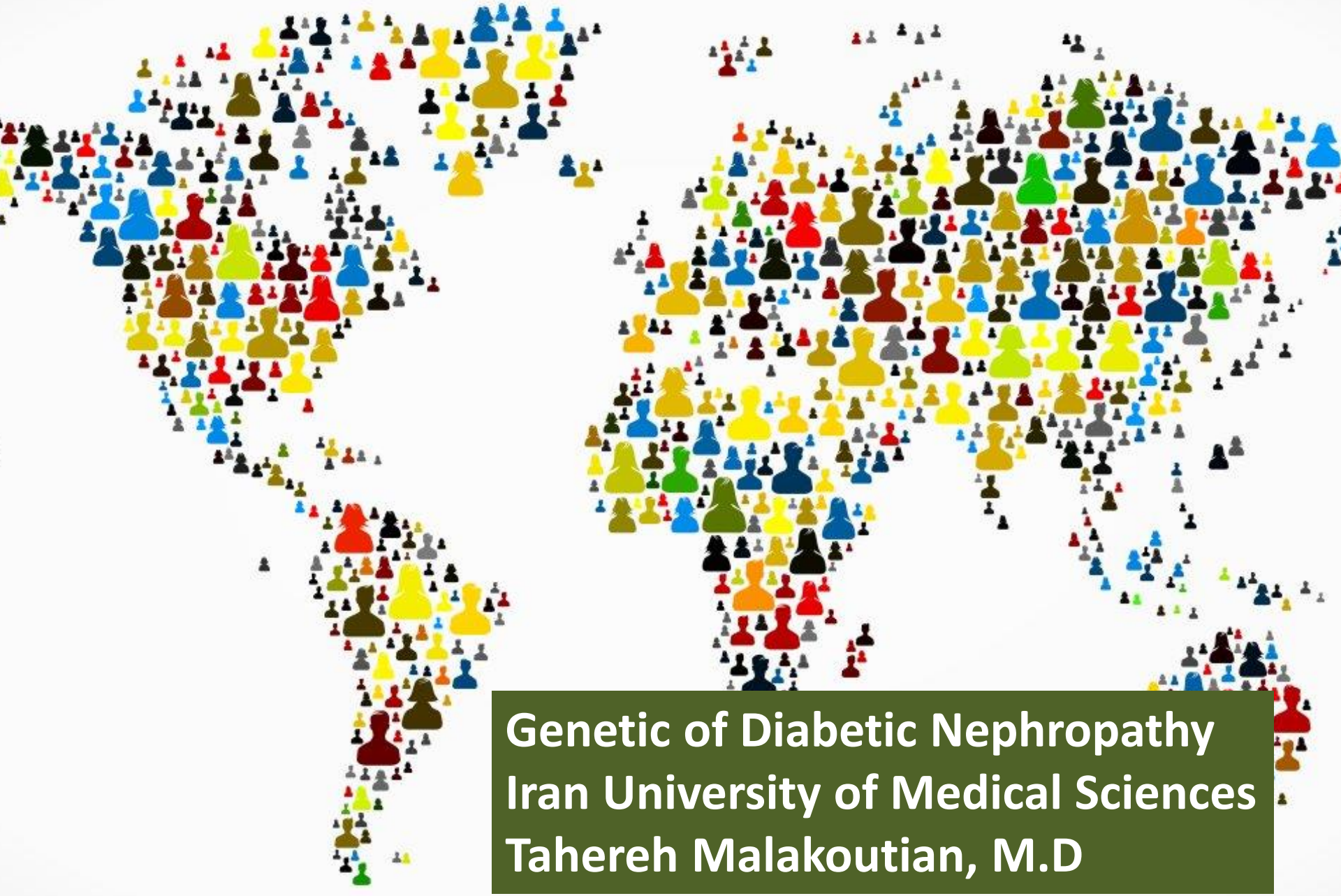


Genetic of Diabetic Nephropathy

Iran University of Medical Sciences
Tahereh Malakoutian, M.D

Multifactorial disease with complex inheritance mechanisms.

Leading cause of ESRD in the most developed countries.

It is important to note that only 30% to 40% of patients with diabetes develop diabetic nephropathy.

Update on Diabetic Nephropathy: Core Curriculum 2018
Kausik Umanath and Julia B. Lewis

Prediction of diabetic nephropathy

It is impossible.

Duration of diabetes, tightness of glycemic control, and blood pressure are insufficient on their own to predict which patients will develop the complication.

Therefore, a patient with poor blood pressure and glycemic control might not develop diabetic renal disease even many years.

The role of genetic susceptibility in diabetic nephropathy: evidence from family studies . Stephen Fava1,2002

Familial clustering

Patients with DM with a first-degree relative with T1/T2DM and diabetic nephropathy have substantially more risk for developing diabetic nephropathy than those without an affected relative.

Variation among racial and ethnic groups

Native Americans / European Americans

Update on Diabetic Nephropathy: Core Curriculum 2018
Kausik Umanath and Julia B. Lewis

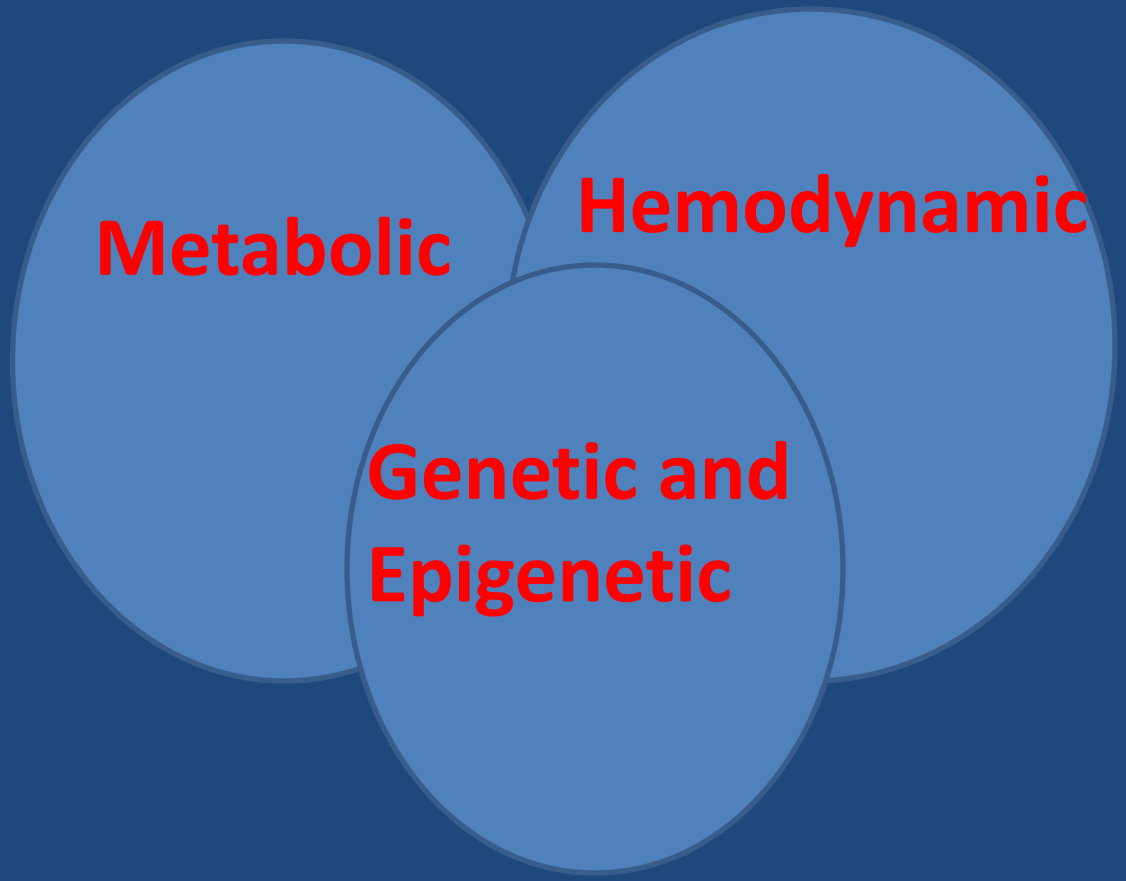
Familial aggregation of DN is independent from family size, the number of relatives affected with diabetes and hypertension,socioeconomic status, and inadequate access to health care.

The prevalence of diabetic nephropathy varies worldwide .

Singapore / Denmark

Genetic Factors in Diabetic Nephropathy. Barry I. 2007

Factors Contributing to Development of DN



Clinical manifestations

Micro-albuminuria

Albuminuria

↑ BP

- Glomerulosclerosis
- Tubulointerstitial fibrosis
- Progressive decline in GFR

↑ Risk of cardiovascular complications

Pathophysiological mechanisms

↑ Permeability

↓ Vasorelaxation

↑ ECM deposition
↓ ECM degradation

Monocyte infiltration of vascular wall

↓ eNOS/NO function

The contribution of a single gene to the development of diabetic nephropathy might be small, but diabetic nephropathy would develop in those with combination of a number of ‘bad genes’ and of environmental factors (dosage effect). Environmental factors include glycemic control, blood pressure control, and possibly intra-uterine malnutrition.

Polygenic (During the past Decade : identification of at least 75 independent genetic loci

If the contribution of a single gene were small, it would need large studies to be detected and replicated.

Update on Diabetic Nephropathy: Core Curriculum 2018. Kausik Umanath

Genetic Studies

1- Linkage studies

2- Association studies

3- GWAS for millions of SNPs (NGS)

Table 1. Genetic linkage analysis for diabetic nephropathy.

Chromosome region	Population studied	Reference
2q14.1	Caucasian and African-Americans	26
3q	Pima Indians	21,27
7p	African-American-Americans	24,27
7q	Caucasian and African-Americans	25
7q21.1, 7q21.3	Caucasian and African-Americans	26
10p15.3	Caucasian and African-Americans	26
14q23.1	Caucasian and African-Americans	26
15q26.3	Caucasian and African-Americans	26
16q13	Japanese	23
18q, 18q22.3-23	Turkish	22,24
20p	Caucasian and African-Americans	27
22q	Caucasian and African-Americans	25

Genetic association analysis for diabetic nephropathy

Polymorphism	Candidate gene	Reference
rs1805101	*ENPP1/PC-1*	17,39
rs35448603	*CATALASE*	41
rs4673	*CYBA*	43
rs1800625	*RAGE*	44
rs1800624	*RAGE*	44
rs1799883	*FABP2*	45
rs1801282	*PPARγ2*	46
rs39059	*CPVL/CHN2*	21
rs39075	*CPVL/CHN2*	21
rs1888747	*FRMD3*	21
rs10868025	*FRMD3*	21
rs739401	*CARS*	21
rs451041	*CARS*	21
rs1411766	*IRS2/MYO16*	21
rs39075	*CPVL/CHN2*	21
rs1888746	*FRMD3*	21
rs13289150	*FRMD3*	21
rs451041	*CARS*	21

Table 1. Summary of results from genome-wide linkage scans for diabetic nephropathy[a]

Chromosome	Region[b]	Maximum LOD	Population	Study	Phenotype	Characteristics	Reference
3q	13	4.55	Black	Sibling pairs	Type 2 DN	Age at ESRD onset	(23)
	21.3	2.67	Finnish	Discordant sibling pairs	Type 1 DN		(28)
	25.1	3.1	White	Discordant sibling pairs	Type 1 DN		(27)
7q	12.3	1.84	West African	Sibling pairs	Type 2 DN	CC	(24)
	21.1	(6.0×10^{-4})	White	90% sibling pairs	Predominantly type 2 DN	ACR	(26)
	21.3	(6.0×10^{-5})	Black	90% sibling pairs	Predominantly type 2 DN	Nephropathy	(26)
	33	2.04 to 2.73	Pima Indian	Sibling pairs	Type 2 DN	Nephropathy and retinopathy	(25)
	36.2	3.1	94% white	Families	Type 2 DN	ACR	(31)
	(99 cM)	(1.1×10^{-4})	White	90% sibling pairs	Predominantly type 2 DN	Nephropathy	(38)
7p	21.3	4	94% white	Sibling pairs	Type 2 DN	CC-GFR	(14)
	32.1	3.59	Black	Sibling pairs	Type 2 DN	Age at diabetes onset	(23)
	(12 cM)	(1.6×10^{-4})	American Indian	90% sibling pairs	Predominantly type 2 DN	ACR	(38)
	(78 cM)	(1.0×10^{-3})	Mexican American	90% sibling pairs	Predominantly type 2 DN	GFR	(39)
10q	23.31	3.1	94% white	Sibling pairs	Type 2 DN	Diabetic/nondiabetic; CC-GFR	(14)
	26	2.47	Black	Sibling pairs	Type 2 DN	Age at ESRD onset	(32)
18q	22.1	3.72	Black	Sibling pairs	Type 2 DN	Age at diabetes onset	(23)
	22.1	(3.15×10^{-2})	White	Discordant sibling pairs	Predominantly type 2 DN	Nephropathy	(26)
	22.3–23	6.1	Turkish	Families	Type 2 DN	Nephropathy	(29)

[a]*P* values are used where logarithm of odds (LOD) scores were not reported. ACR, albumin-to-creatinine ratio; CC, creatinine clearance; DN, diabetic

Major critics of genetic research on DN

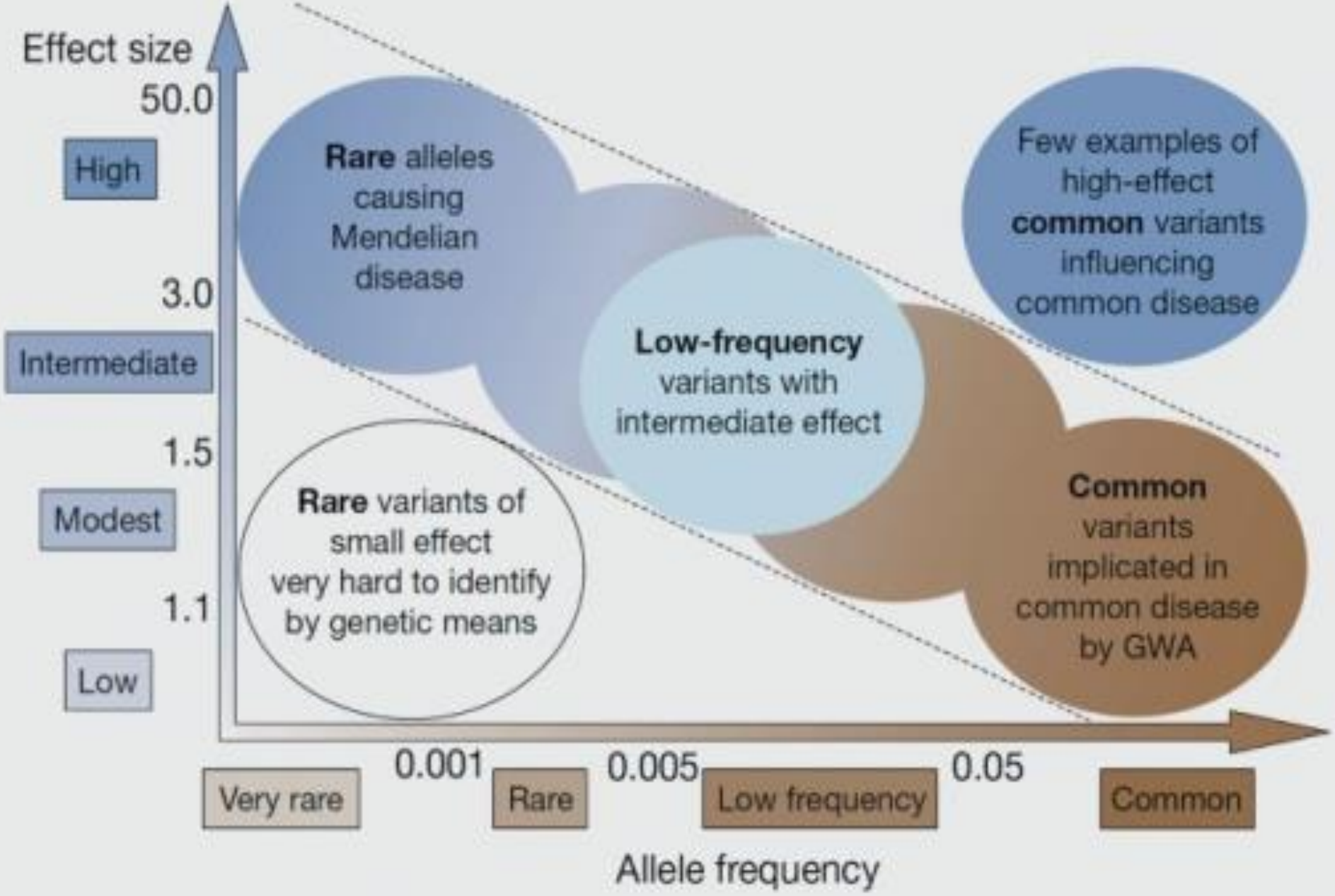
common variants with a relatively low effect size (odds ratio between 1.10 and 1.40) explain only 10–15% of the heritability.

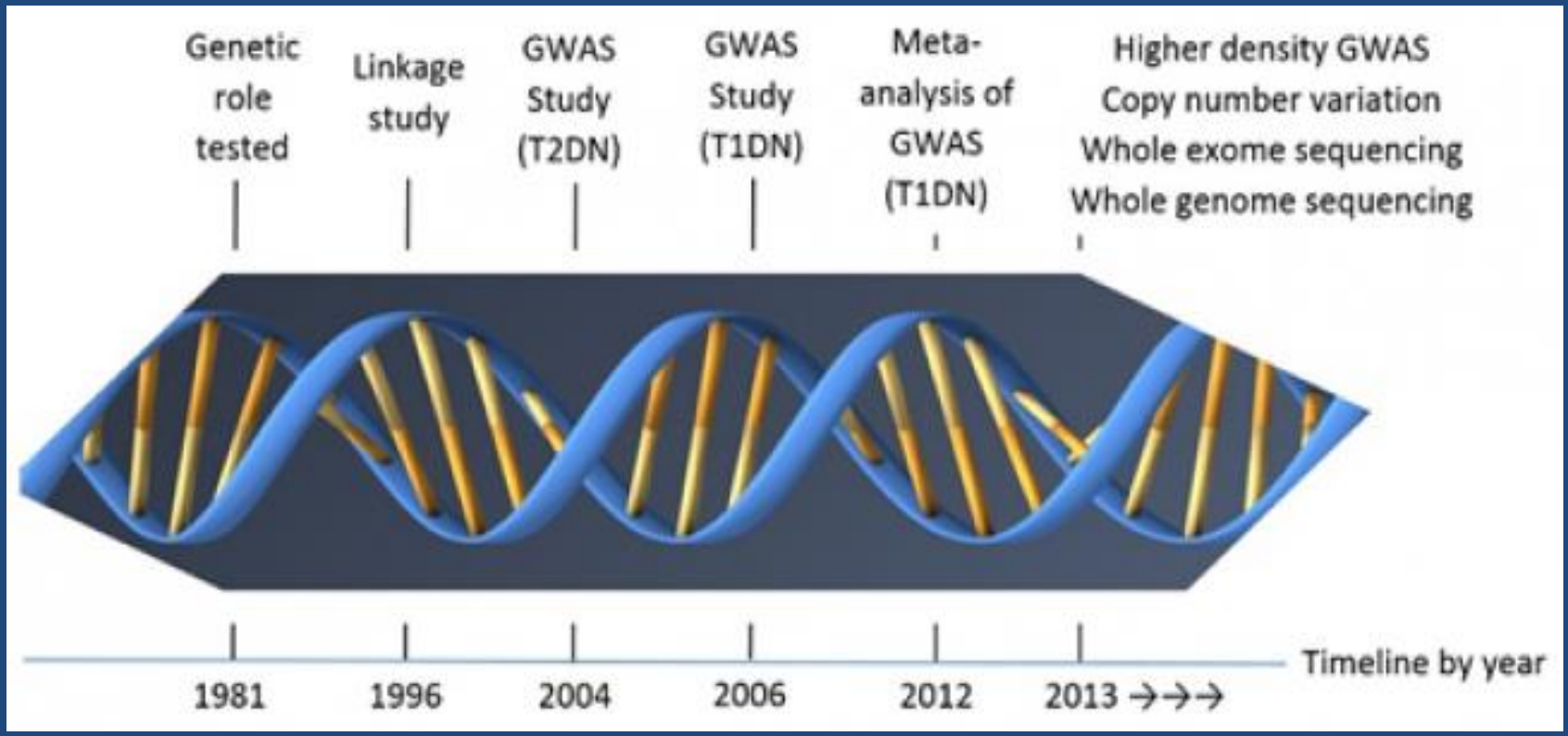
Most of the variants are located at intergenic or intronic region, where it is difficult to explain their functional consequences.

Recent progress in genetic and epigenetic research on type 2 diabetes.
Heon Kwak1 and Kyong Soo Park1,2,3. 2016

Introns and exons are parts of genes. Exons code for proteins.

Introns are parts of genes that do not directly code for proteins. Introns can range in size from 10’s of bps to 1000’s of bps.


Effect size
50.0
High
3.0
Intermediate
1.5
Modest
1.1
Low
Rare alleles causing Mendelian disease
Few examples of high-effect common variants influencing common disease
Low-frequency variants with intermediate effect
Rare variants of small effect very hard to identify by genetic means
Common variants implicated in common disease by GWA
0.001
0.005
0.05
Very rare
Rare
Low frequency
Common
Allele frequency


Genetic role tested
Linkage study
GWAS Study (T2DN)
GWAS Study (T1DN)
Meta-analysis of GWAS (T1DN)
Higher density GWAS
Copy number variation
Whole exome sequencing
Whole genome sequencing
Timeline by year
1981
1996
2004
2006
2012
2013 →→→

International HapMap Project

Intrenational HapMap Projects

The DNA sequence of any two people is more than 99 percent identical.

SNPs (10 million)

Sets of nearby SNPs on the same chromosome are inherited in blocks. This pattern of SNPs on a block is a haplotype.

A few SNPs are enough to uniquely identify the haplotypes in a block.

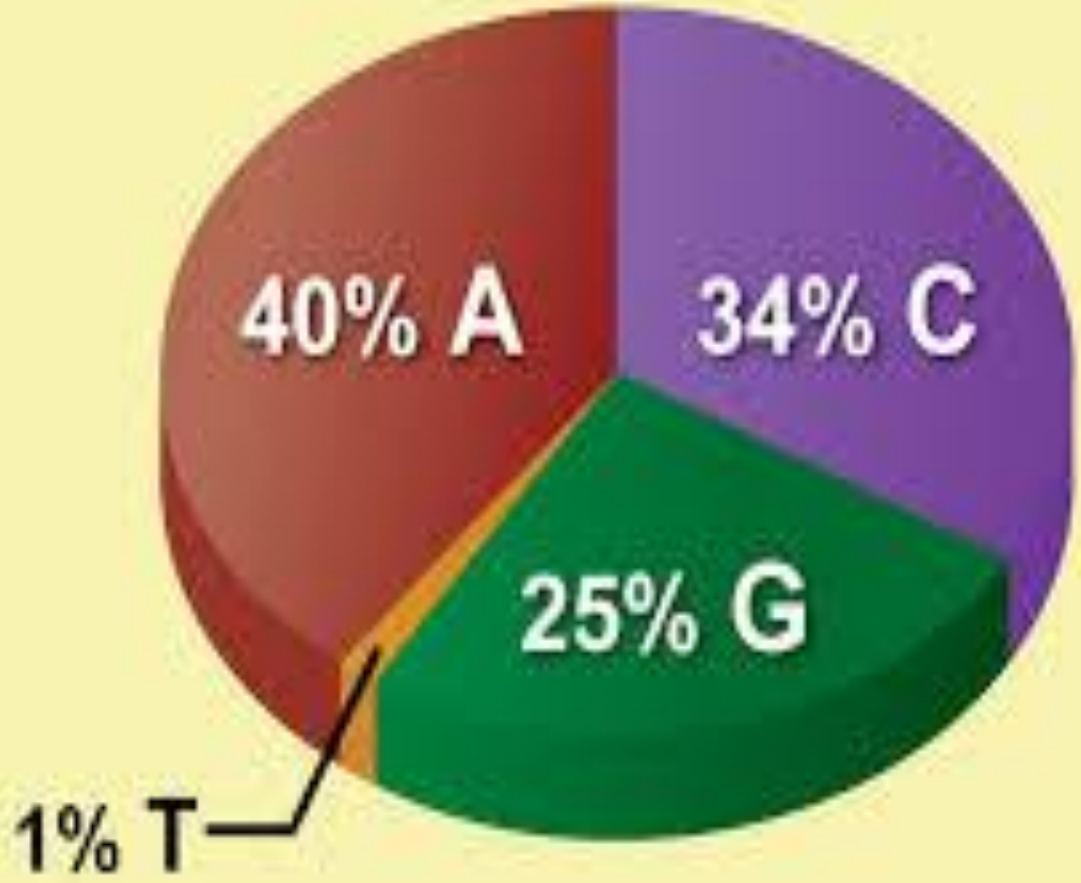
Variation : any change in a DNA sequence away from normal.

Mutation: Changes normal allele (that is prevalent in the population) to a rare and abnormal variant.

Polymorphism : a DNA sequence variation that is common in the population. In this case no single allele is regarded as the standard sequence. (two or more equally acceptable alternatives).

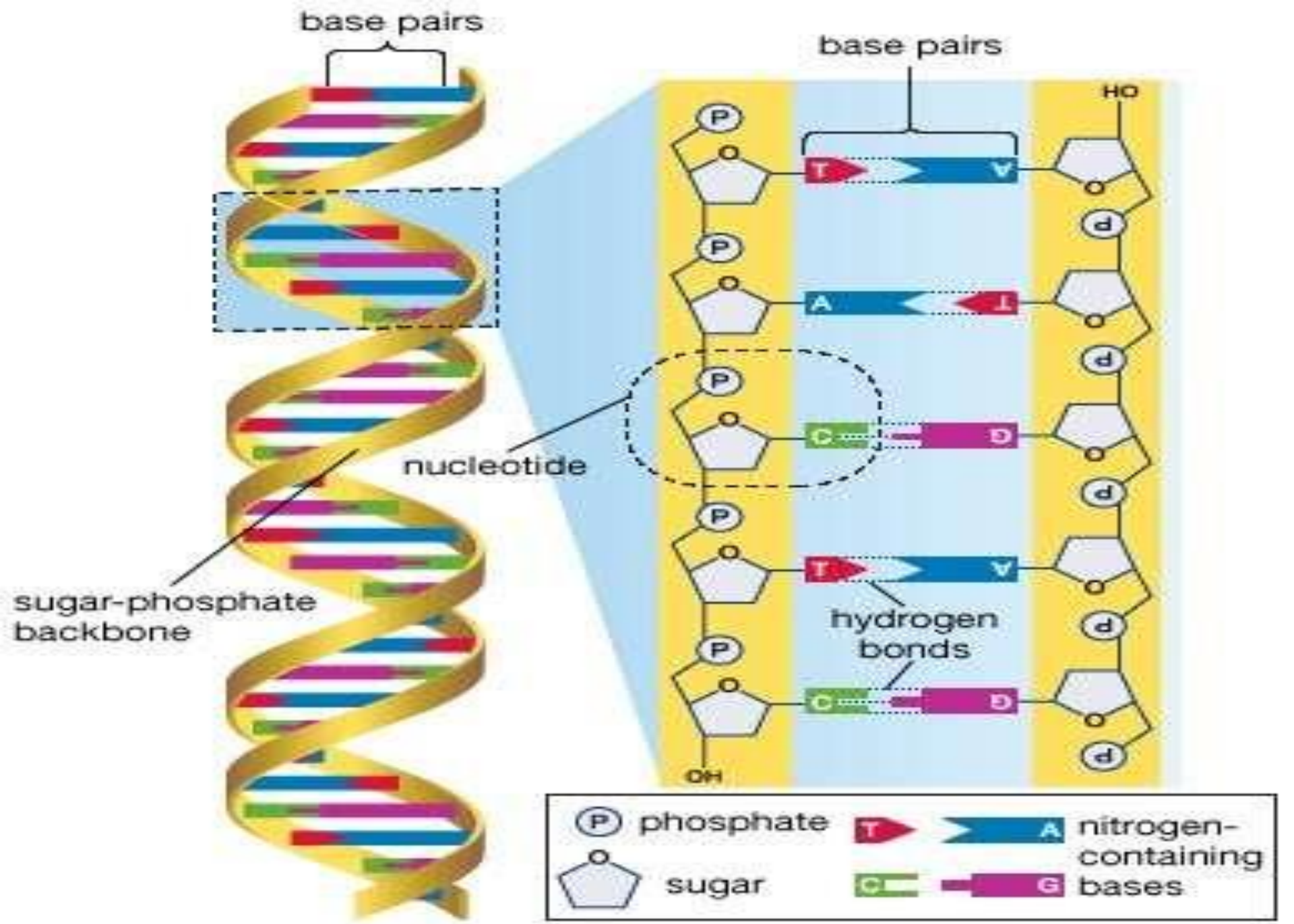
Cut-of point between a mutation and a polymorphism is 1 per cent.

SNP Population Distribution

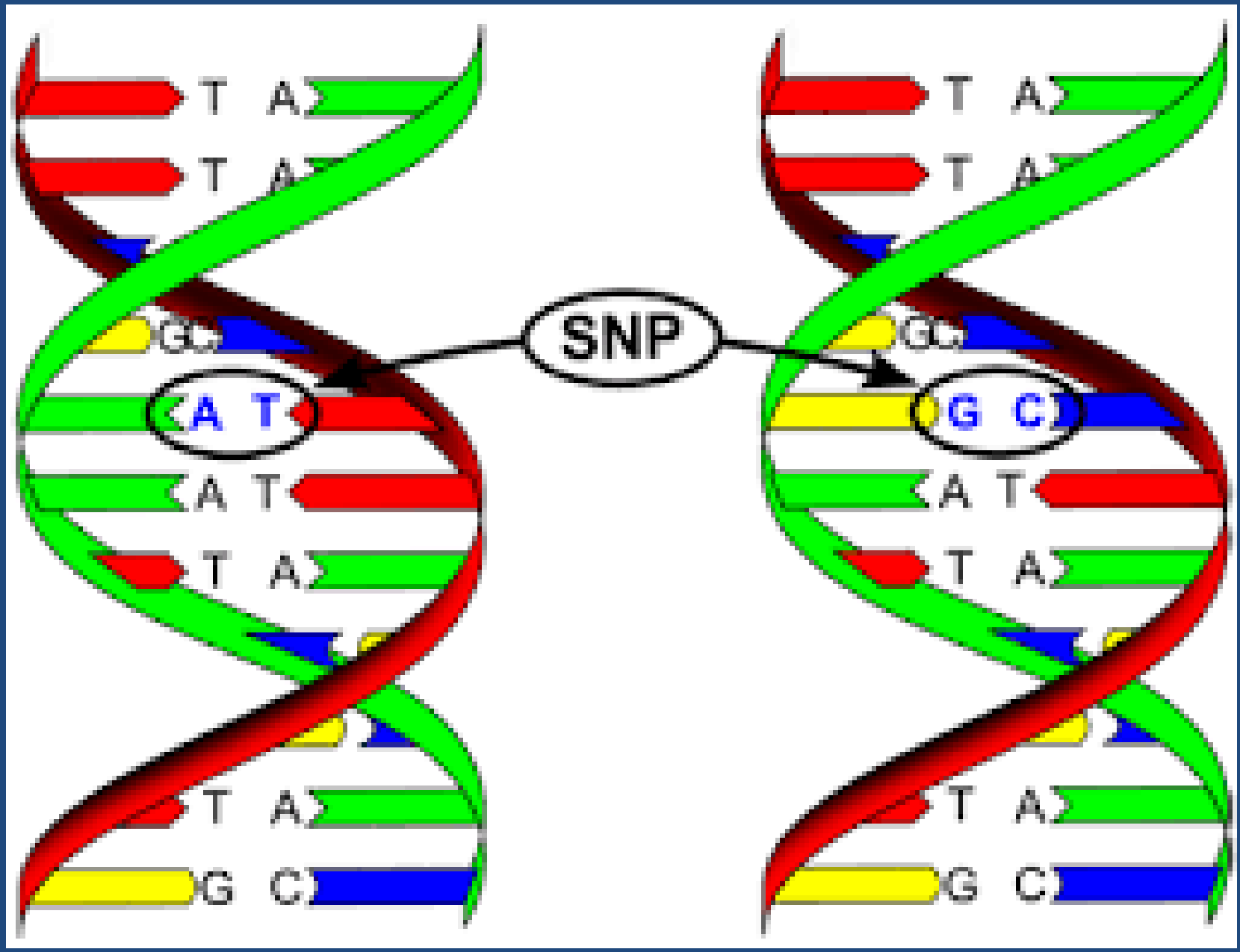


Why is it important to study genetic variation?

- Most common diseases, such as diabetes, are affected by many genes and environmental factors.
- Although any two unrelated people share about 99.9 percent of their DNA sequences, the remaining 0.1 percent is important because it contains the genetic variants that influence how people differ in their risk of disease or response to drugs.



SNPs


T A
T A
G C
A T
A T
T A
T A
G C
SNP
T A
T A
G C
G C
A T
T A
T A
G C

GLUT1, TGF β, NFκB, eNO synthase

Isolating a definitive causal pathway has proved to be elusive

There is no simple Mendelian inheritance.

The interplay of several genes is likely involved

May differ between populations.

Review Article

The Role of Transforming Growth Factor-Beta in Diabetic Nephropathy

Karina Braga Gomes,[1,2,3] Kathryna Fontana Rodrigues,[1,2] and Ana Paula Fernandes[1,2]

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[2] *Faculdade de Farmácia, Universidade Federal de Minas Gerais, 31270-901 Belo Horizonte, MG, Brazil*
[3] *Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Avenida Antônio Carlos 6627, Pampulha, 31270-901 Belo Horizonte, MG, Brazil*

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Academic Editor: George N. Goulielmos

Several studies have demonstrated that chronic and low-grade inflammation is closely linked to type 2 diabetes mellitus. The associated mechanisms are related to synthesis and release of proinflammatory and anti-inflammatory cytokines, mainly by the adipose tissue. Moreover, there are evidences that cytokines and adhesion molecules are important for development of diabetic nephropathy. Among the cytokines associated with inflammatory responses in type 2 diabetes mellitus, the transforming growth factor-β (TGF-β) has been recognized as a central player in the diabetic nephropathy being involved in the development of glomerulosclerosis and interstitial fibrosis, as observed in the course of end-stage renal disease. Although TGF-β1 is classically an anti-inflammatory immune mediator it has been shown that in the presence of IL-6, which increases before the onset of T2D, TGF-β1 favors the differentiation of T helper 17 (Th17) cells that are activated in many pro-inflammatory conditions. Since TGF-β1 mRNA and consequently serum TGF-β1 levels are under genetic control, this review aims to discuss the relationship of TGF-β1 levels and polymorphisms in the development of nephropathy in type 2 diabetes mellitus.

TGF-β

They regulate cellular functions such as proliferation, apoptosis, differentiation, and migration .

Activation of the TGF-β receptor induces

phosphorylation of serine/threonine residues and triggers phosphorylation of intracellular effectors (Smads). Once activated, Smad proteins translocate to the nucleus and induce transcription of their target genes, regulating various processes and cellular functions.

TGF-β: An Important Mediator of Allergic Disease and a Molecule with Dual Activity in Cancer Development .Belen Tirado-Rodriguez,1 Enrique Ortega,2. 2014

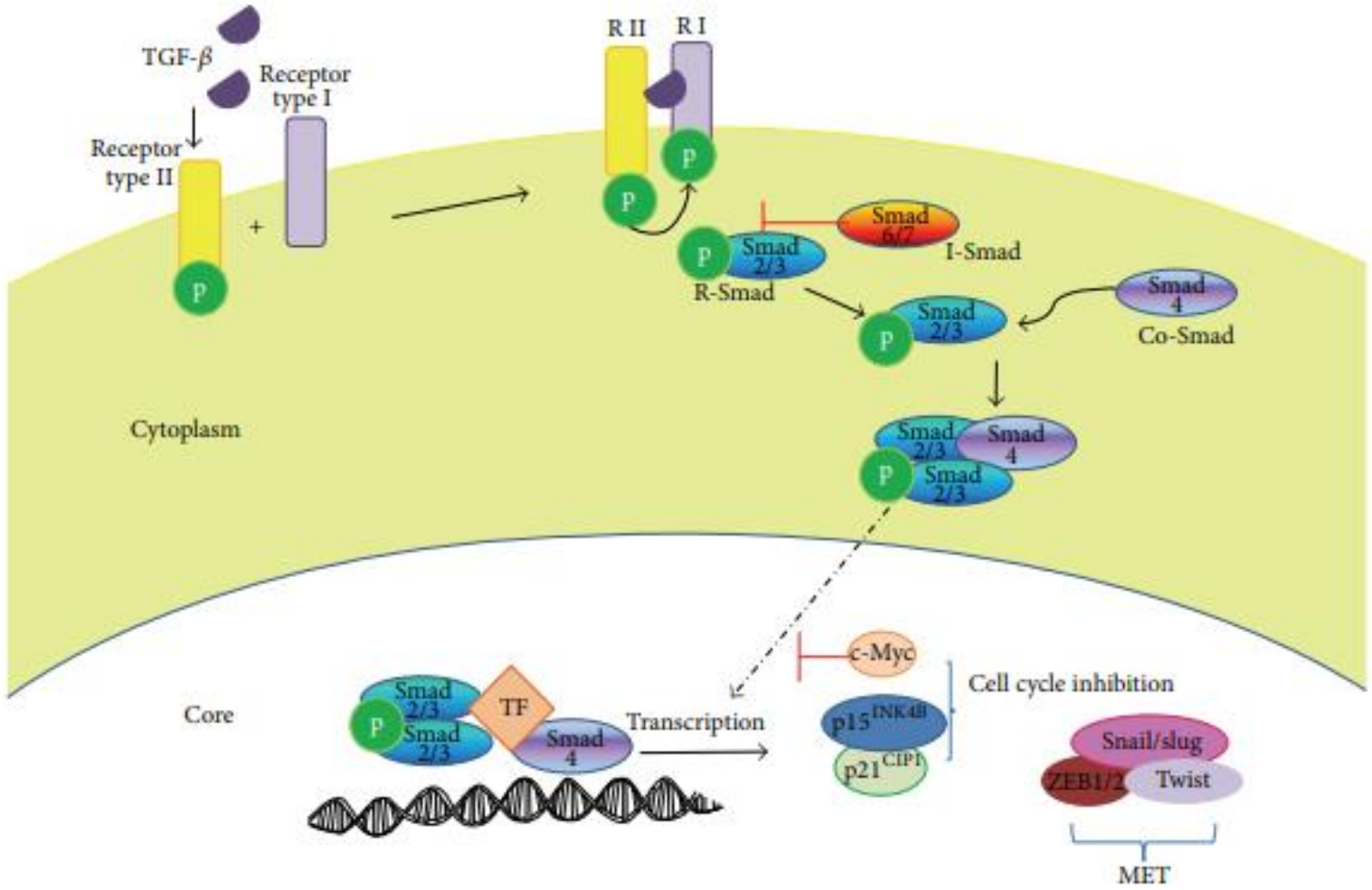

FIGURE 2: The TGF-β canonical signaling pathway. After the ligand binds to TβRII, the TGF-β receptors are dimerized and recruit Smad proteins. The Smad2 and/or Smad3 complex is phosphorylated by TβRI and forms a complex with Smad4. This complex subsequently translocates to the nucleus where it binds to specific transcription factors (TF) and induces the transcription of TGF-β dependent genes.

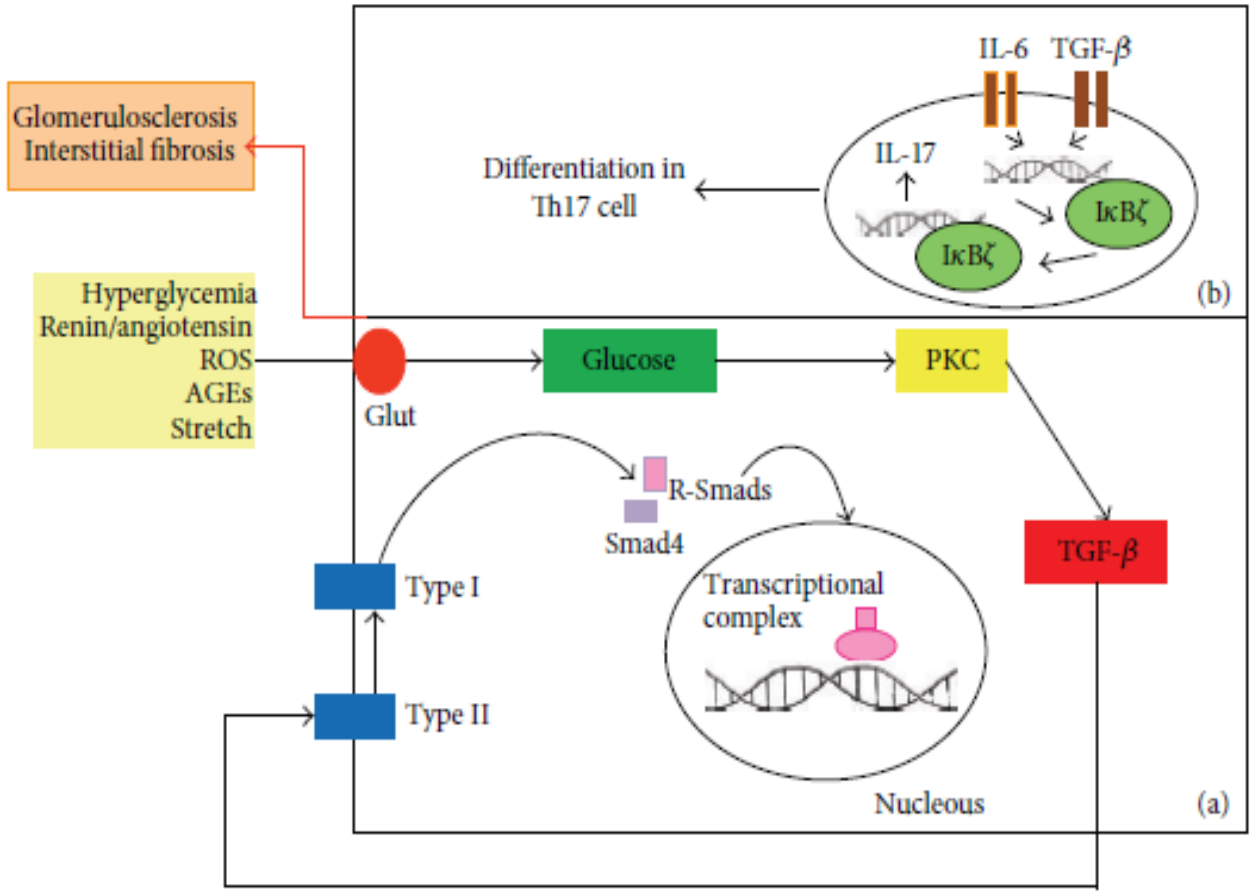

FIGURE 1: Activation of TGF-β synthesis and its role in proinflammatory mechanisms in T2D nephropathy. (a) Increased extracellular glucose levels, mesangial cell stretch, activation of renin-angiotensin system, reactive oxidant species (ROS), and advanced glycation end products (AGEs) activate TGF-β synthesis via protein kinase C. TGF-β stimulates its own pathway through autocrine or paracrine action. TGF-β assembles a receptor complex that activates Smads that regulate nuclear transcription. (b) TGF-β1 and IL-6 promote the differentiation of naive T lymphocytes into proinflammatory T helper that produces IL17 through the transcription factor IκBζ. The outcomes of these processes are glomerulosclerosis and interstitial fibrosis.

More than 10 polymorphic loci

The **T869C** polymorphism in the human TGF-1 gene, leading to the L10P variant of the coding protein, is associated with an increased risk of diabetic nephropathy.(CC/CT genotypes)*

T29C SNP (TT genotype)**

Phenotypic effects of these polymorphisms in TGF-β levels or functionality are largely unknown.

The small sample size

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*Transforming growth factor-1 and diabetic nephropathy
Albert S. Chang, Catherine K. 2016
**The Role of Transforming Growth Factor-Beta I Diabetic Nephropathy
Karina Braga Gomes. 2014

-Continued

The expression of nephrin is decreased in diabetes.

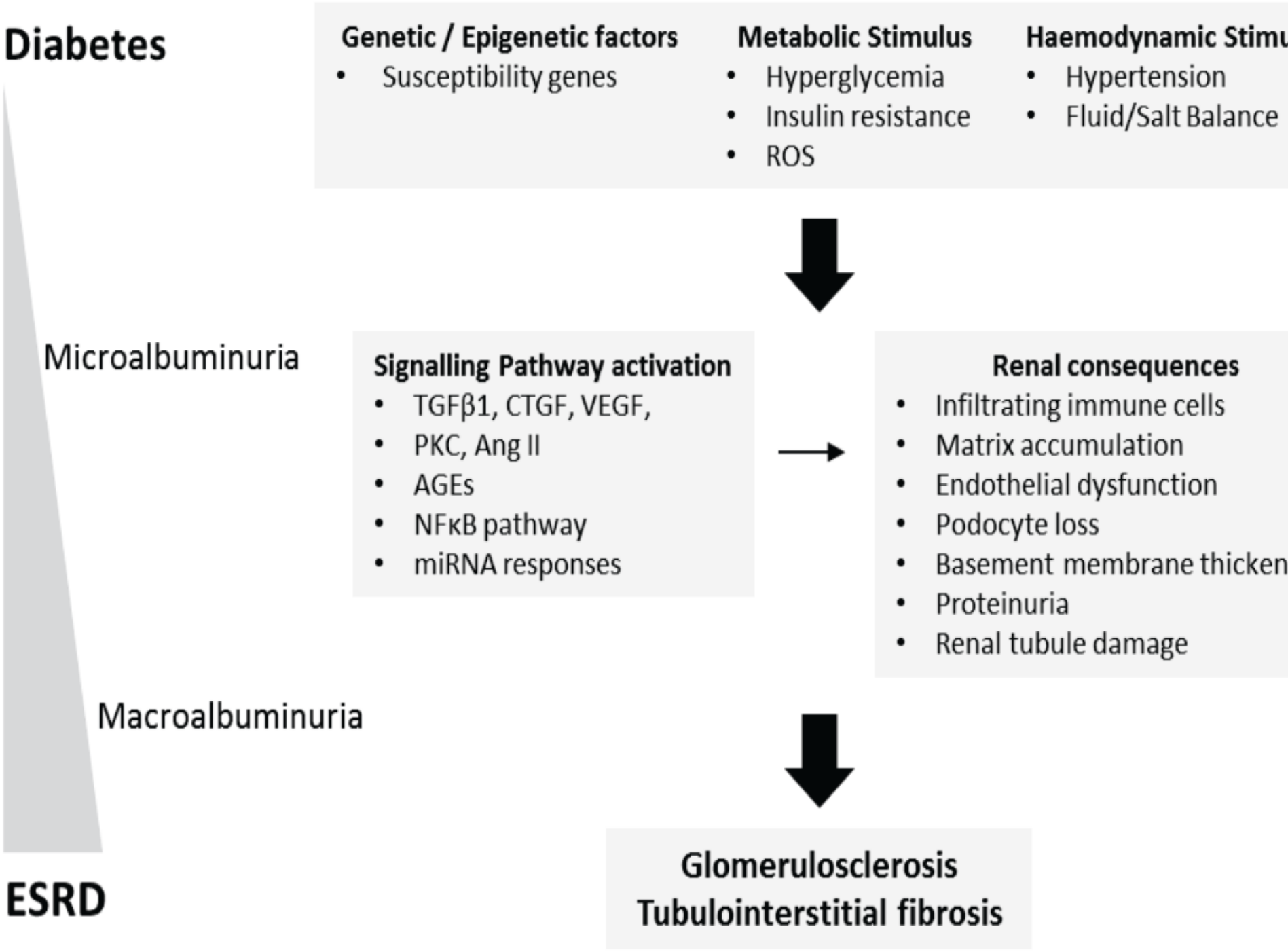
TGF-B1 decreases renal mRNA levels of nephrin and increases the permeability of albumin in the podocyte.

TGF-B1 decreases renal megalin mRNA

levels in Akita type 1 diabetic mice which might attenuate the albumin endocytosis mediated by megalin.

Transforming growth factor-β1 and diabetic nephropathy
Albert S. 2015

manipulations which lead to decreased TGF-1 expression in the podocyte may be useful for preventing/ treating the decline in renal function in diabetic nephropathy.


Diabetes
Genetic / Epigenetic factors
• Susceptibility genes
Metabolic Stimulus
• Hyperglycemia
• Insulin resistance
• ROS
Haemodynamic Stimu
• Hypertension
• Fluid/Salt Balance
Microalbuminuria
Signalling Pathway activation
• TGFβ1, CTGF, VEGF,
• PKC, Ang II
• AGEs
• NFκB pathway
• miRNA responses
Renal consequences
• Infiltrating immune cells
• Matrix accumulation
• Endothelial dysfunction
• Podocyte loss
• Basement membrane thicken
• Proteinuria
• Renal tubule damage
Macroalbuminuria
Glomerulosclerosis
Tubulointerstitial fibrosis
ESRD

RESEARCH ARTICLE

Association between the *ENPP1* K121Q Polymorphism and Risk of Diabetic Kidney Disease: A Systematic Review and Meta-Analysis

Denise Alves Sortica[1,2], Marjorie Piucco Buffon[1,2], Bianca Marmontel Souza[1,2], Bruna Bellicanta Nicoletto[1,2], Andressa Santer[1], Tais Silveira Assmann[1,2], Daisy Crispim[1,2], Luis Henrique Canani[1,2]*

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OPEN ACCESS

Citation: Sortica DA, Buffon MP, Souza BM, Nicoletto BB, Santer A, Assmann TS, et al. (2015) Association between the *ENPP1* K121Q Polymorphism and Risk of Diabetic Kidney Disease: A Systematic Review and Meta-Analysis. PLoS ONE 10(3): e0118416. doi:10.1371/journal.pone.0118416

Academic Editor: Alberico Catapano, University of Milan, ITALY

Received: October 10, 2014

Accepted: January 16, 2015

Published: March 20, 2015

Abstract

The potential association between the K121Q (A/C, rs1044498) polymorphism in the ecto-nucleotide pyrophosphatase/phosphodiesterase (*ENPP1*) gene and risk of diabetic kidney disease (DKD) has been investigated. Nevertheless, the effect of this variant on DKD risk is still under debate, and conflicting results have been reported. To this date, no meta-analysis has evaluated the association of the K121Q polymorphism with DKD. This paper describes the first meta-analysis conducted to evaluate whether the *ENPP1*K121Q polymorphism is associated with DKD. A literature search was conducted to identify all case-control or cross-sectional studies that evaluated associations between the *ENPP1*K121Q polymorphism and DKD. Pooled odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for allele contrast, additive, dominant and recessive inheritance models. Seven studies

GLUT1 Regulation of the Pro-Sclerotic Mediators of Diabetic Nephropathy

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Jamal Salameh[a] N. Stanley Nahman Jr.[c]

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[c]Department of Medicine, Georgia Regents University and Charlie Norwood VAMC, Augusta, Ga., USA

Key Words
GLUT1 · Diabetic nephropathy · Glomerulosclerosis · Glucose transporter · Growth factors · Vascular endothelial growth factor

Abstract
Diabetic glomerulosclerosis is characterized by accumulation of extracellular matrix proteins, mesangial expansion, and tubulointerstitial fibrosis. Hyperglycemia accelerates development of the disease, a direct result of increased intracellular glucose availability. The facilitative glucose transporter GLUT1 mediates mesangial cell glucose flux which leads to activation of signaling cascades favoring glomerulosclerosis, including pathways mediated by angiotensin II tion of Ang II effects suppresses GLUT1 and cellular glucose uptake. GLUT1-mediated glucose flux leads to metabolism of glucose via glycolysis, with induction of DAG, PKC, TGF-β_1, CTGF and VEGF. VEGF in turn triggers both GLUT1 and matrix synthesis. New roles for GLUT1-mTOR and GLUT1-mechano-growth factor interactions in diabetic glomerulosclerosis have also recently been suggested. Recent mouse models confirmed roles for GLUT1 in vivo in stimulating glomerular growth factor expression, growth factor receptors and development of glomerulosclerosis. GLUT1 may therefore act in concert with cytokines and growth factors to induce diabetic glomerulosclerosis. Further clarification of the pathways involved may prove useful for the therapy of diabetic nephropathy. New directions for investigation are discussed.

Submit a Manuscript: http://www.wjgnet.com/esps/ *World J Diabetes* 2017 March 15; 8(3): 112-119

DOI: 10.4239/wjd.v8.i3.112 ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Prospective Study

Role of angiotensin converting enzyme and angiotensinogen gene polymorphisms in angiotensin converting enzyme inhibitor-mediated antiproteinuric action in type 2 diabetic nephropathy patients

Neerja Aggarwal, Pawan Kumar Kare, Parul Varshney, Om Prakash Kalra, Sri Venkata Madhu, Basu Dev Banerjee, Anil Yadav, Alpana Raizada, Ashok Kumar Tripathi

Neerja Aggarwal, Parul Varshney, Om Prakash Kalra, Sri Venkata Madhu, Anil Yadav, Alpana Raizada, Department of Medicine, University College of Medical Sciences (University of Delhi) and Guru Teg Bahadur Hospital, Delhi 110095, India

Data sharing statement: There is no additional data available.

The ACE gene : 17q23

Association with the pathogenesis of DN, The Highly polymorphic (160 polymorphisms)

I/D polymorphism is the most studied

The common polymorphism of the AGT gene is M235T

Original Article: Genetics

Investigation of the association of *BMP* gene variants with nephropathy in Type 1 diabetes mellitus

A. J. McKnight, K. A. Pettigrew, C. C. Patterson*, J. Kilner, D. M. Sadlier†, A. P. Maxwell and the Warren 3/UK GoKinD Study Group

Nephrology Research Group, *Epidemiology Research Group, Queen's University of Belfast, Belfast, UK and †Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland

Accepted 14 January 2010

Abstract

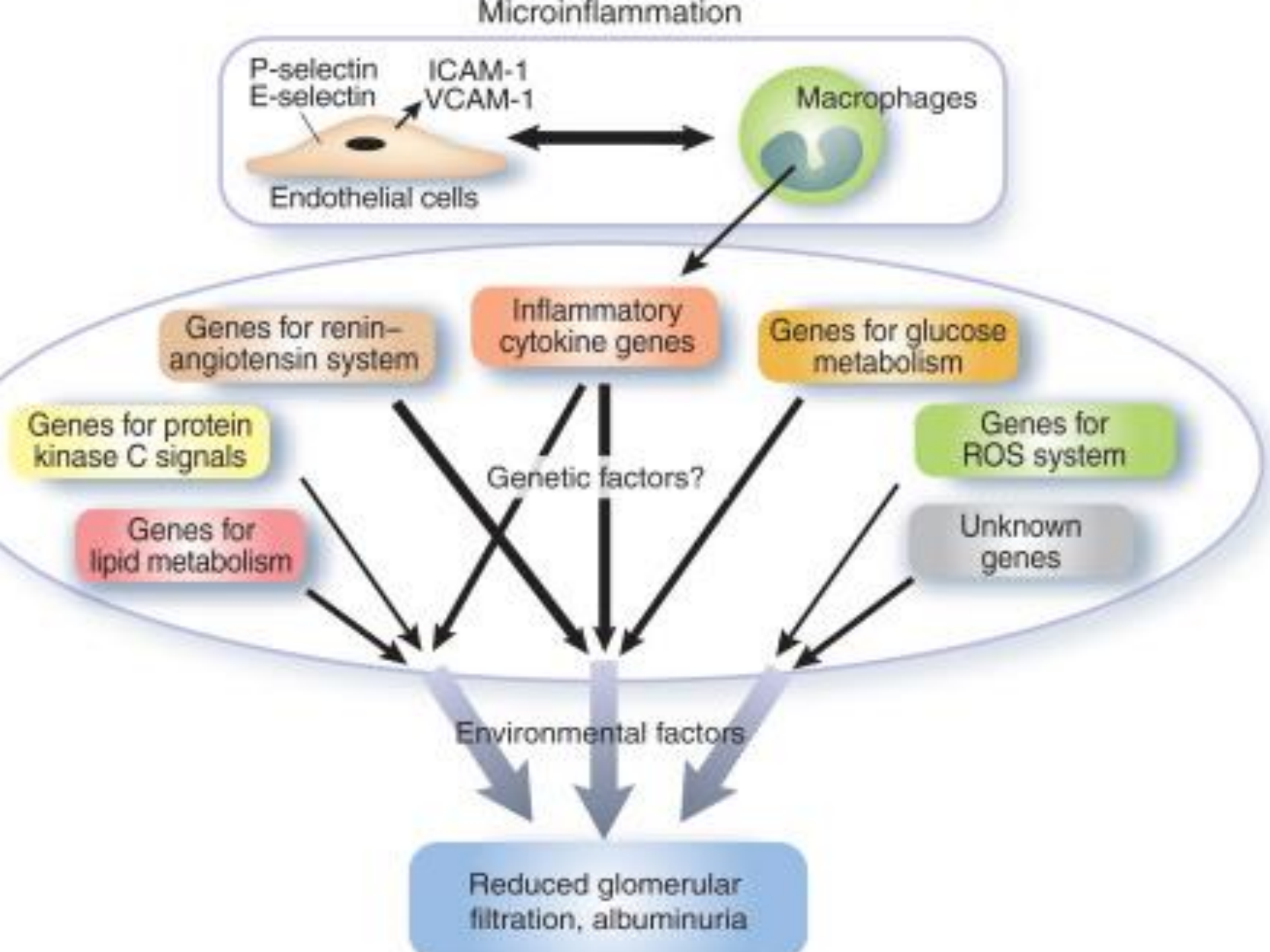
Aims Diabetic nephropathy is a leading cause of end-stage renal disease. The transforming growth factor β–bone morphogenic protein (BMP) pathway is implicated in the pathogenesis of diabetic nephropathy. The *BMP2*, *BMP4* and *BMP7* genes are located near linkage peaks for renal dysfunction, and we hypothesize that genetic polymorphisms in these biological and positional candidate genes may be risk factors for diabetic kidney disease.

Methods The *BMP7* gene was screened, variants identified and allele frequencies determined by bidirectionally sequencing 46 individuals to facilitate selection of tag SNPs ($n = 4$). For *BMP2* and *BMP4* genes, data were downloaded for 19 single nucleotide polymorphisms (SNPs) from the International HapMap project and six tag SNPs selected.

Results The *BMP7* gene was screened for novel genetic polymorphisms, haplotypes were identified, an appropriate subset of variants selected for the investigation of common genetic risk factors, and *BMP2*, *BMP4* and *BMP7* genes assessed for association with diabetic nephropathy in 1808 individuals. Thirty-two SNPs were identified, of which 11 were novel, including an amino-acid changing SNP (+63639C>T). No significant differences ($P > 0.2$) were observed when comparing genotype or

BMP

- The transforming growth factor b–bone
- morphogenic protein (BMP) pathway is implicated in the pathogenesis of diabetic nephropathy. The BMP2, BMP4 and BMP7
- genes are located near linkage peaks for renal dysfunction.
- Common polymorphisms in these BMP genes do not strongly influence genetic susceptibility to diabetic nephropathy in White individuals with Type 1 diabetes mellitus.


Microinflammation
P-selectin
E-selectin
ICAM-1
VCAM-1
Endothelial cells
Macrophages
Genes for renin–angiotensin system
Inflammatory cytokine genes
Genes for glucose metabolism
Genes for protein kinase C signals
Genetic factors?
Genes for ROS system
Genes for lipid metabolism
Unknown genes
Environmental factors
Reduced glomerular filtration, albuminuria

Questions

1-Why a proportion of diabetic individuals appear to be protected from serious complications (Unlike the progression to retinopathy) ?

2-Why not all people with diabetes complications experience more advanced forms of vascular disease?

Genetic variation does not adequately explain the disproportionate **distribution** and **severity** of diabetic vascular complications.

Epigenetics in diabetic nephropathy, immunity and metabolism
Samuel T. Keating1. 2018

Not all people with microalbuminuria progress to macroalbuminuria or ESRD, apparently protected despite decades of chronic hyperglycemia and hemodynamic stress.

Thomas MC . Epigenetic mechanisms in diabetic kidney disease. Curr Diab Rep 16:31,2016

Metabolic Memory

- Clinical and experimental studies have shown that the risk and severity of diabetic complications , including DN, seem to persist even after glucose normalization , suggesting a‘‘metabolic memory’’ of the prior exposure to HG

Epigenetic modifications anddiabetic nephropathy
Marpadga A. 2012

Epigenetic

Epigenetics is the study of changes in gene expression caused by mechanisms other than those that change the underlying DNA sequence, and helps to explain how cells with identical DNA can differentiate into different cell types with different phenotypes.

Epigenetic modifications can be passed from one cell generation to the next and between generations of humans.

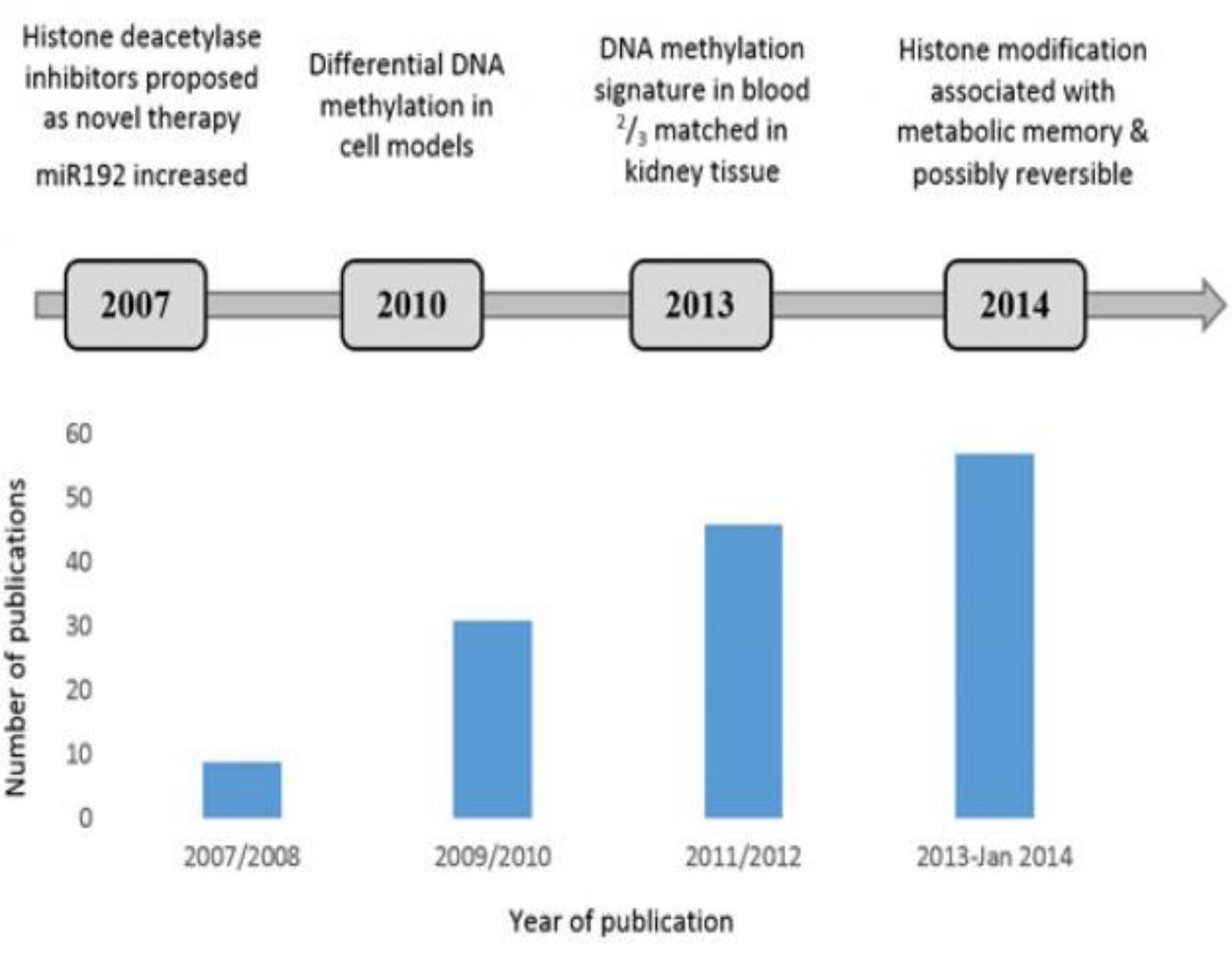
May be regulated by environment factors.

1-DNA methylation (hyperglycemia changes DNAme)

2-Histone modification

3-MicroRNAs

Epigenetic Regulations in Diabetic Nephropathy. Zeyuan Lu. 2017


Histone deacetylase inhibitors proposed as novel therapy
miR192 increased
Differential DNA methylation in cell models
DNA methylation signature in blood 2/3 matched in kidney tissue
Histone modification associated with metabolic memory & possibly reversible
2007
2010
2013
2014
Number of publications
60
50
40
30
20
10
0
2007/2008
2009/2010
2011/2012
2013-Jan 2014
Year of publication

DNA methylation

diabetic status can induce epigenetic Changes.

DNA methylation induced by elevated glucose in multiple target organs and cells, which contribute to the metabolic memory of diabetic vascular complications.

Cytosines in CpG dinucleotides can be methylated to form 5-methylcytosine. In mammals, methylating the cytosine within a gene can change its expression.

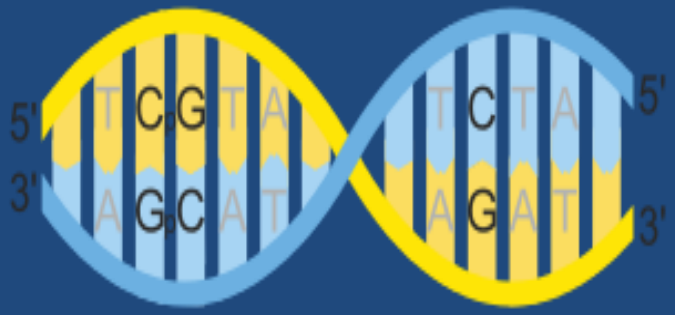
DNA Methylation

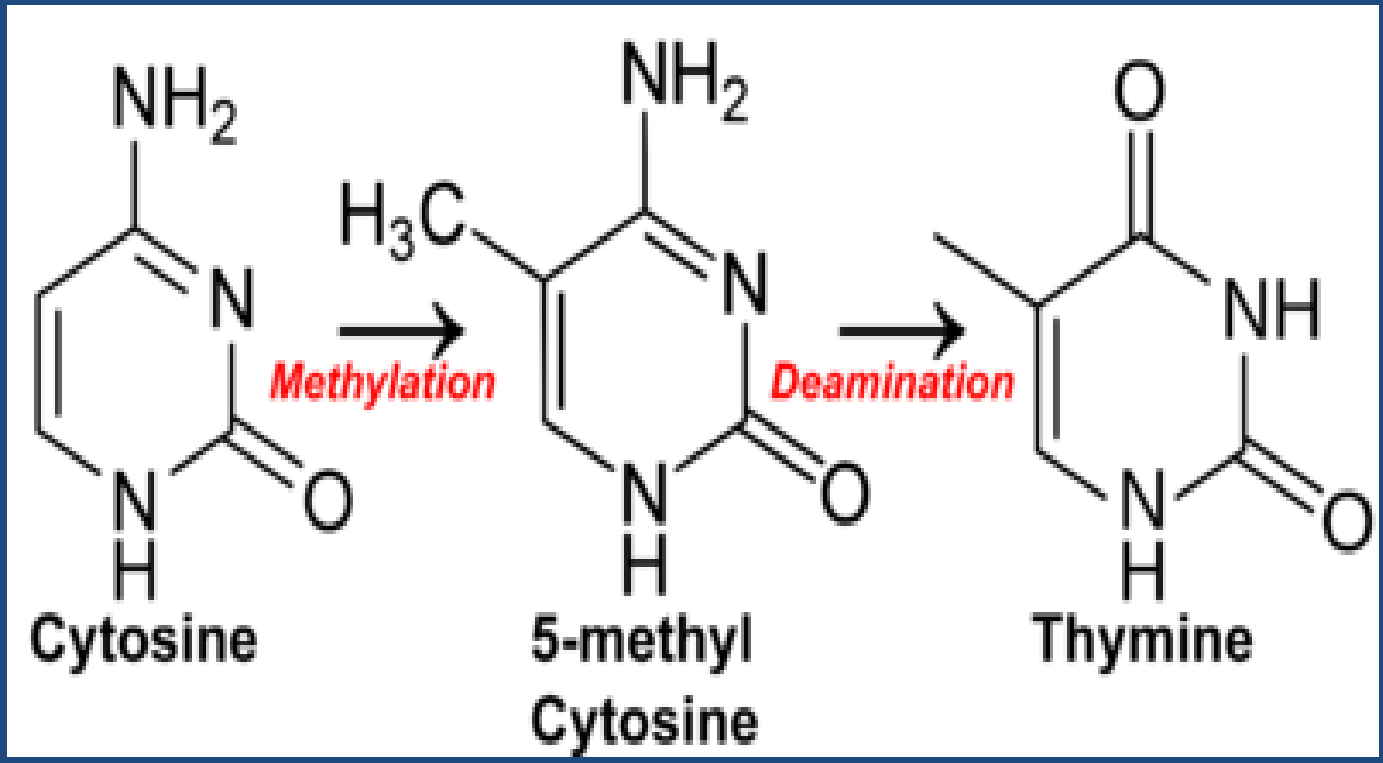
Cytosine bases of the DNA template at CpG dinucleotides and on the tails of chromatinised histones.

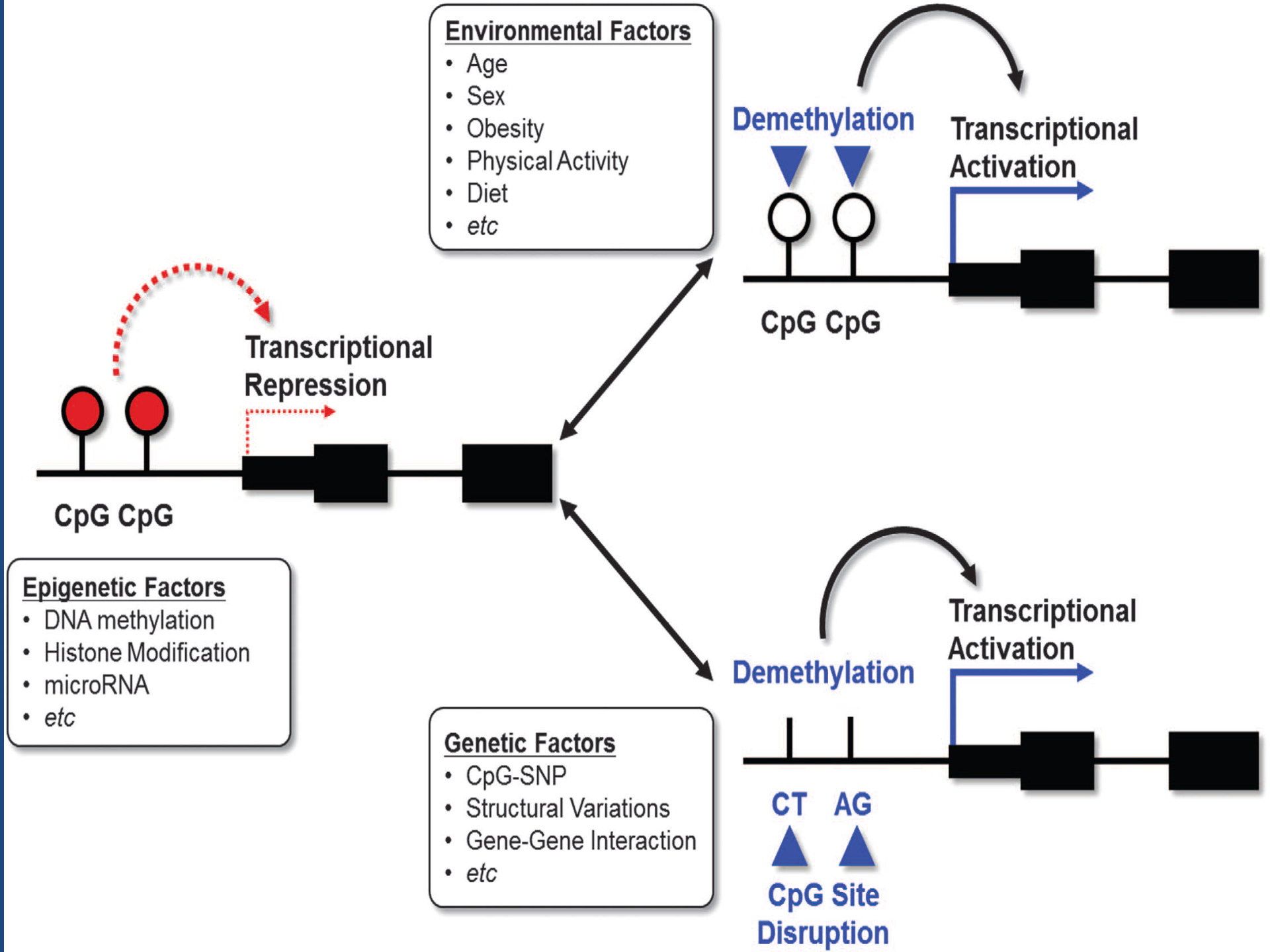
DNMT1, DNMT3a, and DNMT3b in humans

5mC

Transcriptional silencing by recruitment of specific factors that actively remodel the chromatin structure, as well as by the disruption of transcription factor binding sites.


5'
3'
T C G T A
A G C A T
T C T A
A G A T
5'
3'


NH2
N
N
H
O
Cytosine
Methylation
H3C
NH2
N
N
H
O
5-methyl
Cytosine
Deamination
O
NH
N
H
O
Thymine


Environmental Factors
• Age
• Sex
• Obesity
• Physical Activity
• Diet
• etc
Demethylation
Transcriptional Activation
CpG CpG
Transcriptional Repression
CpG CpG
Epigenetic Factors
• DNA methylation
• Histone Modification
• microRNA
• etc
Genetic Factors
• CpG-SNP
• Structural Variations
• Gene-Gene Interaction
• etc
Demethylation
Transcriptional Activation
CT AG
CpG Site Disruption

MicroRNAs(miRNAs)

Are 22-nucleotide non-coding RNAs

that can result in either posttranscriptional silencing or RNA degradation by binding the 30-untranslated region of target mRNAs normally.

miRNAs play critical roles in the tissue response to environmental stimuli without changing DNA sequence with a rapid and reversible means of gene regulation.

microRNA

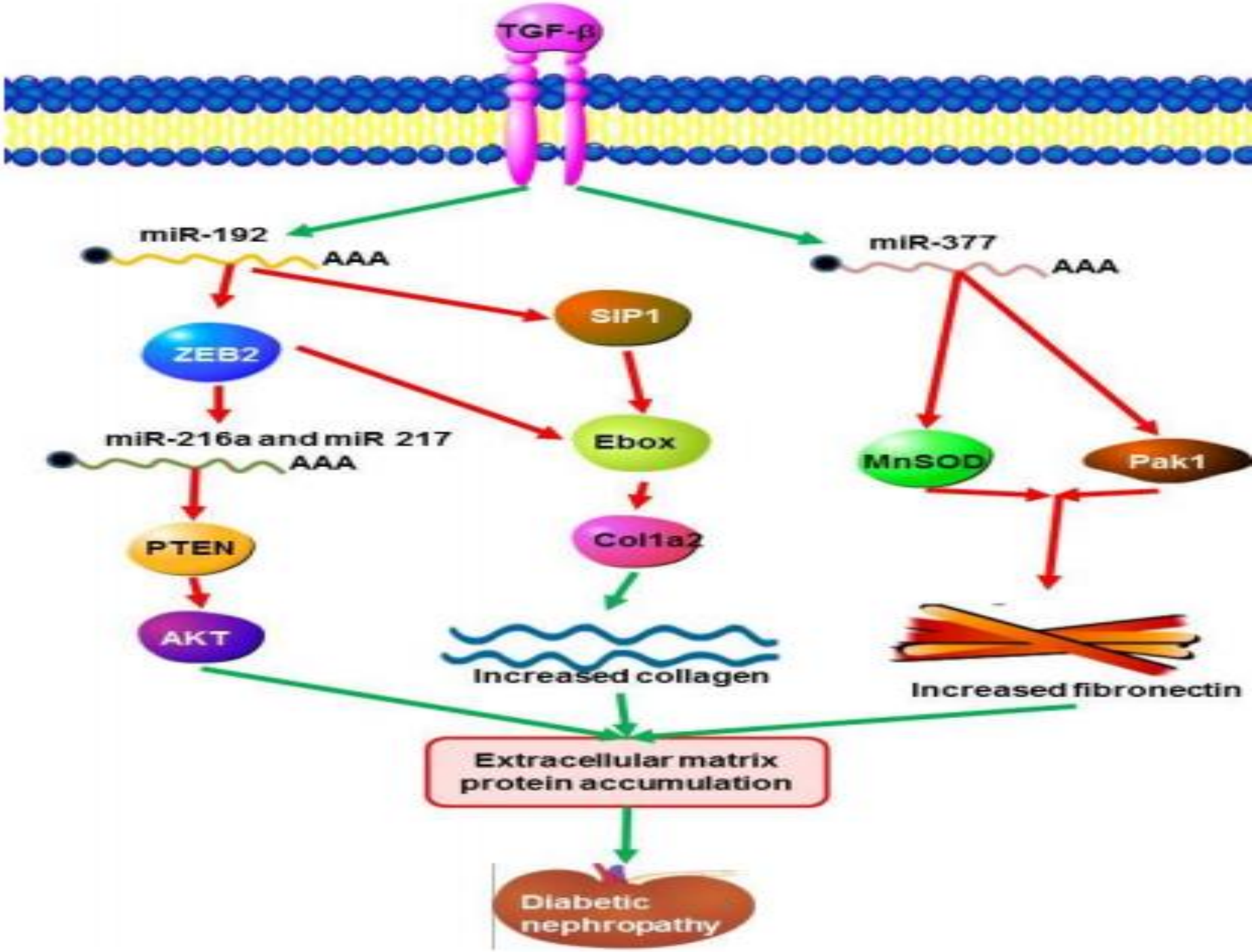
14 up-regulated genes and 430 down-regulated ones were identified. Some DEGs related to cytoskeleton organization (MTSS1, ACTN4 and CALD1), cardiomyopathy (ITGB5) and immune response (C1S and C1R), as well as some regulators

LEF1 and hsa-miR-33a might play pivotal roles in the progression of DN.

Crucial genes associated with diabeti nephropathy explored by microarray analysis. Zhikui Wang. 2016

miRNA involved in diabetic nephropathy

miRNA	Target tissue	Reference
miR-192	Kidney	122
miR-107	Pancreas, adipose	20,38
miR-125(a/b)	Liver, vascular tissue	8,123
miR-216a	Kidney	124,125
miR-217	Kidney	124,125
miR-320	Adipose, vascular endothelium	126,127

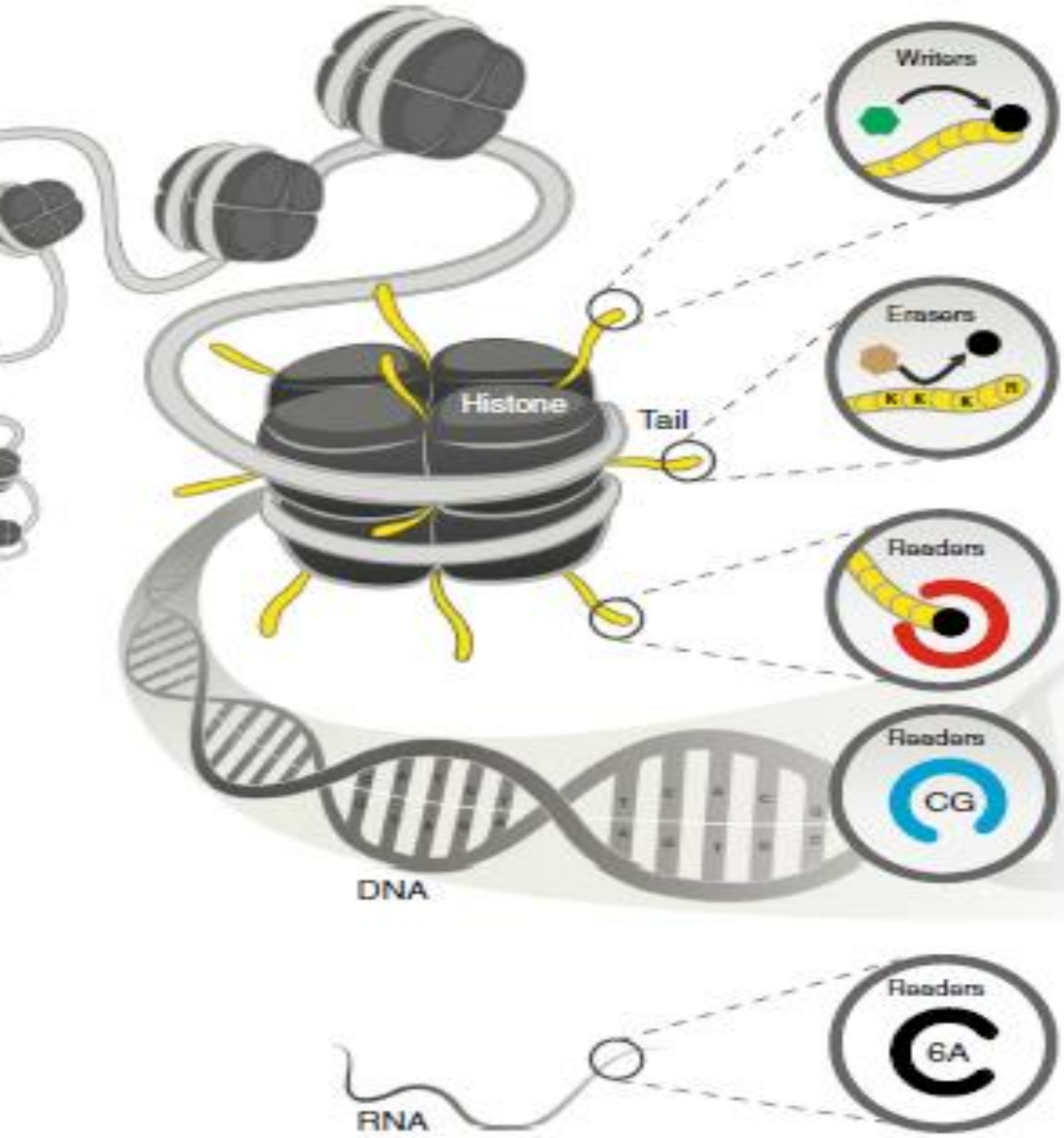

TGF-β
miR-192
AAA
miR-377
AAA
SIP1
ZEB2
miR-216a and miR 217
AAA
Ebox
MnSOD
Pak1
PTEN
Col1a2
AKT
Increased collagen
Increased fibronectin
Extracellular matrix protein accumulation
Diabetic nephropathy

Histone Modification

Epigenetic mechanisms in chromatin :

Regulate gene expression , cellular identity, phenotypic variations , and disease states without any alterations in the underlying DNA sequence.

ROMATIN | NUCLEOSOME | EPIGENETIC CODE | DETERMINANT



Enzymes that add a mark such as acetylases, methylases and phosphorylases

Enzymes that remove a mark such as deacetylases, demethylases and phosphatases

Proteins that interpret histone marks include the bromodomain, chromodomain readers

Proteins that interpret modified cytosine residues such as 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) include MBD and TET

Proteins that interpret modified adenosine residues such as N^6-methyladenosine (m6A) include YTH and HNRNP

Mechanistic studies
SET7 H3K4me
SETDB1 H3K9me
SUV39H1 H3K9me
EZH2 H3K27m
KAT2A H3 acety
GLYATL1 H3 acety

Profiling studies
SET7 H3K4me
SUV39H1/H2 H3K9me
H3K9me

Mechanistic studies
KDM6B H3K27m
PHF2 H3K9me
KDM1A H3K9me
HDAC3
HDAC4
HDAC7

Mechanistic studies
CTCF

Mechanistic studies
KLF4 5mC
SIRT1 5mC
DNMT3B 5mC (no
5mC
5mC and

Profiling studies
5mC
TET2 5hmC

Mechanistic studies
FTO
FTO m6A

Profiling studies
FTO
FTO m6A

IE

Writer | Eraser | Histone mark | Histone reader | DNA reader | C

Table 1. Histone modifications and their function in the transcription regulation*

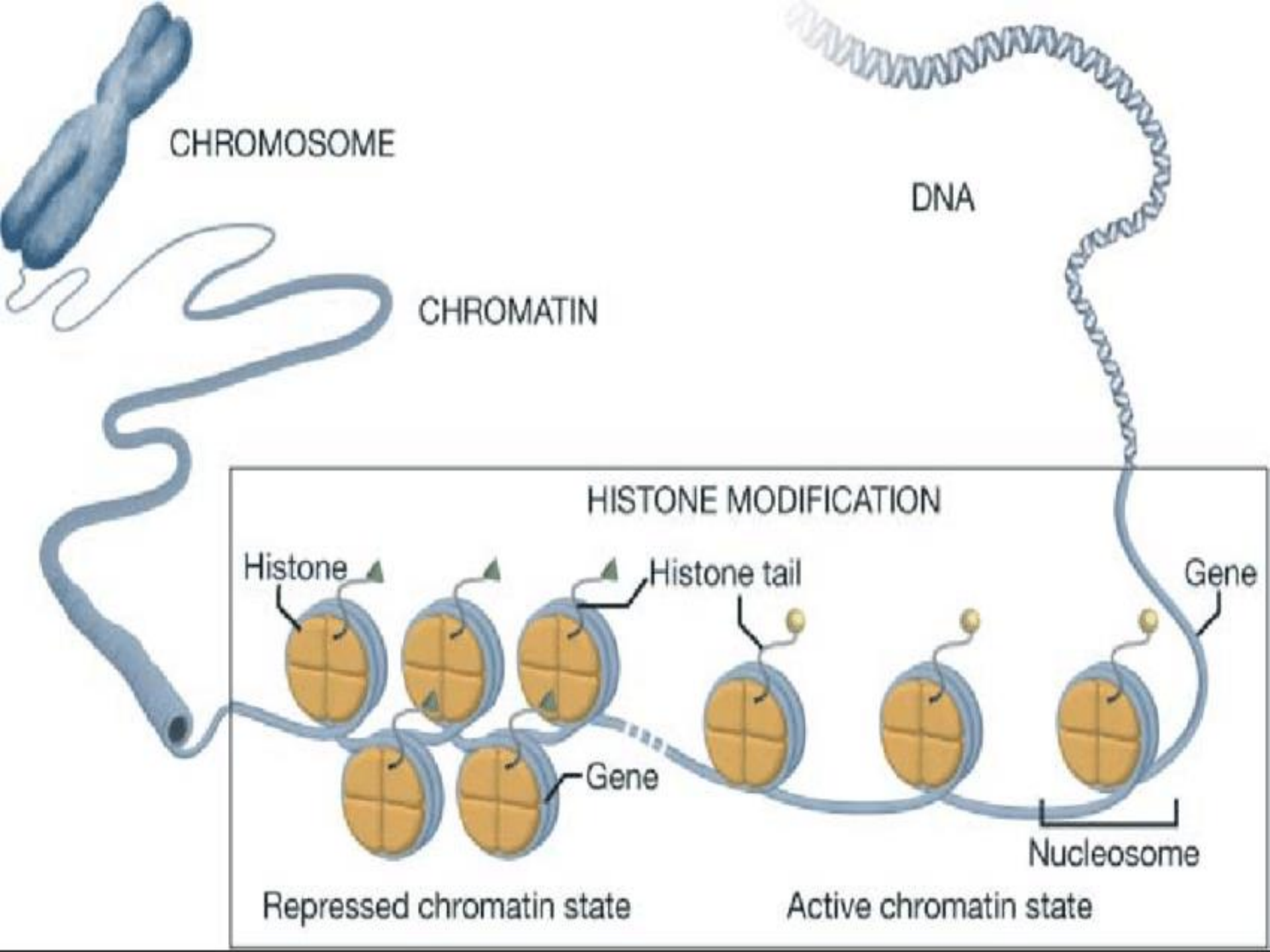
Modification	Histone	Modifying enzyme	Proposed function
Acteylation	H2A, H3, H4	ATF2, ELP3, GCN5, GTF3C4, HAT1, MORF, MOZ, p300, PCAF, SRC-1, TAF1, Tip 60	Activation
Deacetylation	H2A, H3, H4	HDAC1–HDAC11, SIRT1–SIRT7	Repression
Methylation	H1K26, H3K27	Ezh2	Repression
	H3K9	ESET, G9a, SUV39H1, SUV39H2, SETDB1	Repression
	H3K4	MLL, SET7, SET9, SMYD3	Activation
	H3K36	SETD2, NSD1	Activation
	H3K79	DOT1L	Activation
	H4K20	PR-SET7, SUV4-20H1, SUV4-20H2	Repression
	H3R17	CARM1	Activation
	H4R3	PRMT1	Activation
	H3R8	PRMT5	Repression
	H4R3	PRMT5	Repression
Demethylation	H3K4	LSD1	Repression
	H3K4	JARID1A, JARID1B, JARID1C, JARID1D	Repression
	H3K9	JMJD1A	Activation
	H3K9/H3K36	JMJD2A, JMJD2B, JMJD2C, JMJD2D	Activation/Repression
	H3K36	JHDM1A, JHDM1B	Repression
	H3K27	JMJD3, UTX	Activation
Phosphorylation	H2AS1, H3S10, H3S28	MSK1	Repression
	H3S10	Aurora-B, IKK-α, MSK2, RSK2	Activation
	H2AS1, H2AS139, H4S1	ATR, ATM, DNA-PK, CK2, Tel1	DNA repair
Ubiquitylation	H2AK119	RING1B	Activation/repression
	H2BK120	UbcH6	Activation/repression
Biotinylation	H2AK9, H2AK13, H3K4, H3K9, H3K18, H4K12	Biotinidase	Activation

HDACs play an important role in TGFB1-mediated ECM production and kidney fibrosis in DN.

HDACs play a role in the pathogenesis of renal fibrosis and in models of chronic renal injury induced by TGF-b1 modulation of key protective genes.

Losartan

Human genetics of diabetic nephropathy .Zi-Hui Tang, Fengfang Zeng. 2016

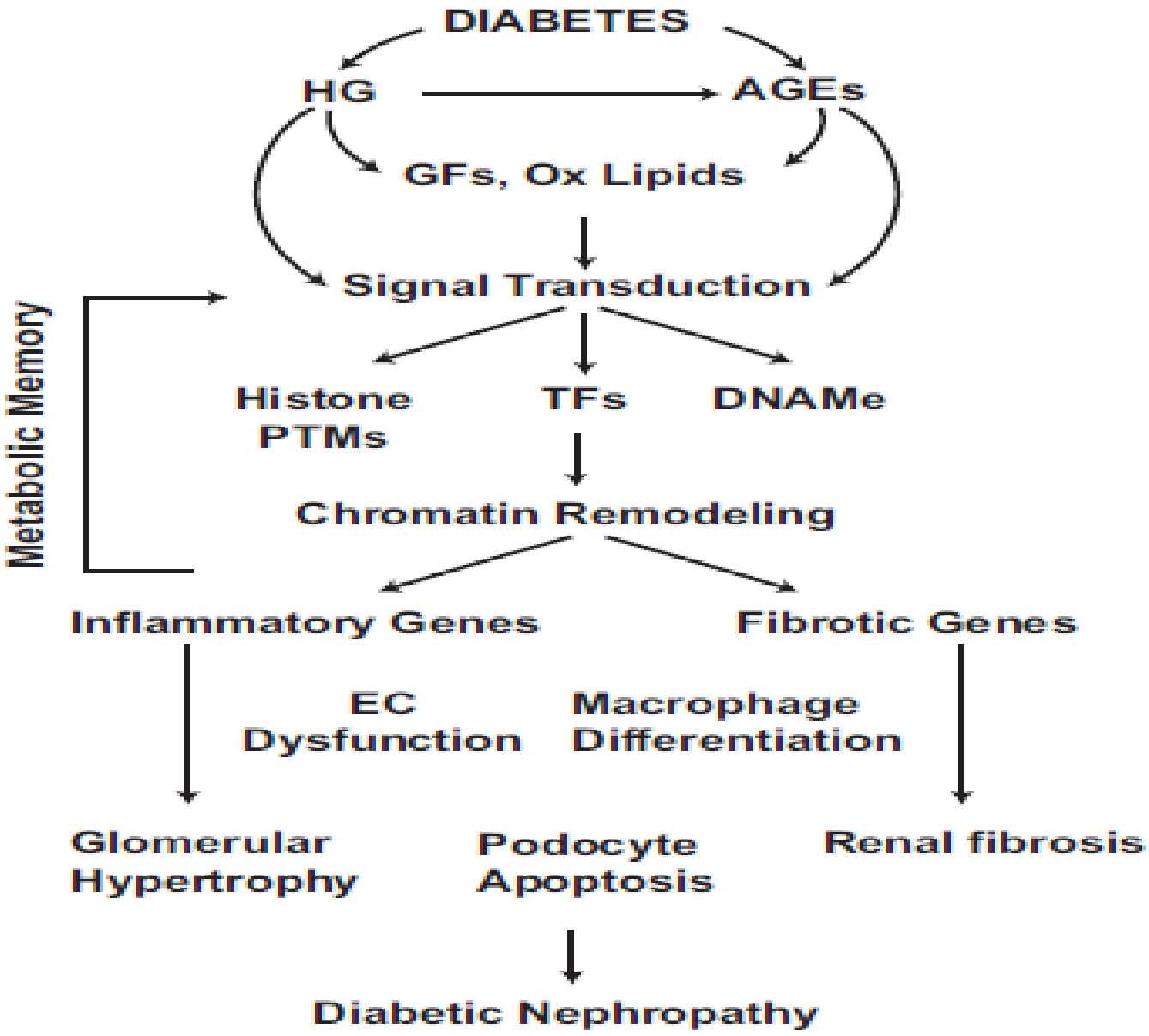

CHROMOSOME
DNA
CHROMATIN
HISTONE MODIFICATION
Histone
Histone tail
Gene
Gene
Nucleosome
Repressed chromatin state
Active chromatin state

Transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia

Assam El-Osta,[1] Daniella Brasacchio,[1] Dachun Yao,[3] Alessandro Pocai,[4] Peter L. Jones,[5] Robert G. Roeder,[6] Mark E. Cooper,[2,3] and Michael Brownlee[3]

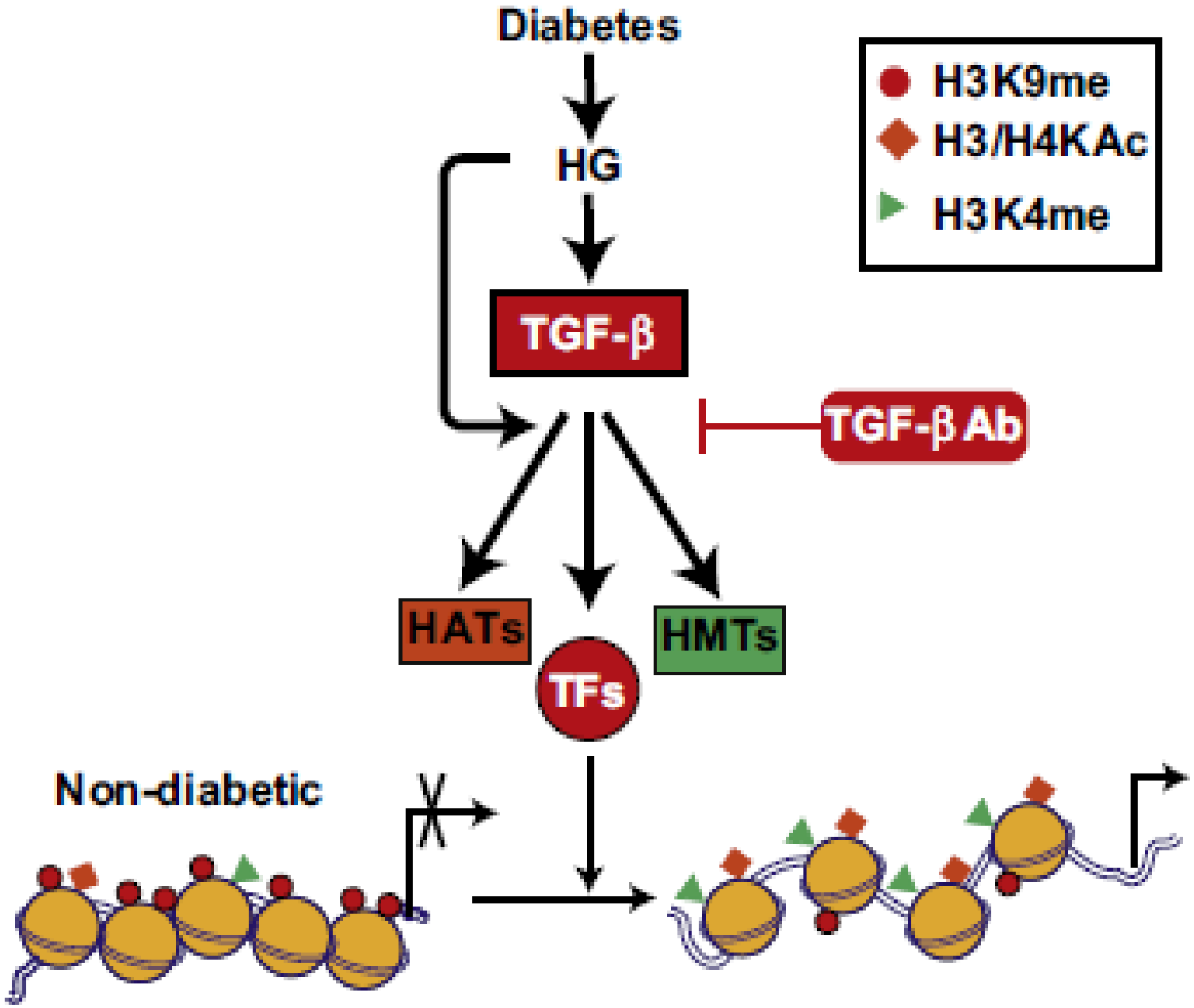
[1]Diabetes and Metabolism Division, Baker Epigenetics in Human Health and Disease, and [2]Diabetes and Metabolism Division, Juvenile Diabetes Research Foundation Danielle Alberti Memorial Centre for Diabetic Complications, Baker IDI Heart and Diabetes Institute, the Alfred Medical Research and Education Precinct, Commercial Road, Melbourne, Victoria 3004, Australia
[3]Juvenile Diabetes Research Foundation International Center for Diabetic Complications Research and [4]Department of Medicine and Diabetes Research Center, Albert Einstein College of Medicine, Bronx, NY 10461
[5]Department of Cell and Structural Biology, University of Illinois at Urbana-Champaign, Urbana, IL 61802
[6]Laboratory of Biochemistry and Molecular Biology, The Rockefeller University, New York, NY 10021

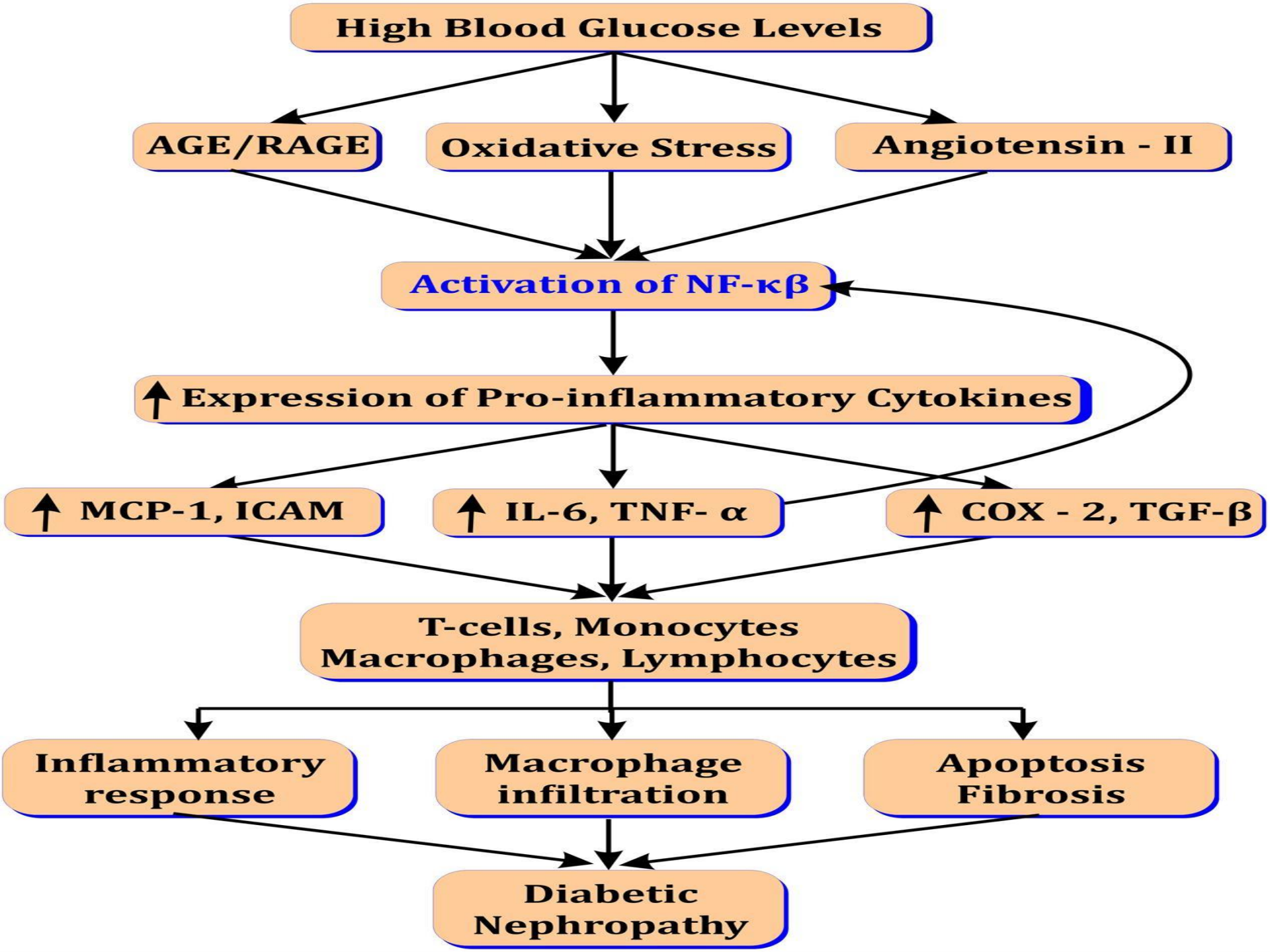
The current goal of diabetes therapy is to reduce time-averaged mean levels of glycemia, measured as HbA1c, to prevent diabetic complications. However, HbA1c only explains <25% of the variation in risk of developing complications. Because HbA1c does not correlate with glycemic variability when adjusted for mean blood glucose, we hypothesized that transient spikes of hyperglycemia may be an HbA1c–independent risk factor for diabetic complications. We show that transient hyperglycemia induces long-lasting activating epigenetic changes in the promoter of the nuclear factor κB (NF-κB) subunit p65 in aortic endothelial cells both in vitro and in nondiabetic mice, which cause increased p65 gene expression. Both the epigenetic changes and the gene expression changes persist for at least 6 d of subsequent normal glycemia, as do NF-κB–induced increases in monocyte chemoattractant protein 1 and vascular cell adhesion molecule 1 expression. Hyperglycemia-induced epigenetic changes and increased p65 expression are prevented by reducing mitochondrial superoxide production or superoxide-induced α-oxoaldehydes. These results


DIABETES
HG
AGEs
GFs, Ox Lipids
Signal Transduction
Metabolic Memory
Histone PTMs
TFs
DNAMe
Chromatin Remodeling
Inflammatory Genes
Fibrotic Genes
EC Dysfunction
Macrophage Differentiation
Glomerular Hypertrophy
Podocyte Apoptosis
Renal fibrosis
Diabetic Nephropathy

TGF- B1

NFkB


Diabetes
HG
TGF-β
TGF-β Ab
HATs
TFs
HMTs
H3K9me
H3/H4KAc
H3K4me
Non-diabetic


High Blood Glucose Levels
AGE/RAGE
Oxidative Stress
Angiotensin - II
Activation of NF-κβ
↑ Expression of Pro-inflammatory Cytokines
↑ MCP-1, ICAM
↑ IL-6, TNF- α
↑ COX - 2, TGF-β
T-cells, Monocytes
Macrophages, Lymphocytes
Inflammatory response
Macrophage infiltration
Apoptosis
Fibrosis
Diabetic Nephropathy

Nephrol Dial Transplant (2004) 19: 2505–2512
doi:10.1093/ndt/gfh207
Advance Access publication 27 July 2004

Nephrology
Dialysis
Transplantation

Original Article

NF-κB activation and overexpression of regulated genes in human diabetic nephropathy

Sergio Mezzano[1], Claudio Aros[1], Alejandra Droguett[1], M. Eugenia Burgos[1], Leopoldo Ardiles[1], Claudio Flores[1], Herman Schneider[1], Marta Ruiz-Ortega[2] and Jesús Egido[2]

[1]Division of Nephrology, School of Medicine, Universidad Austral, Valdivia, Chile and [2]Fundación Jiménez Díaz, Universidad Autónoma, Madrid, Spain

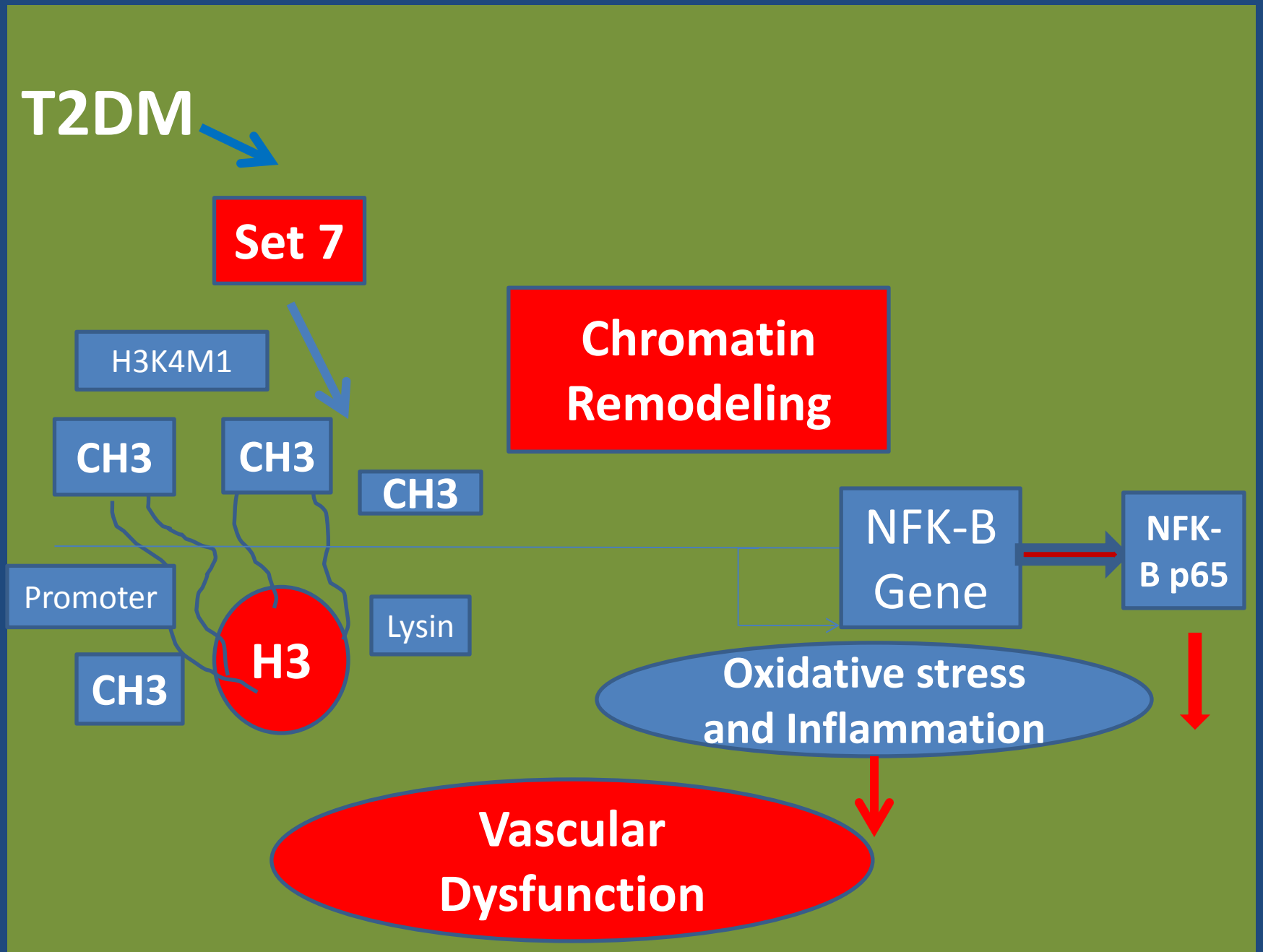
Abstract

Background. Nuclear factor κB (NF-κB) regulates

Proteinuria might be one of the main factors inducing the observed pro-inflammatory phenotype

Set7

Chromatin modifying enzyme Set7 is upregulated in diabetic patients and involved in the regulation of transcription factor NF-kB, inflammation, oxidative stress, and endothelial dysfunction.


T2DM
Set 7
H3K4M1
CH3
CH3
CH3
Chromatin Remodeling
Promoter
CH3
H3
Lysin
NFK-B Gene
NFK-B p65
Oxidative stress and Inflammation
Vascular Dysfunction

Conclusions

Clinical and epidemiological studies have identified a genetic component to DN, although so far no specific gene has been identified.

Combined with classical genetic approaches, epigenomic profiling has potential to identify molecular trajectories underlying diabetic vascular disease development.

The clinical applicability of epigenetic interventions will be greatly advanced by a deeper understanding of the cell type specific functions and interactions of chromatin-modifying machinery in the diabetic vasculature