Role of MMP-9 in Diabetic Retinopathy

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INTRODUCTION

Diabetic retinopathy is a microvascular complication suffered by 35.4% of diabetic patients worldwide and became one of major vision-threatening disease. Generally, the prevalence of retinopathy diabetic in Western countries is higher than in Asia. In Asia, the highest prevalence was found in Singapore (33.9%) and its potential effect in blindness is shown by high prevalence of diabetic cases which tend to increase every year.

Retinopathy diabetic starts when constant hyperglycemia condition occurs in 2 to 6 weeks of diabetes onset. It tends to develop slowly and silently and major cases are detected in severe conditions. Duration of diabetes and glycemic control is the main risk factor of this complication. Diabetic classification, hypertension, obesity, dyslipidemia, and other complications of diabetes are other influencing factor of retinopathy development. Other than oxidative stress, MMPs, protein kinase C and polyol pathways have synergies role in retinopathy pathobiology.

As an endopeptidase, MMP-9 are associated with inflammation, angiogenesis and anti-angiogenesis, mitochondrial dysfunction and also cell apoptosis in retinopathy diabetic. In constant hyperglycemic condition, MMP-9 has caused blood-retinal barrier damage. Decreasing of cell viability and apoptosis of retina Muller cell was found related to the MMP-9 level increased.

DIABETIC RETINOPATHY

Diabetic retinopathy is retinal chronic inflammation and neurodegeneration affected by local and systemic metabolic changes of diabetic condition. The process occurs synergistically in neurovascular in the retina environment by involving large and small blood vessel of neuropiles.

The risk of retinopathy is proportionally increases with longer duration of diabetes. Of DM type 1 patient, the risk is 25% after 5 years and increase up to 80% after 15 years. Retinopathy is suffered by 40% insulin-dependent and 24% non-insulin dependent of type 2 diabetic patients. Each group risk has increased up to 84% and 53% respectively after 19 years of diabetes. Once developed, glycemic control is assumed more importance for retinopathy process than duration of diabetes. Prolonged hyperglycaemia impact on cellular metabolism changes and macromolecules modification that results in structural and functional tissue alteration.

Diabetic retinopathy is classified based on vascular lesions found on ophthalmology examination. Non-proliferative diabetic retinopathy (NPDR) stages are characterized by vascular distortion, retinal hemorrhage, microaneurysm and lipid exudates. Proliferative diabetic retinopathy (PDR) stage is marked by fragile new vessel which may lead to preretinal or vitreous bleeding. Another important category is diabetic macular edema (DME) which shown by abnormal retina thickening and macular cystoid edema resulted from fluid accumulation in retinal nerve tissue.
In normal condition, endothelial vascular cell, pericyte, astrocyte, Muller cell and neuron are working together forming blood-retinal barrier ensuring retinal blood flow. This barrier maintains ionic environment for synaptic transmission and adaptive responses in visual function 10.

Retina microvascular damage mediated by constant hyperglycemic condition begins retinopathy process. Increased polyol and hexosamine pathway flux, oxidative stress, protein kinase C activation, and AGEs are also followed by overproduction of free radical in mitochondria. These conditions aggravate chronic inflammation and oxidative stress in retinal microenvironment 11,15. The vascular response of coupling neurovascular and glia-endothelial disruption in earlier process, decrease dilation response of venules and arteriolas 16. Other than vascular components of endothelial cells and pericytes, retinal neuron cells, macroglia (Muller cells and astrocytes), microglia, immune cells and retinal pigmented epithelium (RPE) are also involved in these inflammation 16. Impact of oxidative stress and inflammatory cytokines also active microglia in retinal perivascular which result in neurotoxicity and tissue impairment 18.

Decreased retinal perfusion and blood-retinal barrier damage in diabetic retinopathy enables cytokines and chemokines entering retina tissue and aggravate neurodegeneration of glutamate production 16,19. Ocludin degradation by MMP-9 in retina tight junction attenuate vascular permeability 20. Other neurotoxic production such as caspase-3, glutamate and MMPs also lead to pericyte and endothelial dysfunction 21.

MATRIX METALLOPROTEINASES (MMPs)

MMPs are endopeptidase that may work on various substrates such as soluble, integral or extracellular protein and proteoglycans. MMPs also may work on cytokines, chemokines, growth factors, growth factor receptors, and cell adhesion molecules. These proteases not only involve in physiologic process, but also in pathologic conditions as cancer and inflammation disease 22-24. MMPs classification based on substrate specificity and primary structural domain result in collagenases, gelsatinases, matrilysins, membranous type and other type MMP 25.

MMPs are able to degrade extracellular matrix and non-matrix substrates. Enzyme regulation is initiated in transcription and translation level, zymogen activation, inhibition by extracellular or endogenous inhibitor, extracellular or subcellular localization and endocytosis internalization 26,27. Generally, MMPs are secreted in zymogen form and then activated in extracellular space by cytokine switch cleavage. MMPs activation creates proteinase network system in tissue. Once activated, MMPs are regulated by common protease inhibitor (a2 macroglobulin and a1-antiprotease) and also specific TIMP 26.

MMP-9

MMP-9 or gelatinase B are produced by various cell including epithelium cell, fibroblast, keratinocytes, dendritic cells, macrophages, granulocytes and T cell 25. MMP-9 may be produced continuously or depend on inflammation signal induction of other cells. Pro-MMP secreted as inactive form and required activation with proteolysis by other MMPs or serine proteases, or even thiol oxidation of reactive oxygen species 24.

MMP-9 may activate and change cytokines such as IL-8 and TGF-β into active form, membrane-bound protein, transmembrane and extracellular molecules 25. By degrading MBP (myelin based protein), MMP-9 increase neuroinflammation and produce encephalitogenic peptides. Shortening of ICAM-1 lead to inactivation of its adhesion function and protection from cytotoxic T cell and NK cell. By occludin and cadherin degradation in tight junction, MMP-9 is able to regulate epithelium barrier permeability 8,30. In intracellular, MMP-9 may work on vesicle, mitochondria, cytoplasm and nucleus protein 29.

Angiogenesis role of MMP-9 is by stimulating VEGF secretion from glia cell and astrocyte 31. MMP-9 also mediates new vessel formation by proteolytic degradation of basal membrane protein, migration and proliferation of endothelial cell. Proinflammatory cytokines also lead to neovascularization by directly activate endothelial cells and indirectly by inducing proangiogenic mediator from endothelial cell 17.

MMP-9 IN DIABETIC RETINOPATHY

There is a positive correlation of MMP-9 with diabetic retinopathy severity 32. Experimental studies of diabetic mice shown decreased diabetic retinopathy risk in MMP-9 gene suppression 6. Constant hyperglycaemia condition result on increased MMP-9 production from endothelial cell, vitreous humor and retinal pigmented epithelium 5,7,8,33. This is affected by AGES formation and oxidative stress in diabetic circulation 5,34.

MMP-9 involve in various mechanisms of diabetic retinopathy from blood-retinal barrier disruption, inflammation, neovascularization, mitochondrial damage and cell apoptosis 35. By occludin and cadherin degradation in retinal endothelial cell tight junction, MMP-9 impair barrier of blood-retina. Ocludin is an important protein in cortical actin preparation in maintaining barrier stability 30. Endothelial leakage also allows leukocyte migration and infiltration mediated by VCAM-1 and ICAM-1 activity and chemotaxis effect MMP-9. These will bring leukostasis and blood vessel occlusion in retina 36,37. Permeable vascular changes will facilitate inflammatory cytokines and chemokines entry into retinal tissue complex 32,35,38.

Intracellularly, MMP-9 affected by H-Ras may induce Raf-1/MEK activation result in dysfuction of mitochondrial permeability. Cytochrome C leakage to cytosol can cause apoptosis of retina capillary cells 39. MMP-9 is known to be able to move into mitochondria mediated by Hsp70/Hsp60 and damage it from within 40. Expression of MMP-9 has an effect on apoptotic protein expressions such as Bax2, Bcl2, PARP-1 and caspase-3 in retinal Muller cell. This protein has been known in decreasing viability and apoptosis induction 7.

The proangiogenic activity of MMP-9 is proved by its activity with VEGF and TGF-β. There is a reciprocal relationship of MMP-9 and VEGF in mediating angiogenesis of retinopathy. Upregulation of VEGF mediated by MMP-9 leads to neovascularization while decreased level of MMP-9 lowering VEGF production. In the vitrous humor of PDR patients, level of VEGF and MMP-9 was found significantly higher 31,41. In retinal vein occlusion cases, TGF-β and MMP-9 concentration was found higher in vitrous humor than control group. The activity of TGF-β and MMP-9 in cytoskeleton arrangement and basal membrane proteolysis resulting in tissue remodeling and angiogenesis 42.

CONCLUSION

Diabetic retinopathy occurs in complex mechanism involving retinal neurovascular components. Hyperglycaemia constant trigger oxidative stress dan increased MMP-9 activity. MMP-9 role in retinopathy by occludin degradation and...
endothelial cell apoptosis that leads to blood-retinal barrier disruption, retina Muller cell damages and angiogenesis.

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