Progress in Retinal and Eye Research 48 (2015) 40–61

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/prer

# Oxidative stress and epigenetic modifications in the pathogenesis of diabetic retinopathy

Renu A. Kowluru [a, b, *, 1], Anjan Kowluru [c, d, 1], Manish Mishra [a, 1], Binit Kumar [a, 1]

[a] Department of Ophthalmology, Wayne State University, Detroit, MI, USA
[b] Department of Anatomy/Cell Biology, Wayne State University, Detroit, MI, USA
[c] Department of Pharmaceutical Sciences, Wayne State University, Detroit, MI, USA
[d] John D Dingell VA Medical Center, Detroit, MI, USA

ARTICLE INFO

*Article history:*
Received 24 February 2015
Received in revised form
29 April 2015
Accepted 1 May 2015
Available online 12 May 2015

*Keywords:*
Diabetic retinopathy
Epigenetic modifications
Mitochondria
Oxidative stress
Reactive oxygen species
Transcriptional regulation

ABSTRACT

Diabetic retinopathy remains the major cause of blindness among working age adults. Although a number of metabolic abnormalities have been associated with its development, due to complex nature of this multi-factorial disease, a link between any specific abnormality and diabetic retinopathy remains largely speculative. Diabetes increases oxidative stress in the retina and its capillary cells, and overwhelming evidence suggests a bidirectional relationship between oxidative stress and other major metabolic abnormalities implicated in the development of diabetic retinopathy. Due to increased production of cytosolic reactive oxygen species, mitochondrial membranes are damaged and their membrane potentials are impaired, and complex III of the electron transport system is compromised. Suboptimal enzymatic and nonenzymatic antioxidant defense system further aids in the accumulation of free radicals. As the duration of the disease progresses, mitochondrial DNA (mtDNA) is damaged and the DNA repair system is compromised, and due to impaired transcription of mtDNA-encoded proteins, the integrity of the electron transport system is encumbered. Due to decreased mtDNA biogenesis and impaired transcription, superoxide accumulation is further increased, and the vicious cycle of free radicals continues to self-propagate. Diabetic milieu also alters enzymes responsible for DNA and histone modifications, and various genes important for mitochondrial homeostasis, including mitochondrial biosynthesis, damage and antioxidant defense, undergo epigenetic modifications. Although antioxidant administration in animal models has yielded encouraging results in preventing diabetic retinopathy, controlled longitudinal human studies remain to be conducted. Furthermore, the role of epigenetic in mitochondrial homeostasis suggests that regulation of such modifications also has potential to inhibit/retard the development of diabetic retinopathy.



**Contents**

1. Introduction ..... 41
2. Development of diabetic retinopathy ..... 41
2.1. Risk factors ..... 42
2.1.1. Hyperglycemia ..... 42
2.1.2. Systemic factors ..... 42

* Corresponding author. Departments of Ophthalmology/Anatomy Cell Biology, Kresge Eye Institute, Wayne State University, Detroit, MI 48201, USA. Tel.: +1 313 993 6714.
*E-mail address:* rkowluru@med.wayne.edu (R.A. Kowluru).

[1] Percentage of work contributed by each author in the production of the manuscript is as follows: Renu A. Kowluru: 50%, Anjan Kowluru: 25%, Manish Mishra: 15%, Binit Kumar: 10%.

http://dx.doi.org/10.1016/j.preteyeres.2015.05.001
1350-9462/

2.1.3. Genetic factors ..... 42
2.1.4. Environmental factors ..... 43
2.2. Biochemical abnormalities induced by hyperglycemia ..... 43
3. Oxidative stress ..... 44
3.1. Major sources of free radicals ..... 44
3.1.1. Cytosolic ROS ..... 44
3.1.2. Mitochondrial ROS ..... 45
4. Oxidative stress and diabetic retinopathy ..... 45
4.1. Oxidative stress and metabolic abnormalities associated with diabetic retinopathy ..... 45
4.2. Role of mitochondria ..... 45
4.3. Antioxidant defense system ..... 46
5. Mitochondria ..... 46
5.1. Mitochondrial DNA damage ..... 47
5.2. Diabetes and mitochondrial damage ..... 47
5.2.1. NADPH oxidase ..... 48
5.2.2. Matrix metalloproteinases ..... 48
6. Epigenetics and gene regulation ..... 49
6.1. DNA methylation ..... 49
6.2. Histone modifications ..... 49
6.3. MicroRNAs ..... 50
7. Epigenetic modifications in diabetes ..... 50
7.1. Epigenetic modifications in diabetic retinopathy ..... 51
7.1.1. DNA methylation ..... 51
7.1.2. Histone modifications ..... 51
7.1.3. MicroRNAs ..... 51
7.2. Oxidative stress, epigenetics and mitochondrial homeostasis ..... 51
8. Epigenetics and mitochondrial homeostasis ..... 52
8.1. Methylation of mtDNA ..... 52
8.2. Mitochondrial miRNAs ..... 52
9. Therapeutic implications ..... 54
9.1. Antioxidant defense system ..... 54
9.1.1. Animal studies ..... 54
9.1.2. Human studies ..... 54
9.2. Regulation of epigenetic modifications ..... 54
10. Perspective and future directions ..... 56
Contributions ..... 57
Acknowledgements ..... 57
References ..... 57

## 1. Introduction

Diabetes is a major public health problem, and is now being considered as an epidemic of the 21st century. According to the numbers released by the International Diabetes Federation, in 2014 about 8.3% world's population (387 million people) have diabetes, and this number is expected to rise to over 590 million in less than 25 years. This is a life-long disease which affects function of multiple organs, leading to reduced quality of life, and, in some cases, to death (Whiting et al., 2011). Though high circulating glucose is the main hallmark of the disease, hyperglycemia could be either due to destruction of insulin producing beta cells, resulting in insulin deficiency (type I diabetes), or due to insulin resistance, which is generally followed by decreased insulin secretion and glucose intolerance (type II diabetes) (Unger, 2008). The disease carries a heavy social and economic burden; as per the International Diabetes Federation, in 2014, ~4 million deaths (9% of the global total) were associated with diabetes, and overall, direct health care costs of diabetes ranged from 2.5% to 15% annual health care budgets, depending on local diabetes prevalence and the sophistication of the treatment available. Despite significant improvement in education, advancement in technology and strategies, the prevalence of diabetes continues to increase and the need to protect the patients from its complications remains very high.

Chronic elevation in circulating blood glucose damages blood vessels, which results in many micro- and macro-vascular complications. Diabetic retinopathy is one of the major microvascular complications affecting the vision, and is the leading cause of blindness in working age adults. With recent progress in the management of diabetes, fortunately the macro-vascular mortality is declining, but, diabetic patients are living longer and the incidence of retinopathy and loss of vision associated with this is increasing. Worldwide, approximately 93 million people have diabetic retinopathy, which includes 17 million with proliferative diabetic retinopathy and 28 million with sight-threatening diabetic retinopathy. As the incidence of diabetes is increasing at an alarming rate, in 2030, ~155 million of diabetic patients are projected to have retinopathy, with more than 51 million among them facing vision-threatening retinopathy (Whiting et al., 2011), and early detection and treatment remain the gold standards for its management.

## 2. Development of diabetic retinopathy

Diabetic retinopathy is a slow progressing chronic disease, at first patients do not show any symptoms, but, when their vision begins to impair, the chances are that retinopathy is already in its advanced stage, and if not controlled, could result in vision loss (Frank, 2004).