
Il Prof. Angelo Avogaro dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Lilly
- Novo
- BMS-AZ
- Boehringer
- Sanofi
- GSK
- Takeda
- Diyki-Sankio
- Servier
- Sigma-Tau



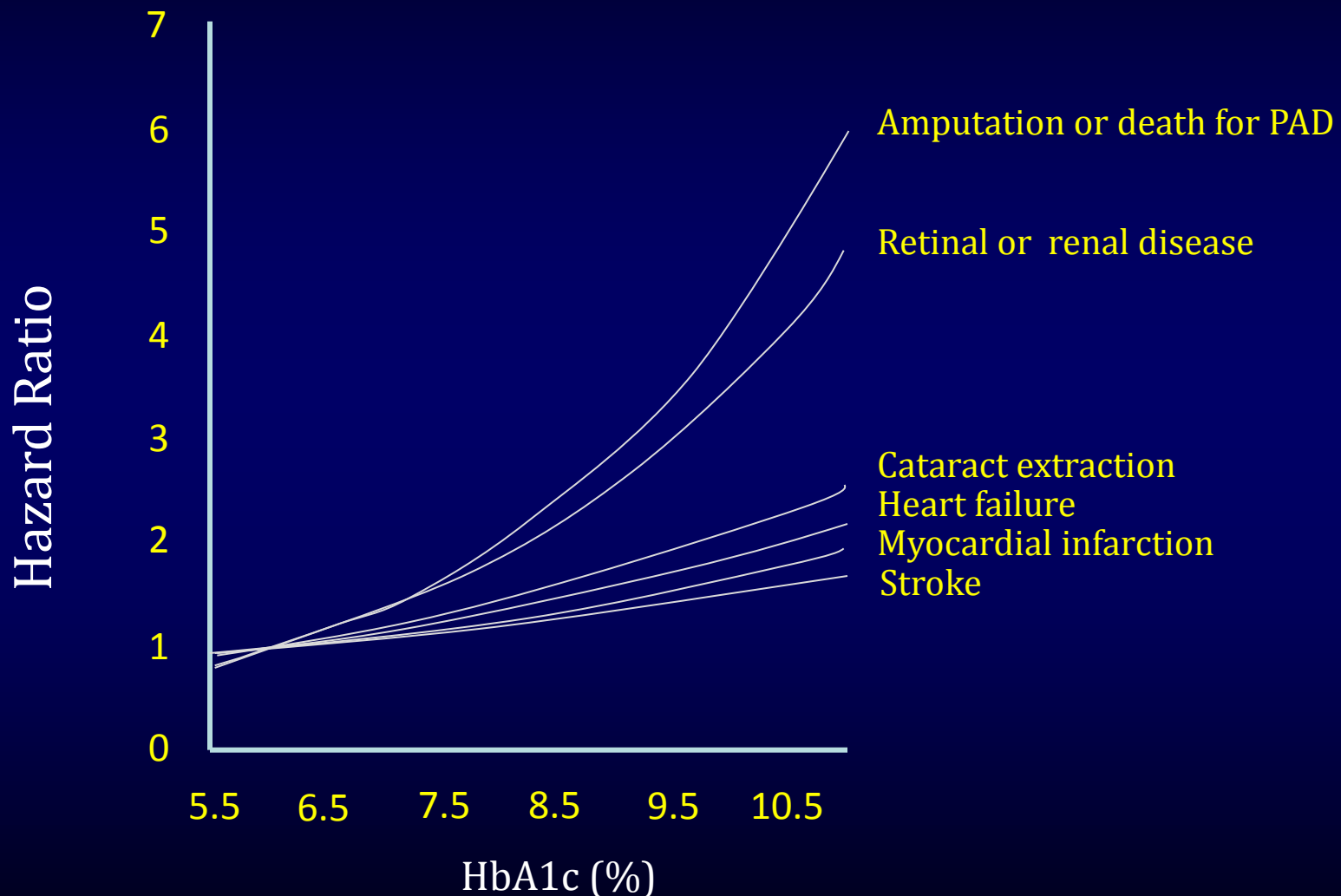
UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Iperglicemia e complicanze vascolari: il ruolo dei geni della longevità

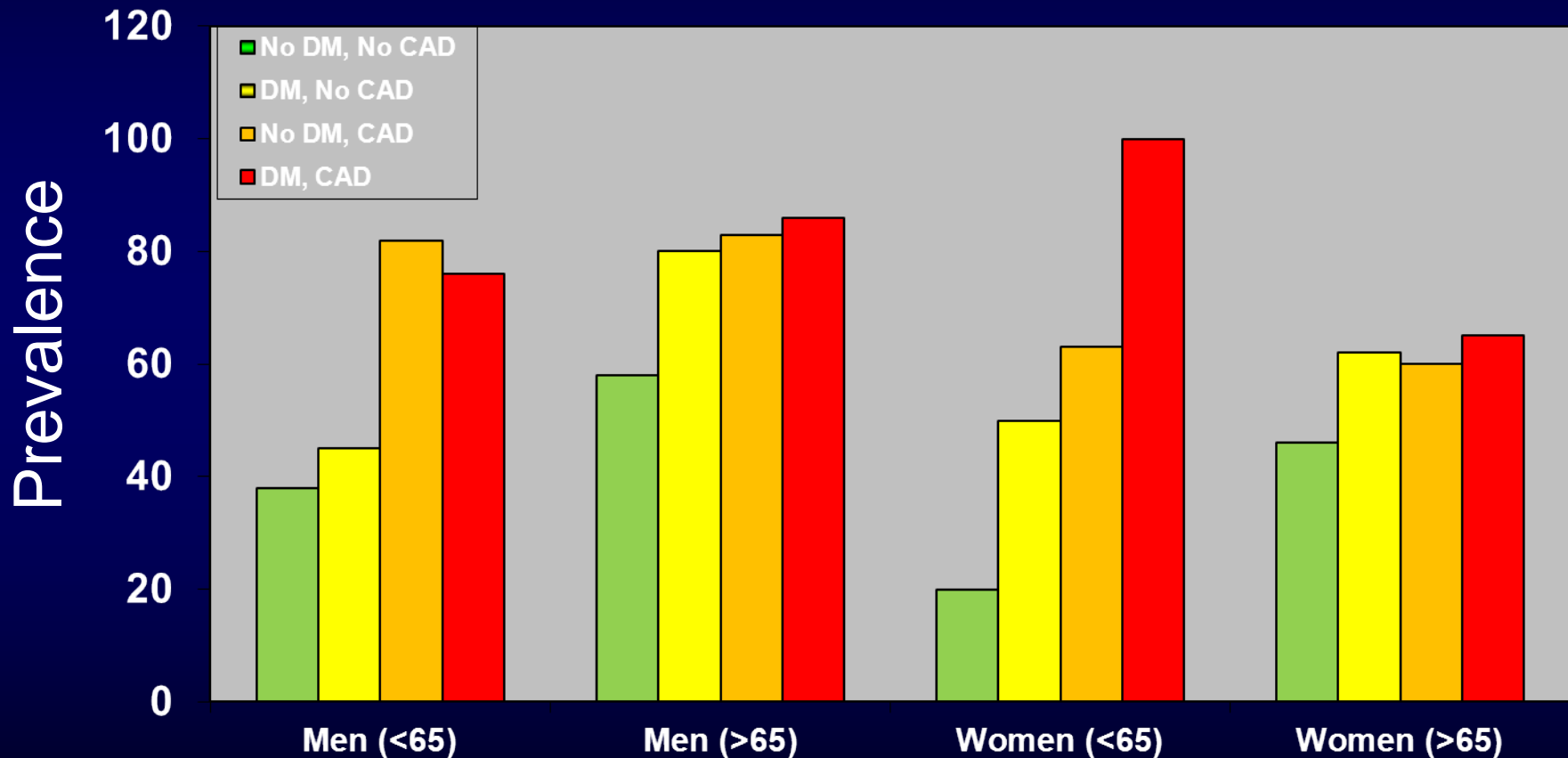
Angelo Avogaro

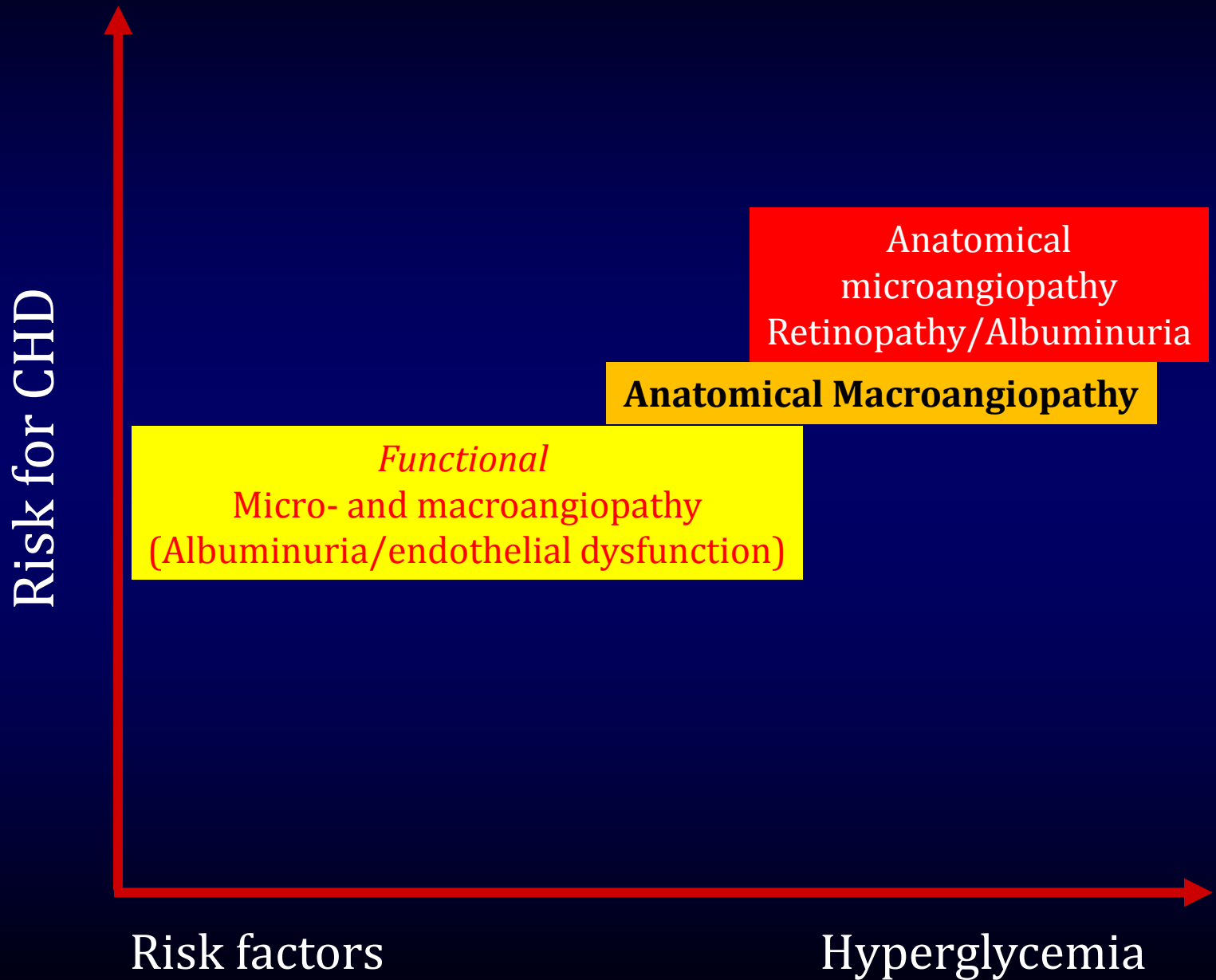
DIMED. Università di Padova

The relationship between updated A1c and the multivariable adjusted hazard of various chronic consequences of diabetes in participants in the UKPDS based on the reported difference per 1% higher A1c level



Prevalence of any high-grade or multivessel coronary atherosclerosis at autopsy

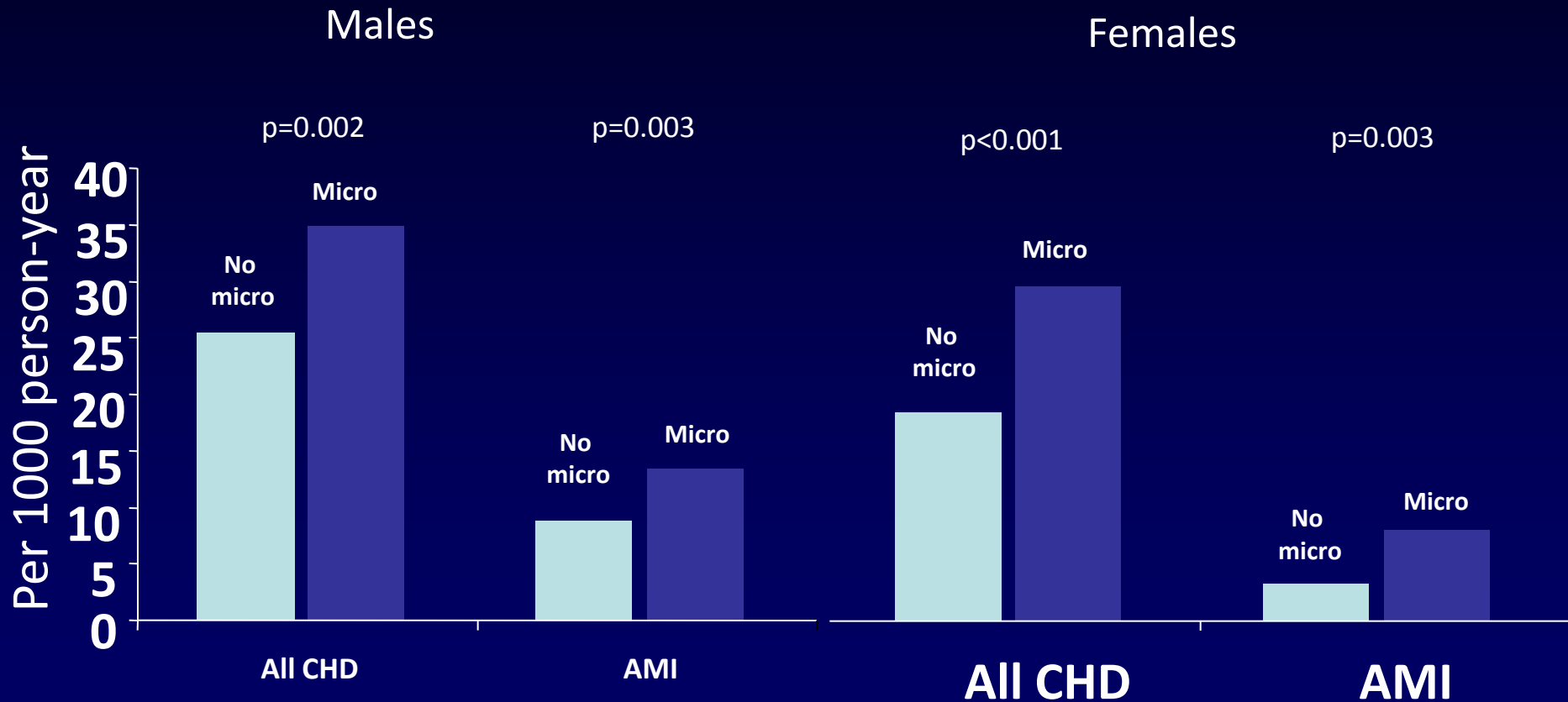






Incidence Rate of CHD Events: The role of microvascular complications

(Avogaro et al. Diabetes Care 2006)



DIABETE MELLITO

Dislipidemia aterogena
(↑ trigliceridi, ↓HDL, LDL piccole dense)

Iperglicemia

Insulino-resistenza

↑ produzione di ROS
↓ riserva antiossidante

↑ AGE
attivazione RAGE

↑ trasduzione segnali
infiammatori
↓ NO

STATO PROTROMBOTICO

Trombosi
Ipercoagulabilità
Attivazione piastrinica
Ridotta fibrinolisi

DISFUNZIONE ENDOTELIALE

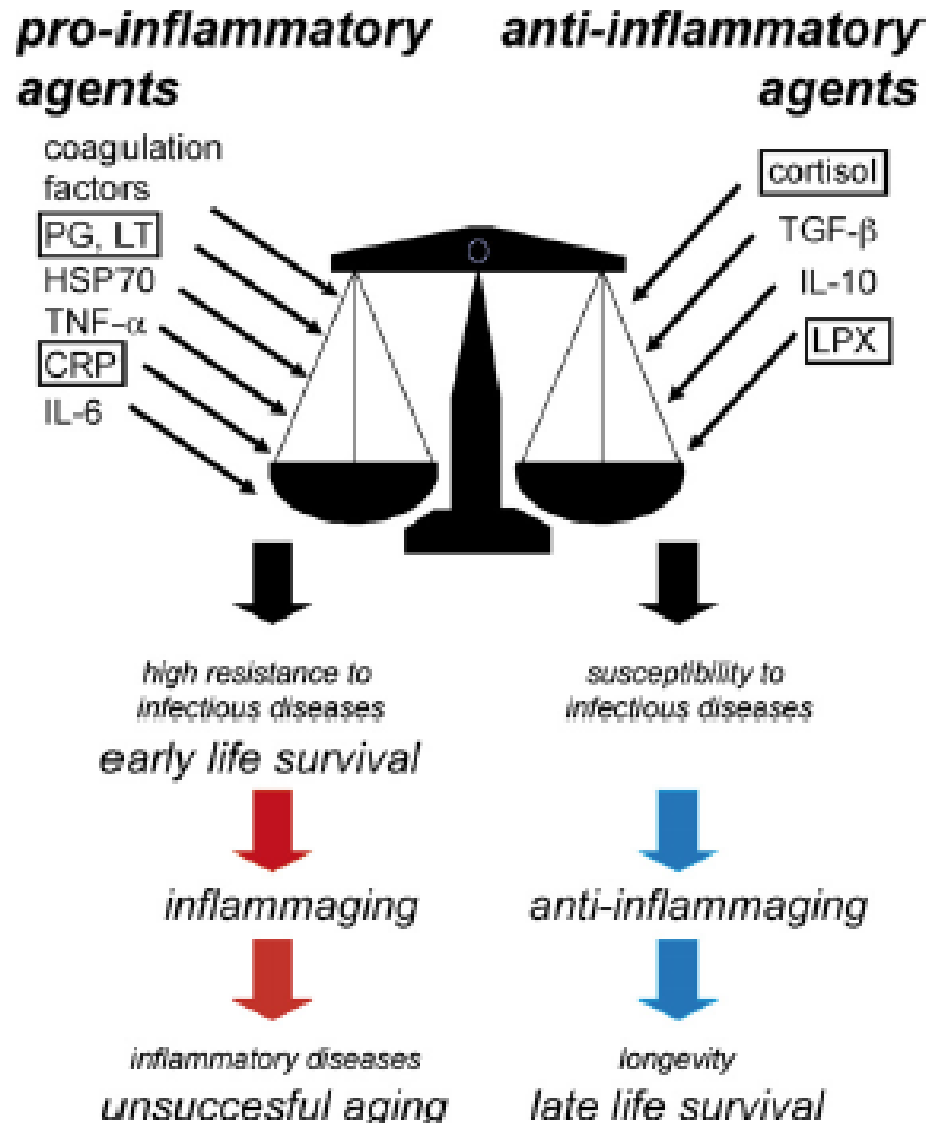
Alterata omeostasi vascolare
Crescita e proliferazione
VSMC
Alterazioni microcircolo

INFIAMMAZIONE VASCOLARE

↑ aumentato rilascio citokine
e chemokine
↑ molecole di adesione
↓ neovasi

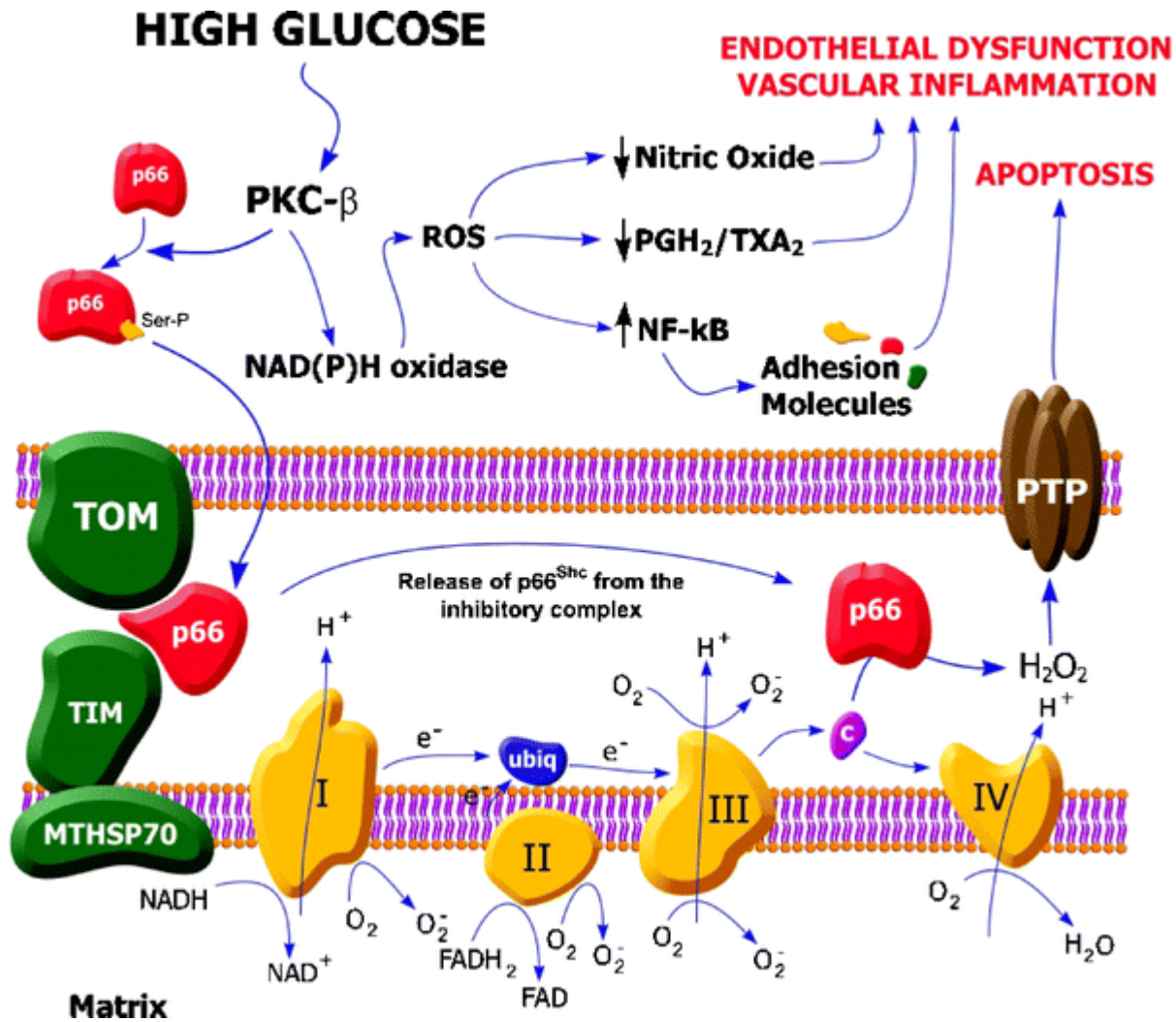
ATEROSCLEROSI ACCELERATA

Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans (Franceschi et al. 2006)

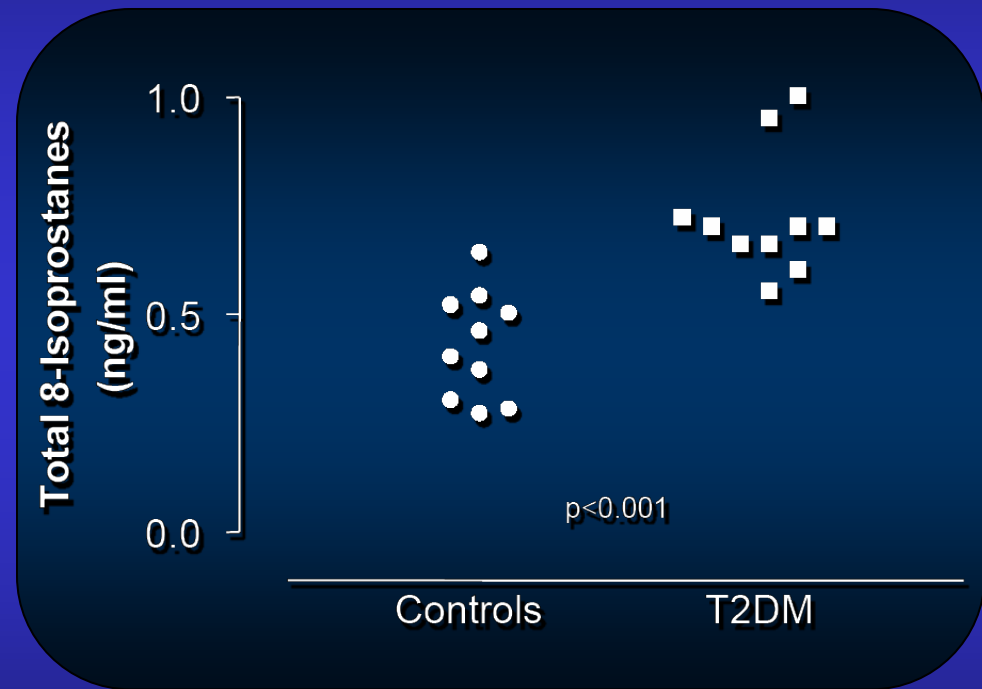
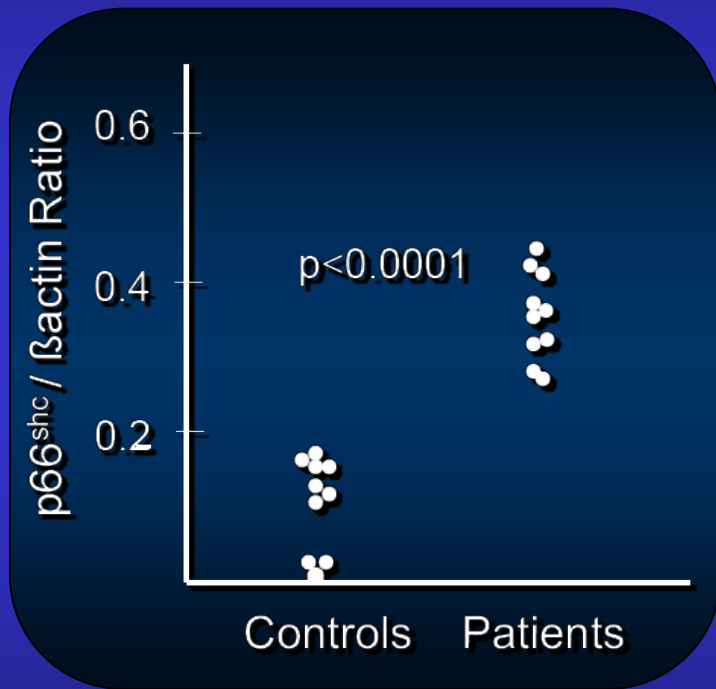


Topi p66^{shc} knock-out:

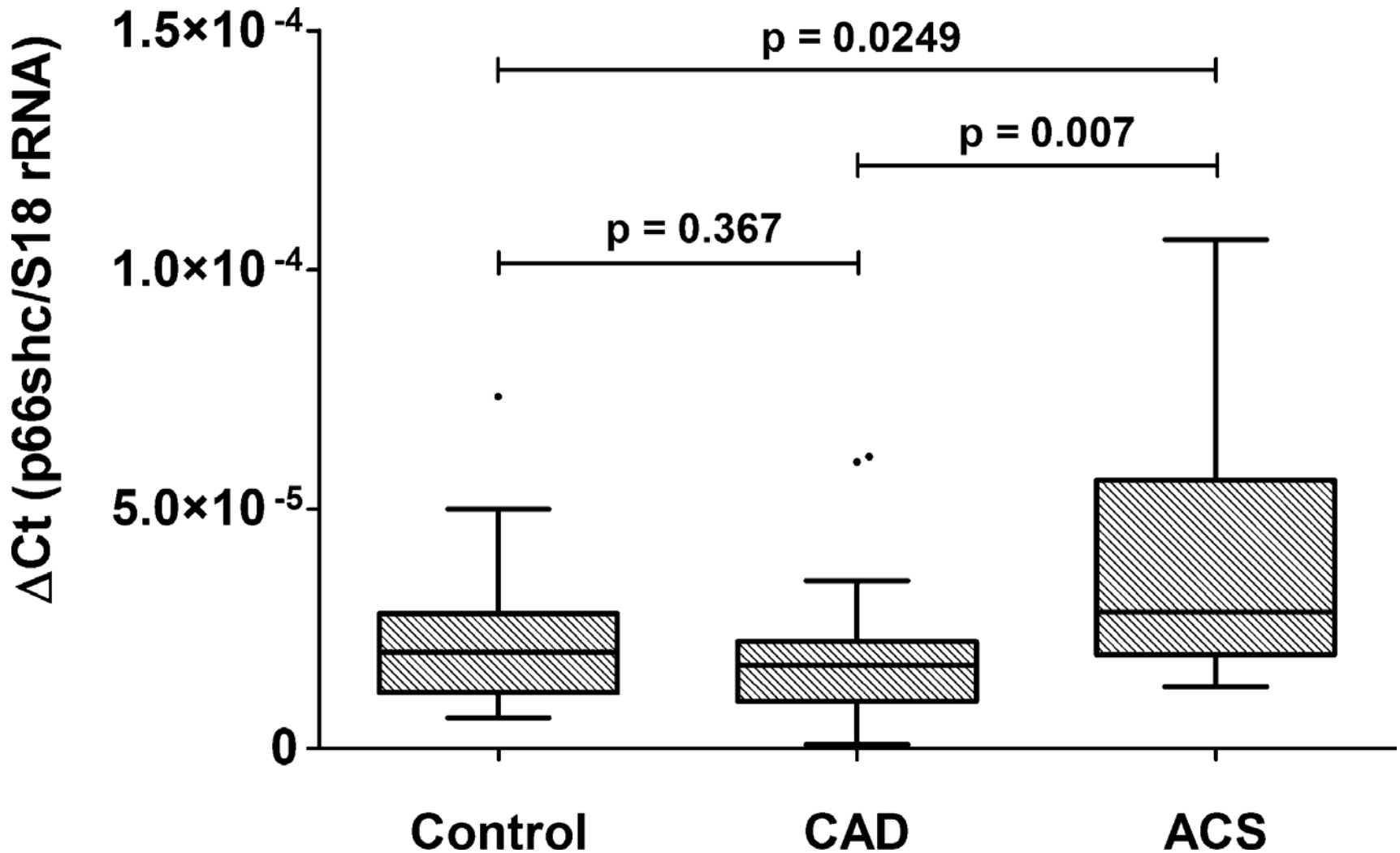
- prolungamento della durata della vita**
- ridotta produzione di ossidanti intracellulari**
- aumento della resistenza allo stress ossidativo**

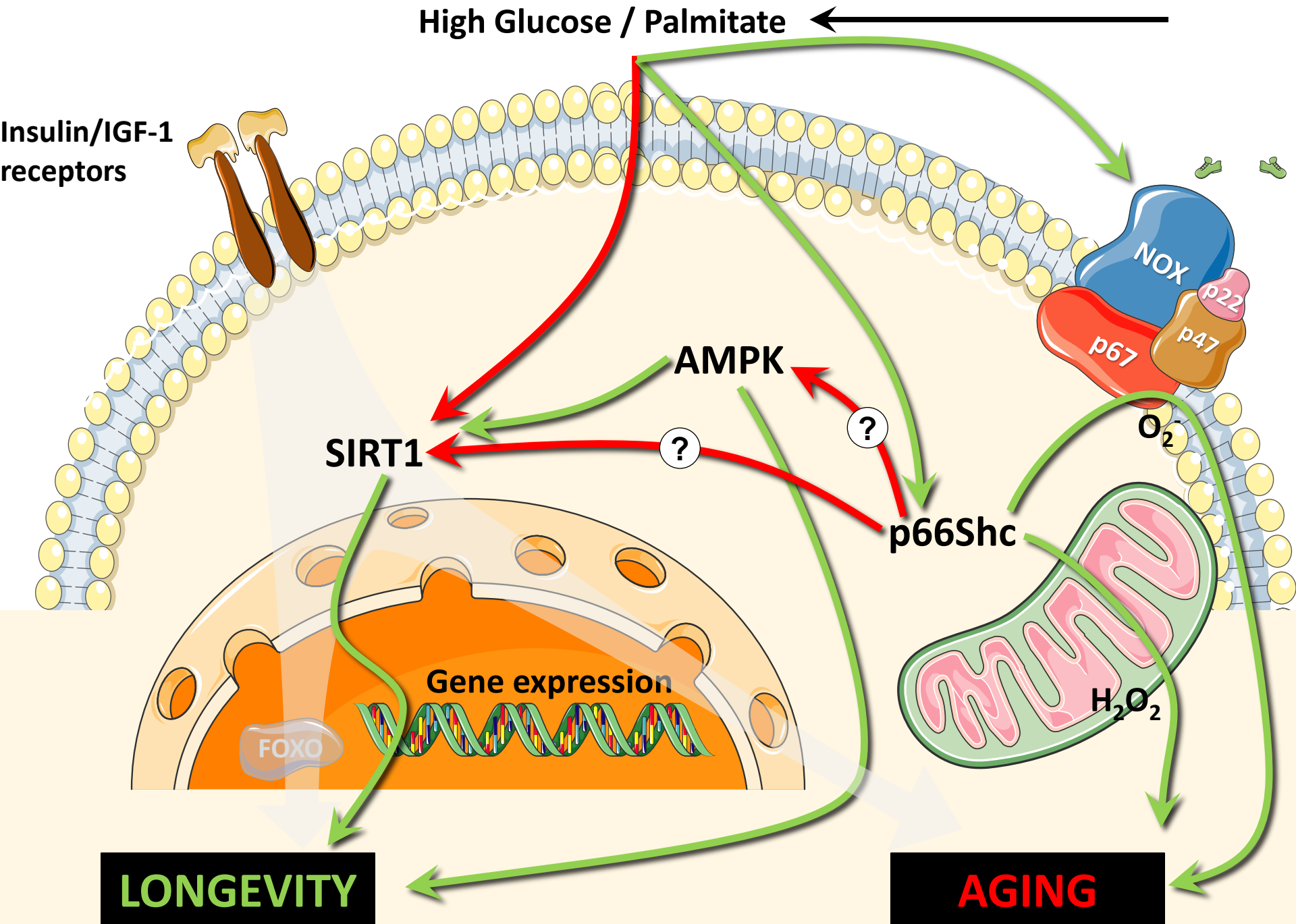


Diabetes Induces p66shc Gene Expression in Human Peripheral Blood Mononuclear Cells: Relationship With Oxidative Stress.

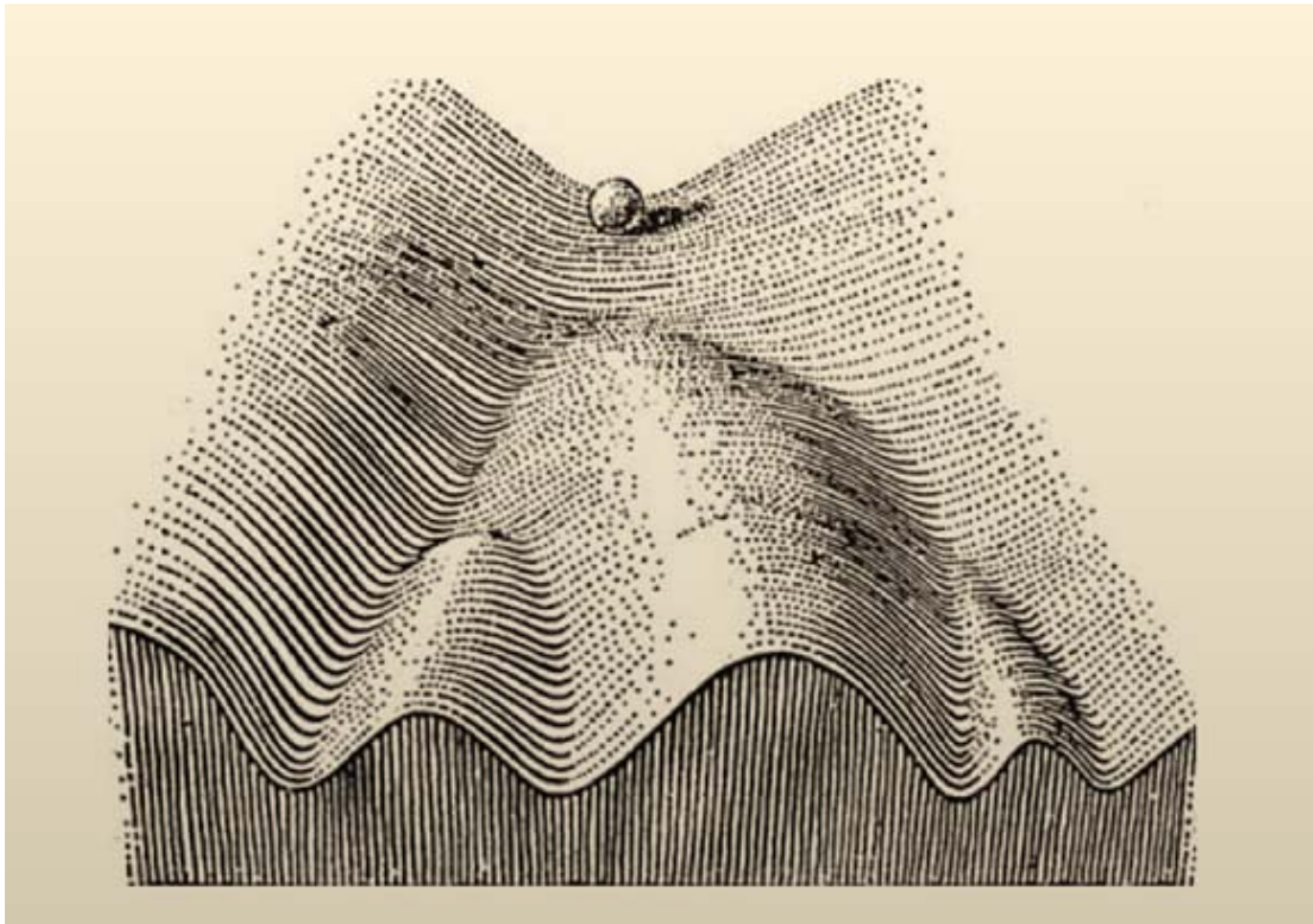


p66Shc mRNA expression, relative to expression of 18S rRNA, in PBMNC from angiographically confirmed CAD-free controls, stable CAD patients and patients with ACS. (Franzeck et al)





Waddington's Classical Epigenetic Landscape (Waddington 1957)

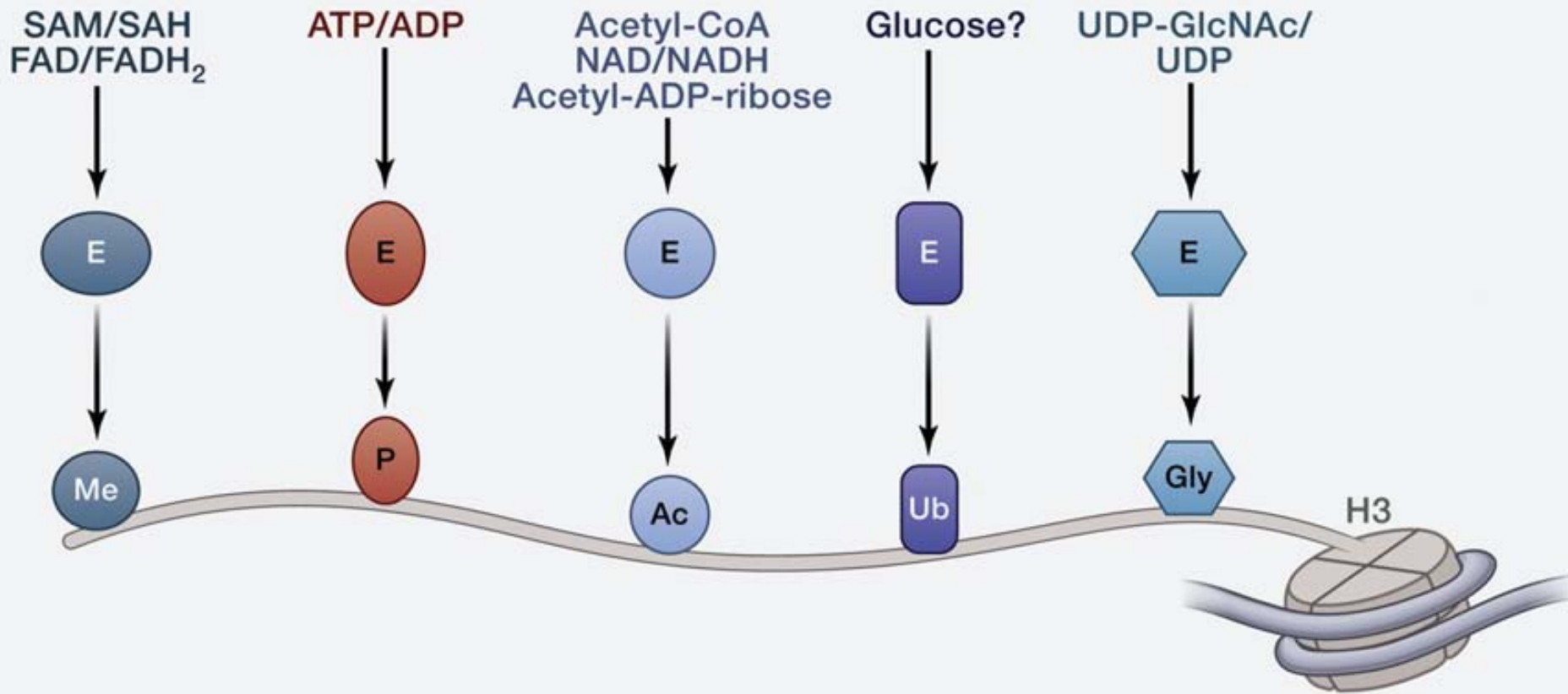


Epigenetics is a bridge between genotype and phenotype. A phenomenon that changes the final outcome of a locus or chromosome without changing the underlying DNA sequence.

Chromatin-Remodeling Enzymes

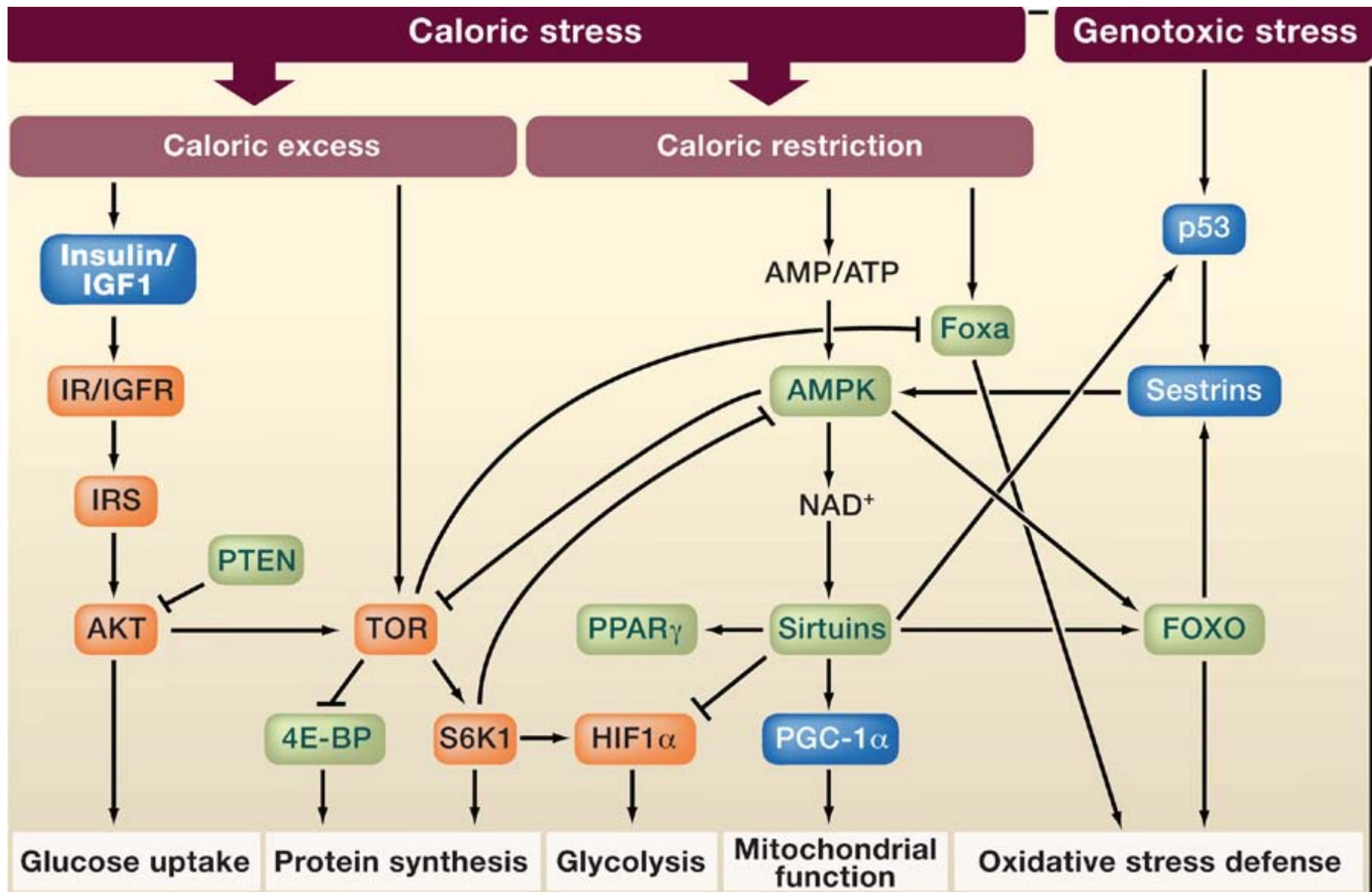
“Sense” Cellular Metabolism

(Katada et al. 2012)

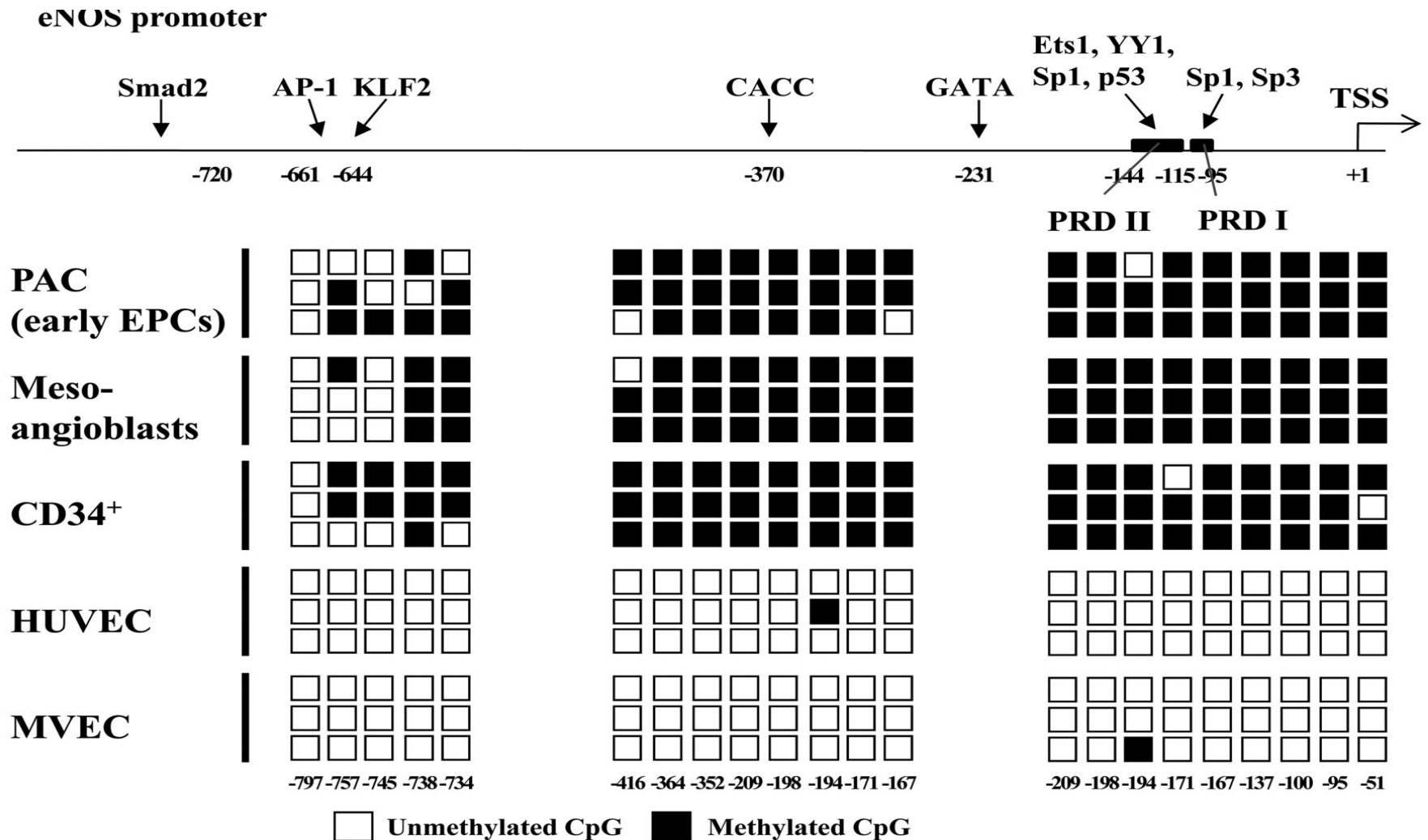


Metabolic Network to Longevity

(Houtkooper et al.)



DNA methylation status of endothelial nitric oxide synthase (eNOS) 5-flanking region in vasculogenic progenitor cells (*Ohtani et al. 2011*)



Histone H3 post-transcriptional alterations induced by hyperglycemia and diabetes mellitus

(Pirola et al.)

Hyperglycemic variability
in primary aortic endothelial cells

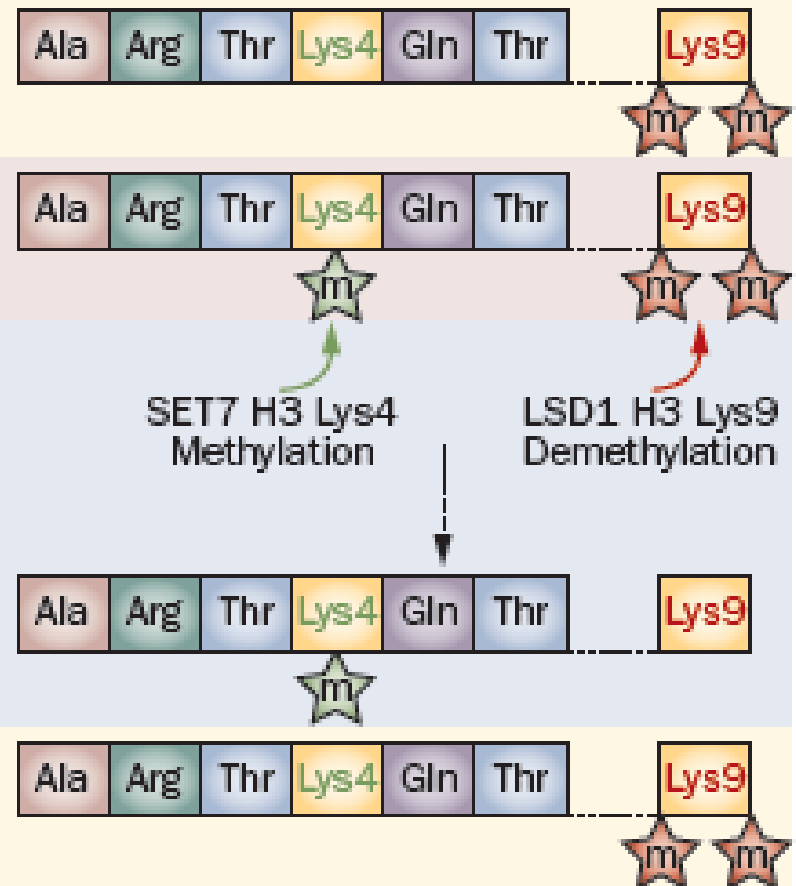
16h Low glucose

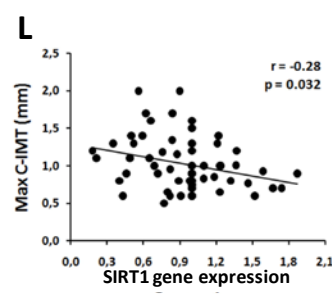
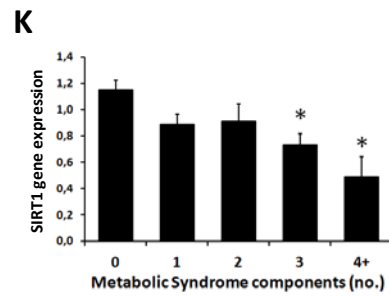
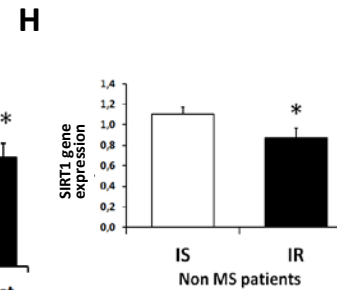
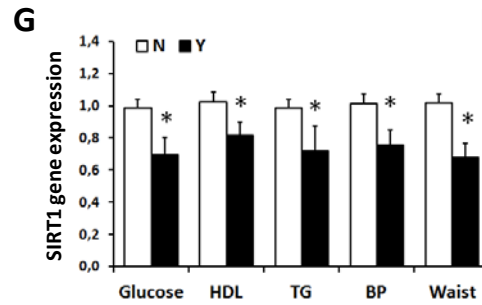
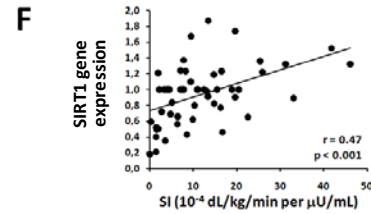
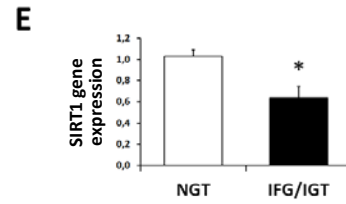
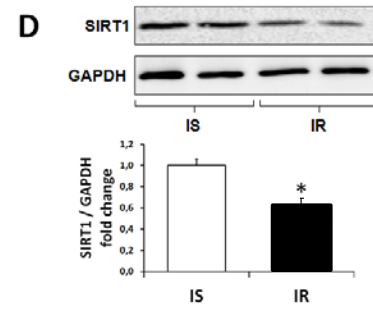
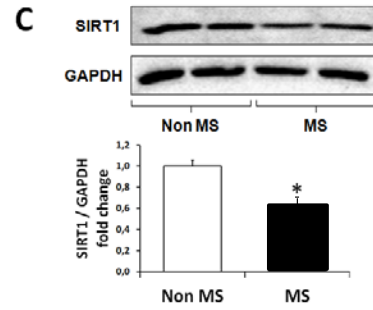
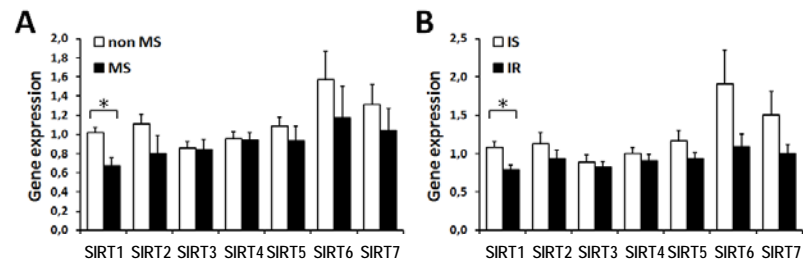
16h Transient high glucose

Return to low glucose up to 6 days

7 day Low glucose

Changes in histone
H3 Lys4 and H3 Lys9 modification





Endothelial cell apoptosis and -regeneration

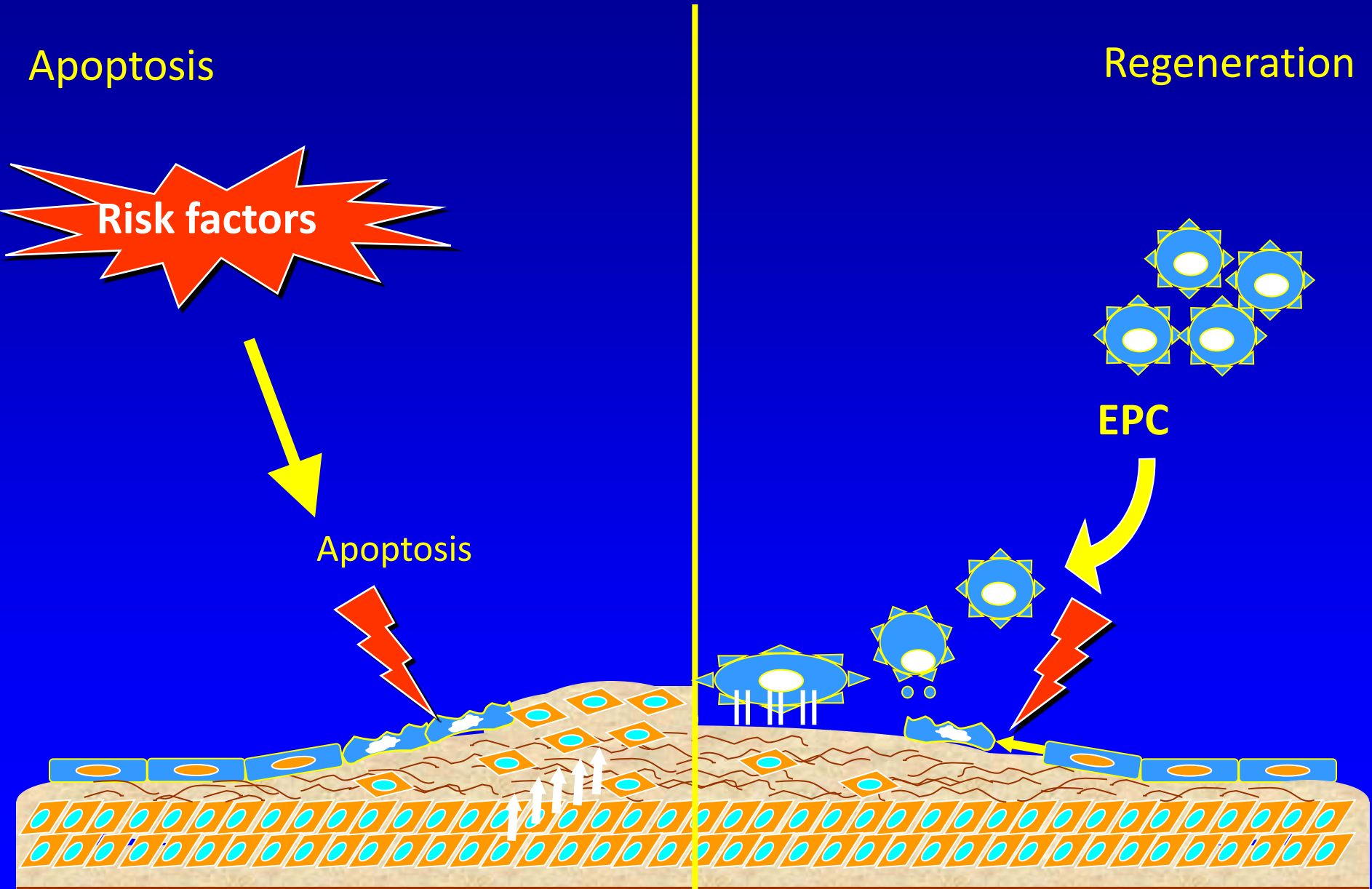
Apoptosis

Regeneration

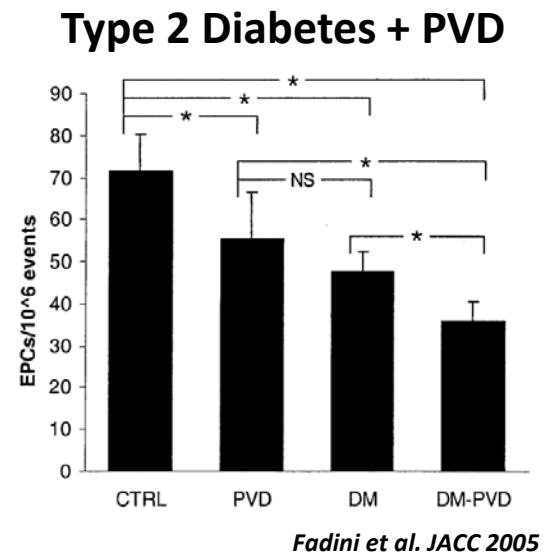
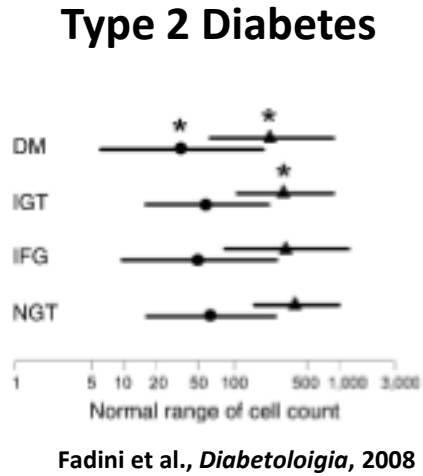
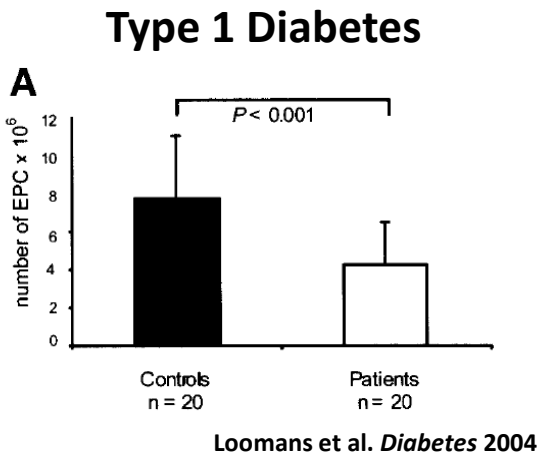
Risk factors

Apoptosis

EPC



Diabetic patients had reduced level of circulating endothelial progenitors



EPC defect may contribute to vascular complication in diabetes

Diabetic retinopathy is associated with bone marrow neuropathy and a depressed peripheral clock

Julia V. Busik,¹ Maria Tikhonenko,¹ Ashay Bhatwadekar,³ Madalina Opreanu,^{1,2} Nafissa Yakubova,¹ Sergio Caballero,³ Danny Player,⁴ Takahiko Nakagawa,⁴ Aqeela Afzal,³ Jennifer Kielczewski,³ Andrew Sochacki,¹ Stephanie Hasty,¹ Sergio Li Calzi,³ Sungjin Kim,² Shane K. Duclas,⁶ Mark S. Segal,⁴ Dennis L. Guberski,⁶ Walter J. Esselman,² Michael E. Boulton,⁵ and Maria B. Grant³

Diabetes induces bone marrow autonomic neuropathy which depresses circulating progenitors and precedes retinopathy.

Busik et al. JEM 2010

Signals from the Sympathetic Nervous System Regulate Hematopoietic Stem Cell Egress from Bone Marrow

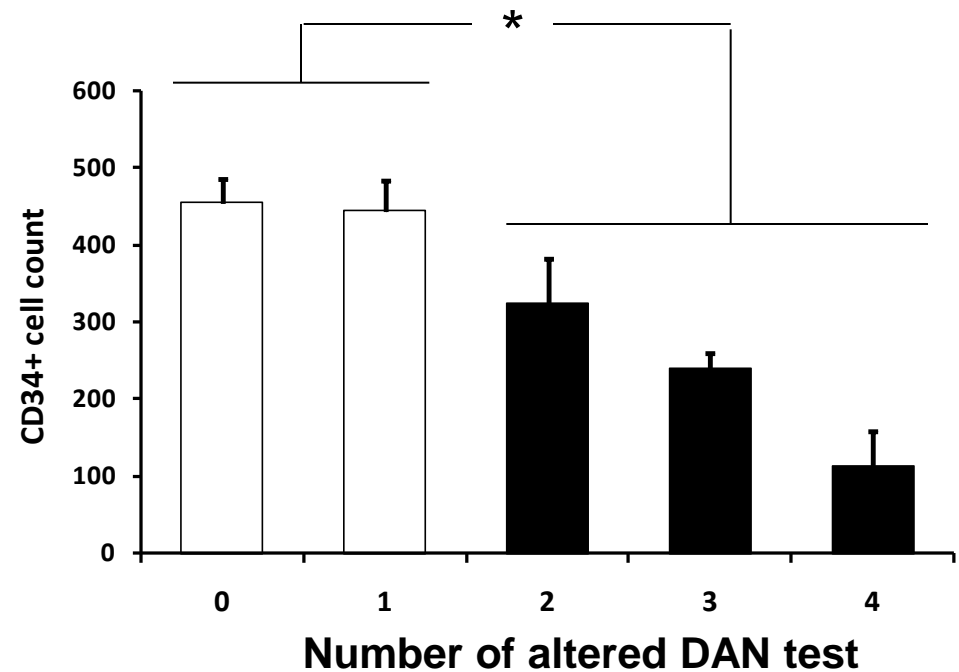
Katayama et al. *Cell* 2006

In humans, diabetic autonomic neuropathy is associated with reduced circulating progenitor cells

**N=100 type 2 diabetic patients,
24 of whom had detectable DAN
(at least 2 altered DAN tests).
Mean age 57, 66% males**

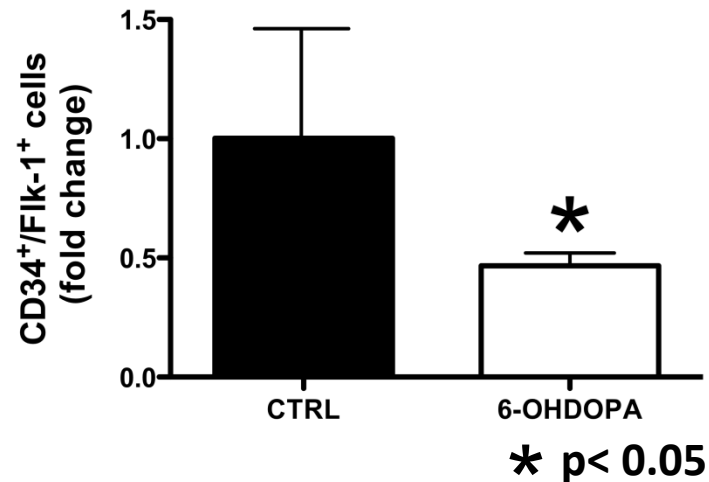
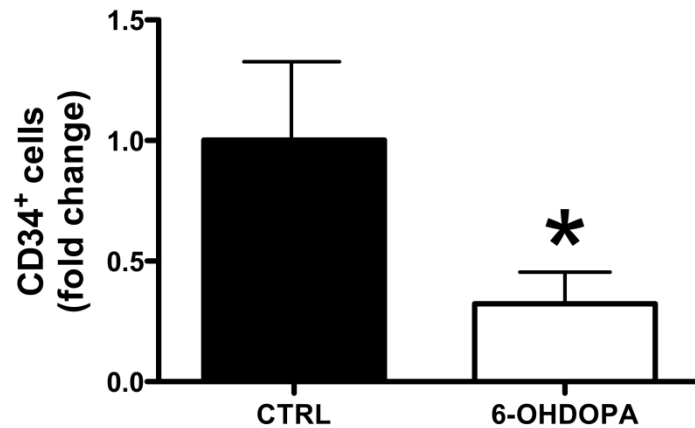
DAN+ vs DAN- patients :

- Higher prevalence of retinopathy;
- Higher HbA1c;
- No difference in diabetes duration, macroangiopathy, adiposity, lipids, therapy;



**Significant negative correlation between
CD34+ cells and number of altered DAN
tests ($r=-0.39$; $p<0.001$)**

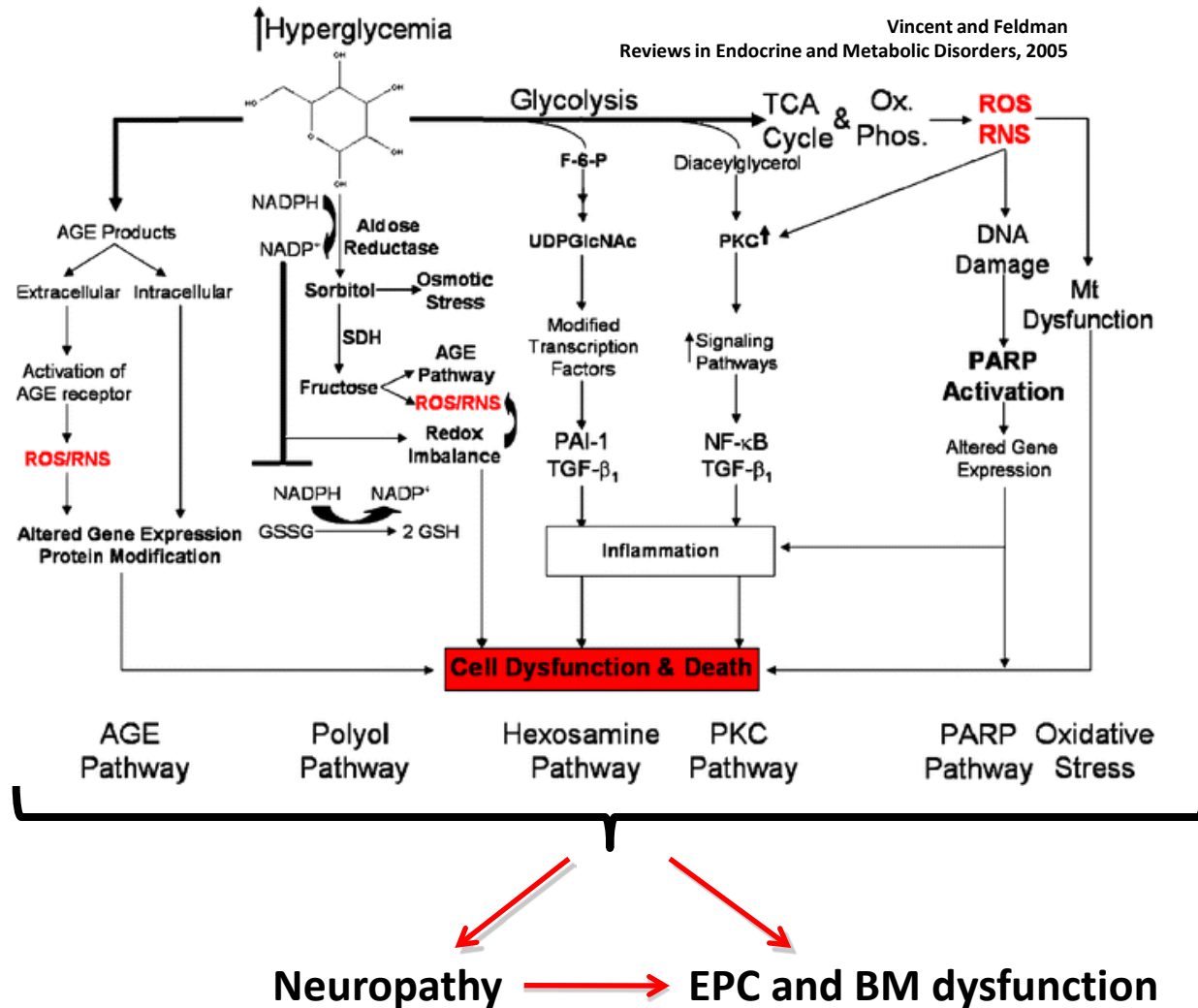
Experimental autonomic neuropathy in mice



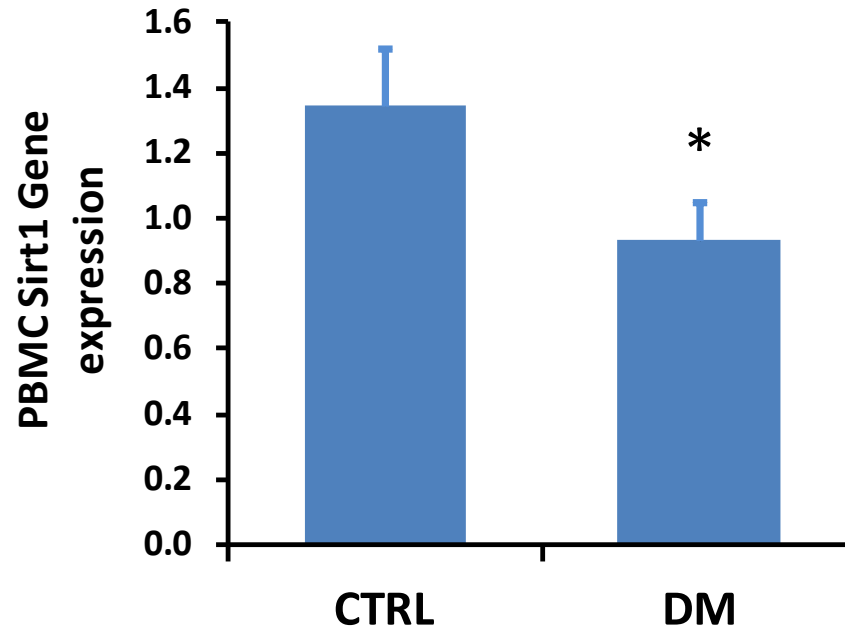
1 month after autonomic denervation, we observed a marked decrease of circulating progenitors.

Autonomic denervation is sufficient to dampen circulating EPC

In diabetes, hyperglycemia and the resulting oxidative stress plays a pivotal role in causing autonomic neuropathy and could affect also endothelial progenitor and bone marrow

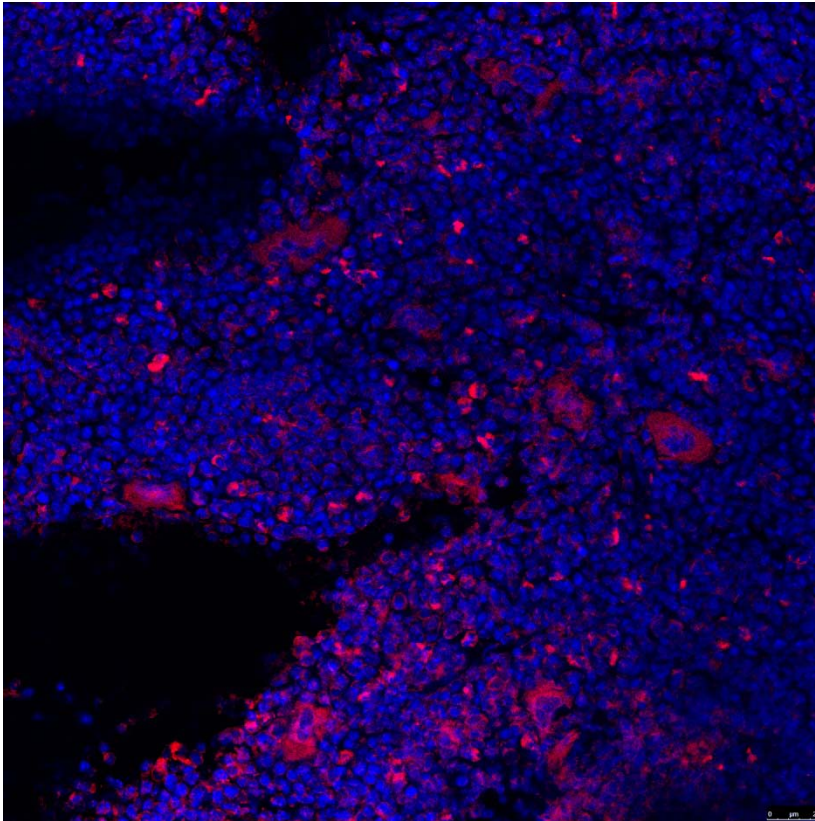


SIRT1 expression is reduced in PBMC of diabetic patients

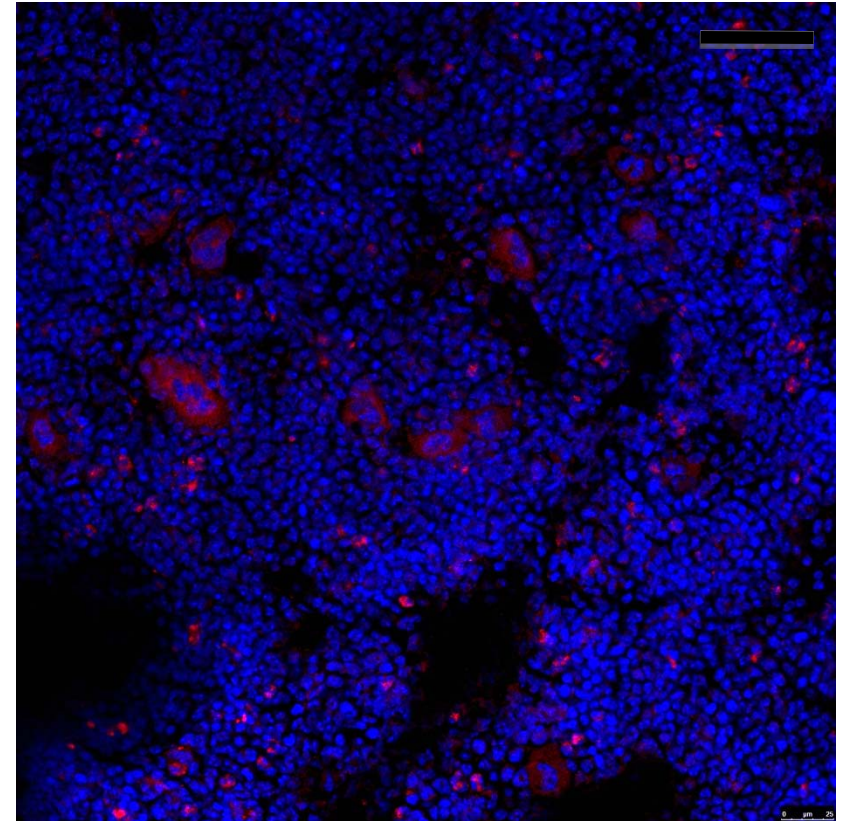


We will explore Sirt1 gene expression in diabetic patients with DAN

SIRT1 expression in the murine bone marrow



CTRL

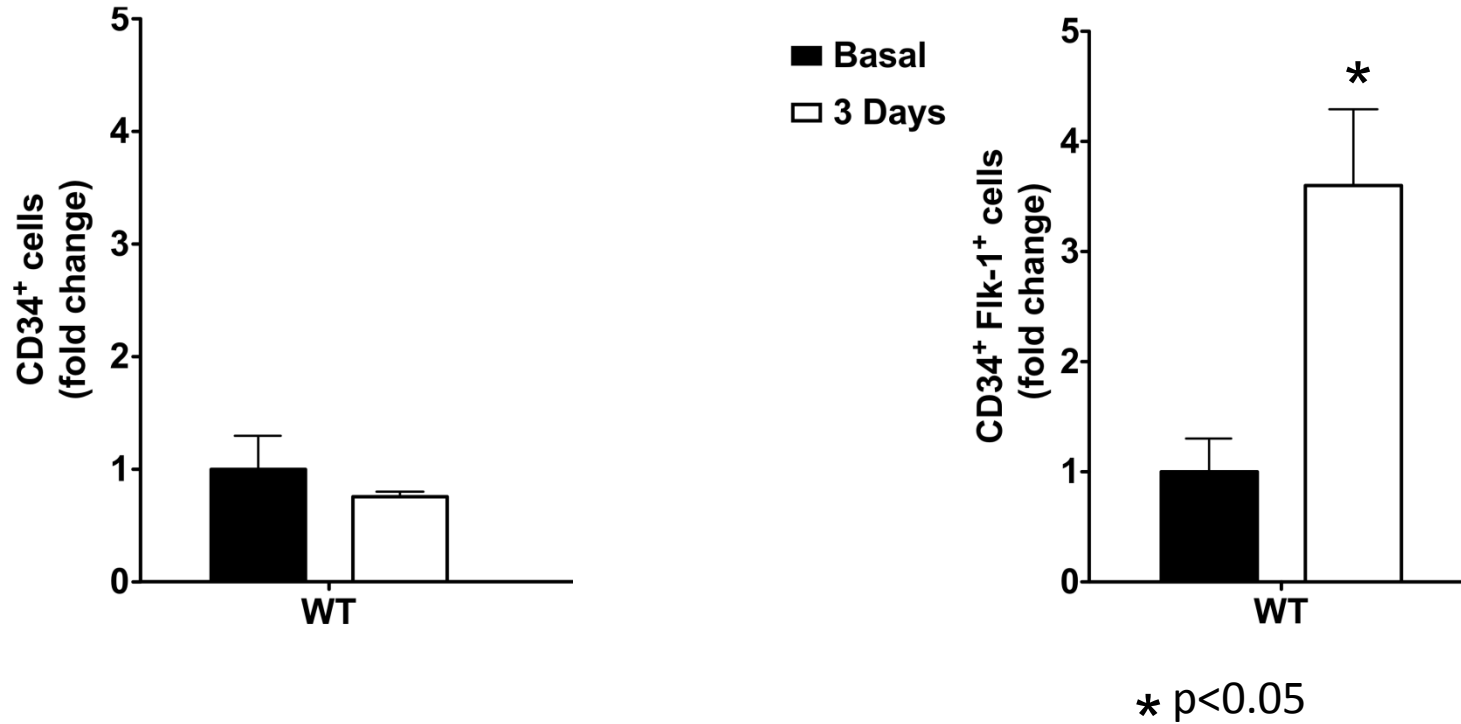


6-OH DOPA

Scale bar: 10 μm

SIRT1 is markedly downregulated in the bone marrow after autonomic denervation

EPC mobilization upon ischemia in mice



VAV-SIRT 1 KO mice do not mobilize EPC upon ischemia

Punti Chiave

Autonomic neuropathy in diabetic patients is strongly associated with **depletion of circulating endothelial progenitor cells**;

Preliminary data in mice suggest that **autonomic neuropathy** within the **bone marrow** account for reduced circulating progenitors;

Autonomic neuropathy is sufficient to **reduced SIRT1** expression within the **bone marrow**;

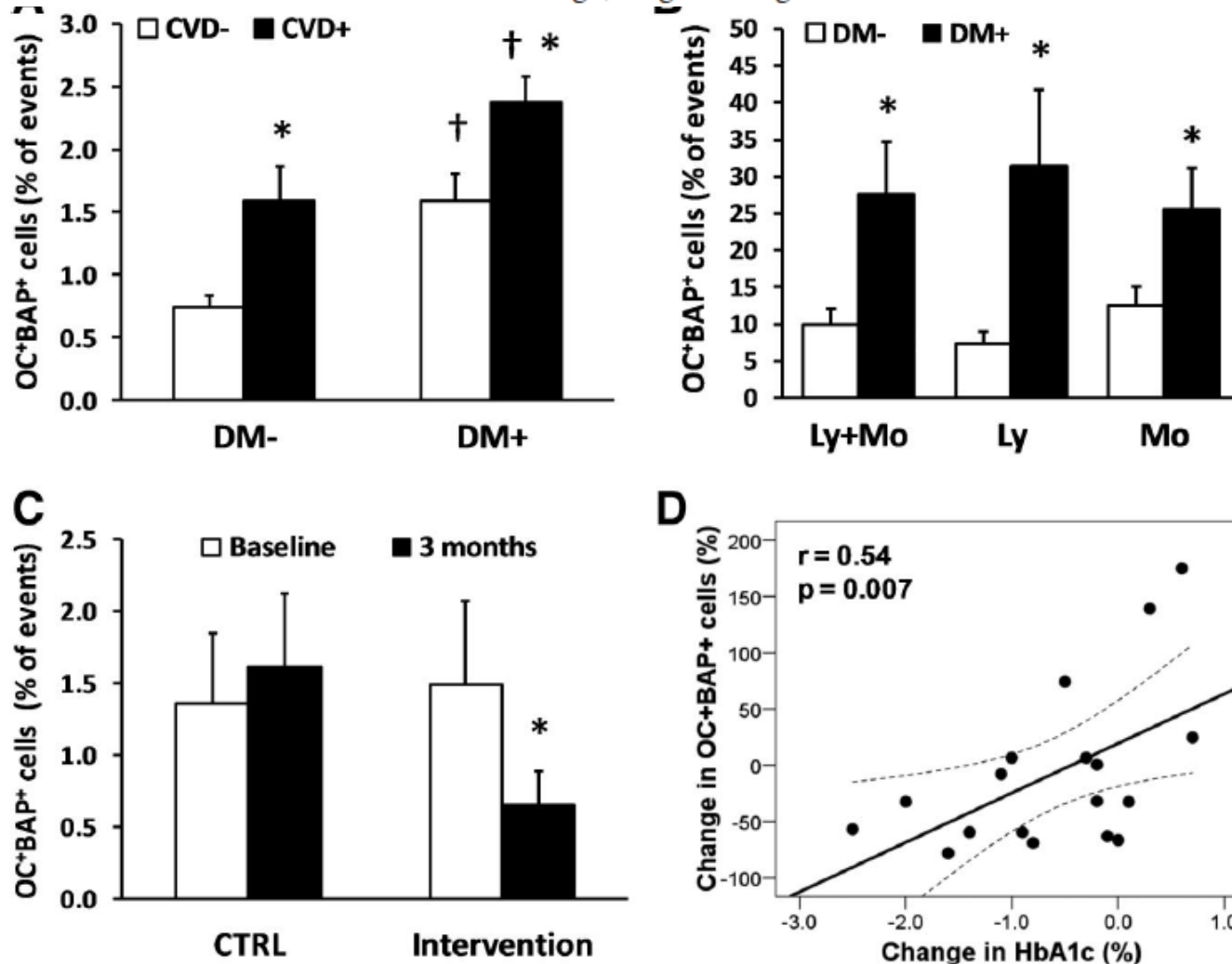
SIRT1 is required for normal trafficking of progenitors from the bone marrow.



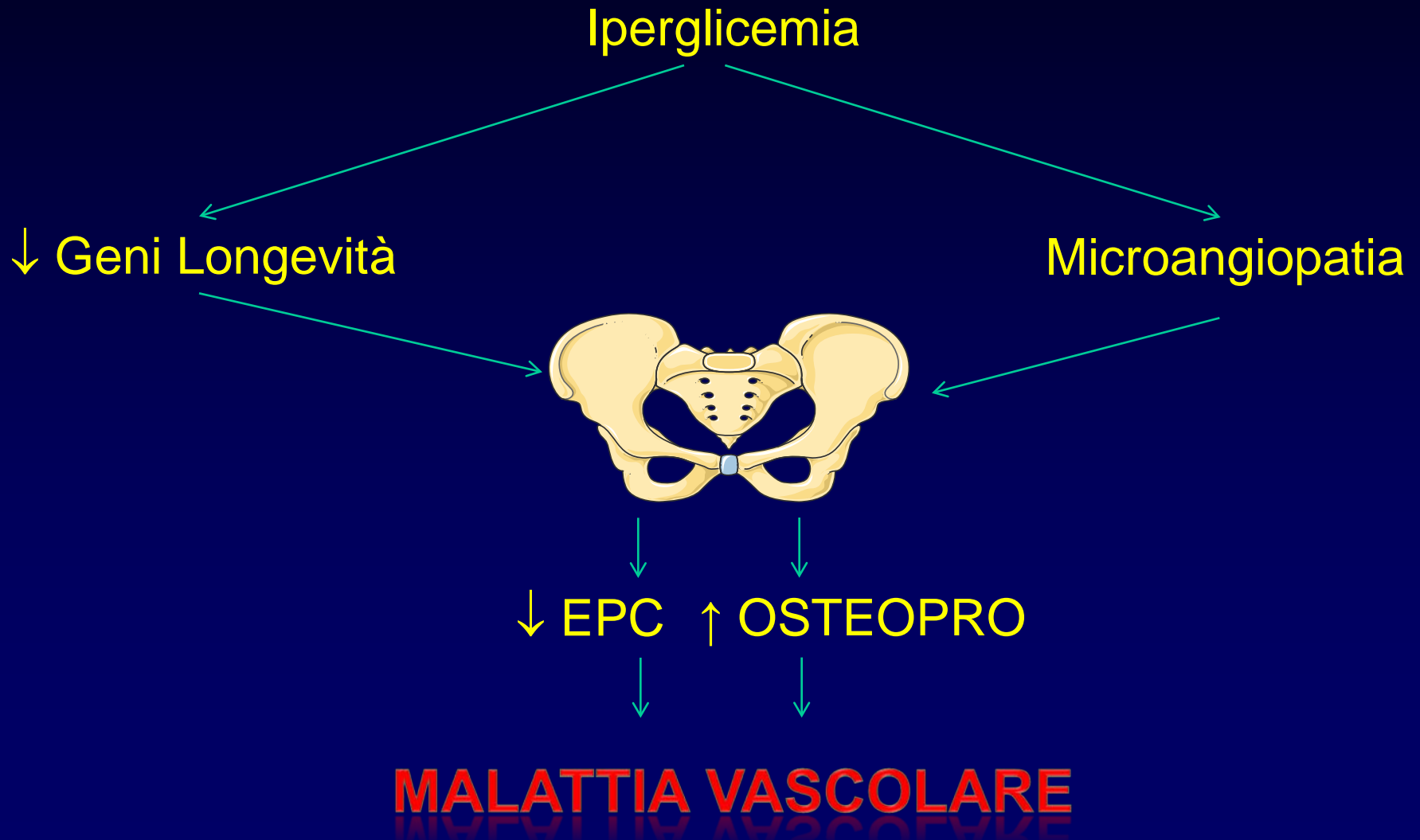
Widespread Increase in Myeloid Calcifying Cells Contributes to Ectopic Vascular Calcification in Type 2 Diabetes

(*Circ Res.* 2011;108:1112-1121.)

Gian Paolo Fadini, Mattia Albiero, Lisa Menegazzo, Elisa Boscaro, Saula Vigili de Kreutzenberg, Carlo Agostini, Anna Cabrelle, Gianni Binotto, Marcello Rattazzi, Elisa Bertacco, Roberta Bertorelle, Lorena Biasini, Monica Mion, Mario Plebani, Giulio Ceolotto, Annalisa Angelini, Chiara Castellani, Mirko Menegolo, Franco Grego, Stefanie Dimmeler, Florian Seeger, Andreas Zeiher, Antonio Tiengo, Angelo Avogaro



Fisiopatologia della malattia vascolare nel diabete mellito: nuovo paradigma



Aknowledgments

Experimental Diabetology Lab, VIMM
Metabolic Division, DMCS

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Giulio Ceolotto

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Clinical Immunology, DMCS

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Molecular Cardiology Lab, VIMM

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Frankfurt, Germany

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