HIF1-alpha, can promote proteasomal degradation of HIF1-alpha modulating hypoxia-induced pathways of retinal neovascularization. Examples of Hsp90 inhibitors include geldanamycin, its analogues and deguelin, which demonstrated promising results in experimental studies [121].

Conclusions

Increasing evidence is indicating the major role of UPS regulation in the pathogenesis of diabetic eye disease. Currently available data indicate that diabetes induced derangements of UPS mainly result from hyperglycemia, increased oxidative stress and hypoxia. These UPS derangements include impaired degradation of oxidized proteins,

ER stress, increased proteasomal degradation of protective and functional proteins (e.g., synaptophysin, rhodopsin, Nrf2), and decreased proteasomal degradation of proteins involved in progression of DR (e.g., HIF1-alpha). Moreover, promising results have been obtained on modulation of UPS in experimental DR. Further studies are needed to improve the understanding of UPS regulation in diabetic eye disease and to promote development of therapies targeting these biomarkers of diabetic microangiopathy.

Conflict of interest. Z.Svikle, B. Pēterfelde, N. Sjakste, K. Baumane, Rasa Verkauskiene, Chi-Juei Jeng report no conflict of interest. J.Sokolovska reports lecture fees and educational grants from Sandoz, Sanofi, MSD, NovoNordisc, AstraZeneca, Grindex outside the submitted work.

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References

1. Shruthi K, Reddy SS, Chitra PS, Reddy GB. Ubiquitin-proteasome system and ER stress in the brain of diabetic rats. J Cell Biochem. 2019 Apr 1;120(4):5962–73.
2. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, Chen

SJ, Dekker JM, Fletcher A, Grauslund J, Haffner S, Hamman RF, Ikram MK, Kayama T, Klein BEK, Klein R, Krishnaiah S, Mayurasakorn K, O'Hare JP, Orchard TJ, Porta M, Rema M, Roy MS, Sharma T, Shaw J, Taylor H, Tielsch JM, Varma R, Wang JJ, Wang N, West S, Zu L, Yasuda M, Zhang X, Mitchell P, Wong TY. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556–64.

3. Langelaan M, De Boer MR, Van Nispen RMA, Wouters B, Moll AC, Van Rens GHMB. Impact of visual impairment on quality of life: A comparison with quality of life in the general population and with other chronic conditions. Ophthalmic Epidemiol. 2007;14(3):119–26.

4. Satofuka S, Ichihara A, Nagai N, Noda K, Ozawa Y, Fukamizu A, Tsubota K, Itoh H, Oike Y, Ishida S. (Pro)renin receptor-mediated signal transduction and tissue renin-angiotensin system contribute to diabetes-induced retinal inflammation. Diabetes. 2009;58(7):1625–33.

5. Ozawa Y, Kurihara T, Sasaki M, Ban N, Yuki K, Kubota S, Tsubota K. Neural degeneration in the retina of the streptozotocin-induced type 1 diabetes model. Exp Diabetes Res. 2011;2011.

6. Kurihara T, Ozawa Y, Nagai N, Shinoda K, Noda K, Imamura Y, Tsubota K, Okano H, Oike Y, Ishida S. Angiotensin II type 1 receptor signaling contributes to synaptophysin degradation and neuronal dysfunction in the diabetic retina. Diabetes. 2008 Aug;57(8):2191–8.

7. Kizawa J, Machida S, Kobayashi T, Gotoh Y, Kurosaka D. Changes of oscillatory potentials and photopic negative response in patients with early diabetic

retinopathy. Jpn J Ophthalmol. 2006;50(4):367–73.

8. Tang J, Kern TS. Inflammation in Diabetic Retinopathy. Prog Retin Eye Res. 2011;September(30(5)):343–358.

9. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther. 2008;88(11):1322–35.

10. Fernandes R, Bento CF, Matafome P, Sena CM, Seiça RM, Pereira P. Atorvastatin-mediated protection of the retina in a model of diabetes with hyperlipidemia. Can J Physiol Pharmacol. 2014 Oct 1;92(12):1037–43.

11. Li J, Wang JJ, Yu Q, Wang M, Zhang SX. Endoplasmic reticulum stress is implicated in retinal inflammation and diabetic retinopathy. FEBS Lett. 2009;583(9):1521–7.

12. Ozawa Y, Kurihara T, Tsubota K, Okano H. Regulation of Posttranscriptional Modification as a Possible Therapeutic Approach for Retinal Neuroprotection. J Ophthalmol. 2011;2011:1–8.

13. Goru SK, Kadakol A, Gaikwad AB. Hidden targets of ubiquitin proteasome system: To prevent diabetic nephropathy. Pharmacol Res. 2017 Jun 1;120:170–9.

14. Shruthi K, Reddy SS, Reddy GB. Ubiquitin-proteasome system and ER stress in the retina of diabetic rats. Arch Biochem Biophys. 2017 Aug 1;627:10–20.

15. Aviv A, Aviv H. Reflections on telomeres, growth, aging, and essential hypertension. Hypertension. 1997;29(5):1067–72.

16. Epel ES, Lin J, Wilhelm FH, Wolkowitz OM, Cawthon R, Adler NE, Dolbier C, Mendes WB, Blackburn EH. Cell aging in relation to stress arousal and cardiovascular disease risk factors. Psychoneuroendocrinology. 2006;31(3):277–

87.

17. Uziel O, Singer JA, Danicek V, Sahar G, Berkov E, Luchansky M, Fraser A, Ram R, Lahav M. Telomere dynamics in arteries and mononuclear cells of diabetic patients: Effect of diabetes and of glycemic control. Exp Gerontol. 2007;42(10):971–8.

18. Sampson MJ, Hughes DA. Chromosomal telomere attrition as a mechanism for the increased risk of epithelial cancers and senescent phenotypes in type 2 diabetes. Diabetologia. 2006;49(8):1726–31.

19. Fyhrquist F, Tiitu A, Saijonmaa O, Forsblom C, Groop PH. Telomere length and progression of diabetic nephropathy in patients with type 1 diabetes. J Intern Med. 2010;267(3):278–86.

20. Tentolouris N, Alexiadou K, Makrilakis K, Liatis S, Jude E, Boulton A. Standard and Emerging Treatment Options for Diabetic Neuropathy. Curr Pharm Des. 2014;20(22):3689–704.

21. Testa R, Olivieri F, Sirolla C, Spazzafumo L, Rippo MR, Marra M, Bonfigli AR, Ceriello A, Antonicelli R, Franceschi C, Castellucci C, Testa I, Procopio AD. Leukocyte telomere length is associated with complications of Type 2 diabetes mellitus. Diabet Med. 2011;28(11):1388–94.

22. Verzola D, Gandolfo MT, Gaetani G, Ferraris A, Mangerini R, Ferrario F, Villaggio B, Gianiorio F, Tosetti F, Weiss U, Traverso P, Mji M, Deferrari G, Garibotto G. Accelerated senescence in the kidneys of patients with type 2 diabetic nephropathy. Am J Physiol - Ren Physiol. 2008;295(5):1563–73.

23. Sharma R, Gupta A, Thungapathra M, Bansal R. Telomere mean length in

patients with diabetic retinopathy. Sci Rep. 2015;5:1–6.

24. Zhang J, Wang X, Vikash V, Ye Q, Wu D, Liu Y, Dong W. ROS and ROS-Mediated Cellular Signaling. Oxid Med Cell Longev. 2016;2016:4350965.

25. Bard J, Goodall EA, Greene ER, Jonsson E, Dong KC, Martin A. Structure and Function of the 26S Proteasome. Annu Rev Biochem. 2018;87:697–724.

26. Lim KL, Tan JMM. Role of the ubiquitin proteasome system in Parkinson's disease. BMC Biochem. 2007;8(SUPPL. 1):1–10.

27. Shukla SK, Rafiq K. Proteasome biology and therapeutics in cardiac diseases. Transl Res. 2019 Mar 1;205:64–76.

28. Thibaudeau TA, Smith DM. A practical review of proteasome pharmacology. Pharmacol Rev. 2019 Apr 1;71(2):170–97.

29. Bai T, Wang F, Mellen N, Zheng Y, Cai L. Diabetic cardiomyopathy: role of the E3 ubiquitin ligase. Am J Physiol Endocrinol Metab. 2016;310:473–83.

30. Qian LL, Liu XY, Yu ZM, Wang RX. BK Channel Dysfunction in Diabetic Coronary Artery: Role of the E3 Ubiquitin Ligases. Front Physiol. 2020 May 29;11:453.

31. Nakayama KI, Nakayama K. Ubiquitin ligases: Cell-cycle control and cancer. Nat Rev Cancer. 2006;6(5):369–81.

32. Pickart CM. Mechanisms Underlying Ubiquitination. Annu Rev Biochem. 2001;70(1):503–33.

33. Ling TY, Yi F, Lu T, Wang XL, Sun X, Willis MS, Wu LQ, Shen WK, Adelman JP, Lee HC. F-box protein-32 down-regulates small-conductance calcium-activated potassium channel 2 in diabetic mouse atria. J Biol Chem. 2019 Mar 15;294(11):4160–8.

34. Homma T, Fujii J. Emerging connections between oxidative stress, defective proteolysis, and metabolic diseases. Free Radic Res. 2020;1–16.
35. Arendt CS, Hochstrasser M. Identification of the yeast 20S proteasome catalytic centers and subunit interactions required for active-site formation. Proc Natl Acad Sci U S A. 1997;94(14):7156–61.
36. Jung T, Catalgol B, Grune T. The proteasomal system. Mol Aspects Med. 2009;30(4):191–296.
37. Groll M, Huber R. Substrate access and processing by the 20S proteasome core particle. Int J Biochem Cell Biol. 2003;35(5):606–16.
38. Korovila I, Hugo M, Castro JP, Weber D, Höhn A, Grune T, Jung T. Proteostasis, oxidative stress and aging. Redox Biol. 2017 Oct 1;13:550–67.
39. Köhler A, Cascio P, Leggett DS, Woo KM, Goldberg AL, Finley D. The axial channel of the proteasome core particle is gated by the Rpt2 ATPase and controls both substrate entry and product release. Mol Cell. 2001;7(6):1143–52.
40. de Poot SAH, Tian G, Finley D. Meddling with Fate: The Proteasomal Deubiquitinating Enzymes. J Mol Biol. 2017;429(22):3525–45.
41. Hershko A. The ubiquitin system for protein degradation and some of its roles in the control of the cell-division cycle (Nobel Lecture). Angew Chemie - Int Ed. 2005;44(37):5932–43.
42. Tanaka K, Mizushima T, Saeki Y. The proteasome: Molecular machinery and pathophysiological roles. Biol Chem. 2012;393(4):217–34.
43. Kudriaeva AA, Belogurov AA. Proteasome: a Nanomachinery of Creative Destruction. Biochem. 2019 Jan 1;84:159–92.

44. Chapiro J, Claverol S, Piette F, Ma W, Stroobant V, Guillaume B, Gairin J-E, Morel S, Burlet-Schiltz O, Monsarrat B, Boon T, Van den Eynde BJ. Destructive Cleavage of Antigenic Peptides Either by the Immunoproteasome or by the Standard Proteasome Results in Differential Antigen Presentation. J Immunol. 2006;176(2):1053–61.

45. Qureshi N, Morrison DC, Reis J. Proteasome protease mediated regulation of cytokine induction and inflammation. Biochim Biophys Acta - Mol Cell Res. 2012;1823(11):2087–93.

46. Kuehn L, Dahlmann B. Proteasome activator PA28 and its interaction with 20 S proteasomes. Arch Biochem Biophys. 1996;329(1):87–96.

47. Mao I, Liu J, Li X, Luo H. REGγ, a proteasome activator and beyond? Cell Mol Life Sci. 2008;65(24):3971–80.

48. Ferrington DA, Gregerson DS. Immunoproteasomes: structure, function, and antigen presentation. Prog Mol Biol Transl Sci. 2012;109:75–112.

49. Komander D, Clague MJ, Urbé S. Breaking the chains: Structure and function of the deubiquitinases. Nat Rev Mol Cell Biol. 2009;10(8):550–63.

50. Gupta I, Singh K, Varshney NK, Khan S. Delineating crosstalk mechanisms of the ubiquitin proteasome system that regulate apoptosis. Front Cell Dev Biol. 2018 Feb 9;6:11.

51. Kaneko M, Imaizumi K, Saito A, Kanemoto S, Asada R, Matsuhisa K, Ohtake Y. ER Stress and Disease: Toward Prevention and Treatment. Biol Pharm Bull. 2017;40(9):1337–43.

52. Kaneko M, Ishiguro M, Niinuma Y, Uesugi M, Nomura Y. Human HRD1 protects

against ER stress-induced apoptosis through ER-associated degradation. FEBS Lett. 2002;532(1–2):147–52.

53. Kaneko M, Nomura Y. ER signaling in unfolded protein response. Life Sci. 2003;74(2–3):199–205.

54. Back SH, Kaufman RJ. Endoplasmic reticulum stress and type 2 diabetes. Annu Rev Biochem. 2012;81(March):767–93.

55. Tang C, Yeung LSN, Koulajian K, Zhang L, Tai K, Volchuk A, Giacca A. Glucose-induced B-cell dysfunction in vivo: Evidence for a causal role of C-jun N-terminal kinase pathway. Endocrinology. 2018;159(11):3643–54.

56. Broca C, Varin E, Armanet M, Tourrel-Cuzin C, Bosco D, Dalle S, Wojtusciszyn A. Proteasome dysfunction mediates high glucose-induced apoptosis in rodent beta cells and human islets. PLoS One. 2014 Mar 18;9(3):e92066.

57. Lenna S, Han R, Trojanowska M. Endoplasmic reticulum stress and endothelial dysfunction. IUBMB Life. 2014;66(8):530–7.

58. Hotamisligil GS. Endoplasmic Reticulum Stress and the Inflammatory Basis of Metabolic Disease. Cell. 2010;140(6):900–17.

59. Eizirik DL, Cnop M. ER stress in pancreatic β cells: The thin red line between adaptation and failure. Sci Signal. 2010;3(110):1–4.

60. Liu M, Hodish I, Haataja L, Lara-Lemus, Roberto RG, Jordan W, Peter A. Proinsulin misfolding and diabetes: Mutant INS gene-induced Diabetes of Youth. Trends Endocrinol Metab. 2010;November(21(11)):652–659.

61. Thomaidou S, Zaldumbide A, Roep BO. Islet stress, degradation and autoimmunity. Diabetes, Obes Metab. 2018 Sep 1;20:88–94.

511 62. Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulitis and B-cell loss in
512 type 1 diabetes. Nat Rev Endocrinol. 2009;5(4):219–26.
513 63. Oyadomari S, Koizumi A, Takeda K, Gotoh T, Akira S, Araki E, Mori M. Targeted
514 disruption of the Chop gene delays endoplasmic reticulum stress-mediated
515 diabetes. J Clin Invest. 2002;109(4):525–32.
516 64. Catrysse L, Vereecke L, Beyaert R, van Loo G. A20 in inflammation and
517 autoimmunity. Trends Immunol. 2014;35(1):22–31.
518 65. Fukaya M, Brorsson CA, Meyerovich K, Catrysse L, Delaroche D, Vanzela EC,
519 Ortis F, Beyaert R, Nielsen LB, Andersen ML, Mortensen HB, Pociot F, van Loo
520 G, Størling J, Cardozo AK. A20 inhibits β-cell apoptosis by multiple mechanisms
521 and predicts residual β-cell function in type 1 diabetes. Mol Endocrinol.
522 2016;30(1):48–61.
523 66. Bergholdt R, Brorsson C, Palleja A, Berchtold LA, Fløyel T, Bang-Berthelsen CH,
524 Frederiksen KS, Jensen LJ, Størling J, Pociot F. Identification of novel type 1
525 diabetes candidate genes by integrating genome-wide association data, protein-
526 protein interactions, and human pancreatic islet gene expression. Diabetes.
527 2012;61(4):954–62.
528 67. Yu LY, Lin B, Zhang ZL, Guo LH. Direct transfer of A20 gene into pancreas
529 protected mice from streptozotocin-induced diabetes. Acta Pharmacol Sin.
530 2004;25(6):721–6.
531 68. Sjakste T, Paramonova N, Osina K, Dokane K, Sokolovska J, Sjakste N. Genetic
532 variations in the PSMA3, PSMA6 and PSMC6 genes are associated with type 1
533 diabetes in latvians and with expression level of number of UPS-related and

534 T1DM-susceptible genes in HapMap individuals. Mol Genet Genomics. 2016 Apr
535 1;291(2):891–903.
536 69. Sjakste T, Poudziunas I, Ninio E, Perret C, Pirags V, Nicaud V, Lazdins M,
537 Evanss A, Morrison C, Cambien F, Sjakste N. SNPs of PSMA6 gene--
538 investigation of possible association with myocardial infarction and type 2
539 diabetes mellitus. Genetika. 2007 Apr;43(4):553–9.
540 70. Sjakste T, Kalis M, Poudziunas I, Pirags V, Lazdins M, Groop L, Sjakste N.
541 Association of microsatellite polymorphisms of the human 14q13.2 region with
542 type 2 diabetes mellitus in Latvian and Finnish populations. Ann Hum Genet.
543 2007 Nov;71(Pt 6):772–6.
544 71. Gragnoli C. Proteasome modulator 9 gene is linked to diabetic and non-diabetic
545 retinopathy in T2D. Ophthalmic Genet. 2011 Nov 1;32(4):228–30.
546 72. Gragnoli C. T2D-nephropathy linkage within 12q24 locus. Diabetes Res Clin
547 Pract. 2011 Jun;92(3):e73-5.
548 73. Gragnoli C. PSMD9 is linked to type 2 diabetes neuropathy. J Diabetes
549 Complications. 2011;25(5):329–31.
550 74. Gragnoli C. PSMD9 gene in the NIDDM2 locus is linked to type 2 diabetes in
551 Italians. J Cell Physiol. 2010 Feb;222(2):265—267.
552 75. Gragnoli C. PSMD9 is linked to MODY3. J Cell Physiol. 2010 Apr 1;223:1–5.
553 76. Zaiss DMW, Bekker CPJ, Gröne A, Lie BA, Sijts AJAM. Proteasome
554 immunosubunits protect against the development of CD8 T cell-mediated
555 autoimmune diseases. J Immunol. 2011 Sep;187(5):2302–9.
556 77. Ding H, Cheng H, Fu Z, Yan L, Yang G. Relationship of large multifunctional

proteasome 7 gene polymorphism with susceptibility to type 1 diabetes mellitus and DR3 gene. Chin Med J (Engl). 2001 Dec;114(12):1263–6.

78. Xu Y, Liu G, Zhou Y, Lu Z, Shi Z, Wang J. The genetic association between LMP2 and LMP7 polymorphisms and susceptibility of insulin dependent diabetes mellitus: A meta-analysis. Medicine (Baltimore). 2020 Mar;99(13):e19482.

79. Zhang J, Chen Z, Zhou Z, Yang P, Wang C-Y. Sumoylation Modulates the Susceptibility to Type 1 Diabetes. Adv Exp Med Biol. 2017;963:299–322.

80. Wang CY, Podolsky R, She JX. Genetic and functional evidence supporting SUMO4 as a type 1 diabetes susceptibility gene. Ann N Y Acad Sci. 2006;1079:257–67.

81. Smyth DJ, Howson JMM, Lowe CE, Walker NM, Lam AC, Nutland S, Hutchings J, Tuomilehto-Wolf E, Tuomilehto J, Guja C, Ionescu-Tîrgoviste C, Undlien DE, Rønningen KS, Savage D, Dunger DB, Twells RCJ, McArdle WL, Strachan DP, Todd JA. Assessing the validity of the association between the SUMO4 M55V variant and risk of type 1 diabetes. Nat Genet. 2005 Feb;37(2):110–3.

82. Ma J, Wu H, Zhao CY, Panchapakesan U, Pollock C, Chadban SJ. Requirement for TLR2 in the development of albuminuria, inflammation and fibrosis in experimental diabetic nephropathy. Int J Clin Exp Pathol. 2014;7(2):481–95.

83. Kanwar YS, Wada J, Sun L, Xie P, Wallner EI, Chen S, Chugh S, Danesh FR. Diabetic nephropathy: Mechanisms of renal disease progression. Exp Biol Med. 2008;233(1):4–11.

84. Li Y, Huang W, Xu Y, Zhou L, Liang Y, Gao C, Long Y, Xu Y. CYLD Deubiquitinase Negatively Regulates High Glucose-Induced NF-κB Inflammatory

Signaling in Mesangial Cells. Biomed Res Int. 2017;2017:3982906.

85. Dyson HJ, Komives EA. Role of disorder in IκB-NFκB interaction. IUBMB Life. 2012;64(6):499–505.

86. Yadranji Aghdam S, Mahmoudpour A. Proteasome Activators, PA28α and PA28β, Govern Development of Microvascular Injury in Diabetic Nephropathy and Retinopathy. Kaneko K, editor. Int J Nephrol. 2016;2016:3846573.

87. Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. Diabetes. 2005;54(6):1615–25.

88. Reinheckel T, Ullrich O, Sitte N, Grune T. Differential impairment of 20S and 26S proteasome activities in human hematopoietic K562 cells during oxidative stress. Arch Biochem Biophys. 2000;377(1):65–8.

89. Dong X, Liu J, Zheng H, Glasford JW, Huang W, Chen QH, Harden NR, Li F, Gerdes AM, Wang X. In situ dynamically monitoring the proteolytic function of the ubiquitin-proteasome system in cultured cardiac myocytes. Am J Physiol - Hear Circ Physiol. 2004;287(3 56-3):1417–26.

90. Menéndez-Benito V, Verhoef LGGC, Masucci MG, Dantuma NP. Endoplasmic reticulum stress compromises the ubiquitin-proteasome system. Hum Mol Genet. 2005;14(19):2787–99.

91. Sasaki M, Ozawa Y, Kurihara T, Kubota S, Yuki K, Noda K, Kobayashi S, Ishida S, Tsubota K. Neurodegenerative influence of oxidative stress in the retina of a murine model of diabetes. Diabetologia. 2010;53(5):971–9.

92. Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. Exp Diabesity Res. 2007;2007:43603.

603 93. Zhang X, Chen J, Graham SH, Du L, Kochanek PM, Draviam R, Guo F, Nathaniel
604 PD, Szabó C, Watkins SC, Clark RSB. Intranuclear localization of apoptosis-
605 inducing factor (AIF) and large scale DNA fragmentation after traumatic brain
606 injury in rats and in neuronal cultures exposed to peroxynitrite. J Neurochem.
607 2002;82(1):181–91.
608 94. Chapple SJ, Siow RCM, Mann GE. Crosstalk between Nrf2 and the proteasome:
609 Therapeutic potential of Nrf2 inducers in vascular disease and aging. Int J
610 Biochem Cell Biol. 2012;44(8):1315–20.
611 95. Mishra M, Zhong Q, Kowluru RA. Epigenetic modifications of Keap1 regulate its
612 interaction with the protective factor Nrf2 in the development of diabetic
613 retinopathy. Invest Ophthalmol Vis Sci. 2014;55(11):7256–65.
614 96. Miller WP, Sunilkumar S, Giordano JF, Toro AL, Barber AJ, Dennis MD. The
615 stress response protein REDD1 promotes diabetes-induced oxidative stress in the
616 retina by Keap1-independent Nrf2 degradation. J Biol Chem. 2020
617 May;295(21):7350–61.
618 97. Yang S, He H, Ma QS, Zhang Y, Zhu Y, Wan X, Wang FW, Wang SS, Liu L, Li B.
619 Experimental study of the protective effects of SYVN1 against diabetic
620 retinopathy. Sci Rep. 2015;5:1–11.
621 98. Aghdam SY, Sheibani N. The Ubiquitin-Proteasome System and Microvascular
622 Complications of Diabetes. J Ophthalmic Vis Res. 2013;8(3):244–56.
623 99. Aghdam SY, Gurel Z, Ghaffarieh A, Sorenson CM, Sheibani N. High glucose and
624 diabetes modulate cellular proteasome function: Implications in the pathogenesis
625 of diabetes complications. Biochem Biophys Res Commun. 2013 Mar

626 8;432(2):339–44.
627 100. Zhong Y, Wang JJ, Zhang SX. Intermittent but not constant high glucose induces
628 ER stress and inflammation in human retinal pericytes. Adv Exp Med Biol.
629 2012;723:285–92.
630 101. Kurihara T, Ozawa Y, Shinoda K, Nagai N, Inoue M, Oike Y, Tsubota K, Ishida S,
631 Okano H. Neuroprotective effects of angiotensin II type 1 receptor (AT1R)
632 blocker, telmisartan, via modulating AT1R and AT2R signaling in retinal
633 inflammation. Investig Ophthalmol Vis Sci. 2006;47(12):5545–52.
634 102. Zhan S, Beyreuther K, HP Schmitt. Quantitative assessment of the synaptophysin
635 immuno-reactivity of the cortical neuropil in various neurodegenerative disorders
636 with dementia. Dementia. 1993;Mar-Apr(4(2)):66–74.
637 103. Sun C, Li H, Leng L, Raizada MK, Bucala R, Sumners C. Macrophage migration
638 inhibitory factor: An intracellular inhibitor of angiotensin II-induced increases in
639 neuronal activity. J Neurosci. 2004;24(44):9944–52.
640 104. Malechka V V., Moiseyev G, Takahashi Y, Shin Y, Ma J xing. Impaired Rhodopsin
641 Generation in the Rat Model of Diabetic Retinopathy. Am J Pathol.
642 2017;187(10):2222–31.
643 105. Ozawa Y, Nakao K, Kurihara T, Shimazaki T, Shimmura S, Ishida S, Yoshimura
644 A, Tsubota K, Okano H. Roles of STAT3/SOCS3 pathway in regulating the visual
645 function and ubiquitin-proteasome-dependent degradation of rhodopsin during
646 retinal inflammation. J Biol Chem. 2008;283(36):24561–70.
647 106. Bonfanti L, Candeo P, Piccinini M, Carmignoto G, Comelli MC, Ghidella S, Bruno
648 R, Gobetto A, Merighi A. Distribution of protein gene product 9.5 (PGP 9.5) in the

vertebrate retina: Evidence that immunoreactivity is restricted to mammalian horizontal and ganglion cells. J Comp Neurol. 1992;322(1):35–44.

107. Ristic G, Tsou WL, Todi S V. An optimal ubiquitin-proteasome pathway in the nervous system: The role of deubiquitinating enzymes. Front Mol Neurosci. 2014;7(AUG):1–15.

108. Takiyama Y, Haneda M. Hypoxia in diabetic kidneys. Biomed Res Int. 2014;2014.

109. Miyata T, Suzuki N, Van Ypersele De Strihou C. Diabetic nephropathy: Are there new and potentially promising therapies targeting oxygen biology? Kidney Int. 2013;84(4):693–702.

110. Hirakawa Y, Tanaka T, Nangaku M. Mechanisms of metabolic memory and renal hypoxia as a therapeutic target in diabetic kidney disease. J Diabetes Investig. 2017;8(3):261–71.

111. Hussain RM, Neiweem AE, Kansara V, Harris A, Ciulla TA. Tie-2/Angiopoietin pathway modulation as a therapeutic strategy for retinal disease. Expert Opin Investig Drugs. 2019;28(10):861–9.

112. Fernandes R, Carvalho AL, Kumagai A, Seica R, Hosoya KI, Terasaki T, Murta J, Pereira P, Faro C. Downregulation of retinal GLUT1 in diabetes by ubiquitinylation. Mol Vis. 2004;10(December 2003):618–28.

113. Fernandes R, Hosoya K-I, Pereira P. Reactive oxygen species downregulate glucose transport system in retinal endothelial cells. J Physiol Cell Physiol. 2011;300:927–36.

114. Wieman HL, Wofford JA, Rathmell JC. Cytokine Stimulation Promotes Glucose Uptake via Phosphatidylinositol-3 Kinase/Akt Regulation of Glut1 Activity and

672 Trafficking Heather. Mol Biol Cell. 2007;18(April):1437–1446.
673 115. Hakami NY, Dusting GJ, Peshavariya HM. Trichostatin A, a histone deacetylase
674 inhibitor suppresses NADPH Oxidase 4-Derived Redox Signalling and
675 Angiogenesis. J Cell Mol Med. 2016;20(10):1932–44.
676 116. Huang W, Yang C, Nan Q, Gao C, Feng H, Gou F, Chen G, Zhang Z, Yan P,
677 Peng J, Xu Y. The proteasome inhibitor, MG132, attenuates diabetic nephropathy
678 by inhibiting SnoN degradation in vivo and in vitro. Biomed Res Int.
679 2014;2014:684765.
680 117. Kong L, Wang Y, Luo M, Tan Y, Cui W, Miao L. Prevention of Streptozotocin-
681 Induced Diabetic Nephropathy by MG132: Possible Roles of Nrf2 and IκB. Oxid
682 Med Cell Longev. 2017;2017:3671751.
683 118. Luo ZF, Qi W, Feng B, Mu J, Zeng W, Guo YH, Pang Q, Ye ZL, Liu L, Yuan FH.
684 Prevention of diabetic nephropathy in rats through enhanced renal antioxidative
685 capacity by inhibition of the proteasome. Life Sci. 2011;88(11–12):512–20.
686 119. Gao C, Aqie K, Zhu J, Chen G, Xu L, Jiang L, Xu Y. MG132 ameliorates kidney
687 lesions by inhibiting the degradation of smad7 in streptozotocin-induced diabetic
688 nephropathy. J Diabetes Res. 2014;2014:1–9.
689 120. Gao C, Chen G, Liu L, Li X, He J, Jiang L, Zhu J, Xu Y. Impact of high glucose
690 and proteasome inhibitor MG132 on histone H2A and H2B ubiquitination in rat
691 glomerular mesangial cells. J Diabetes Res. 2013;2013:589474.
692 121. Vadlapatla RK, Vadlapudi AD, Mitra AK. Hypoxia-inducible factor-1 (HIF-1): a
693 potential target for intervention in ocular neovascular diseases. Curr Drug
694 Targets. 2013 Jul;14(8):919–35.

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Figure 1. Involvement of ubiquitine-proteasome system in the pathogenesis of diabetic retinopathy. UPS – ubiquitine–proteasome system; NF-kB – nuclear factor kB; HIF1-α – hypoxia-inducible factor 1α; Nrf2 - nuclear factor erythroid 2–related factor 2; ER - endoplasmic reticulum

Figure 1

Involvement of ubiquitine-proteasome system in the pathogenesis of diabetic retinopathy.

UPS – ubiquitine–proteasome system; NF-kB – nuclear factor kB; HIF1-α – hypoxia-inducible factor 1α; Nrf2 - nuclear factor erythroid 2–related factor 2; ER - endoplasmic reticulum