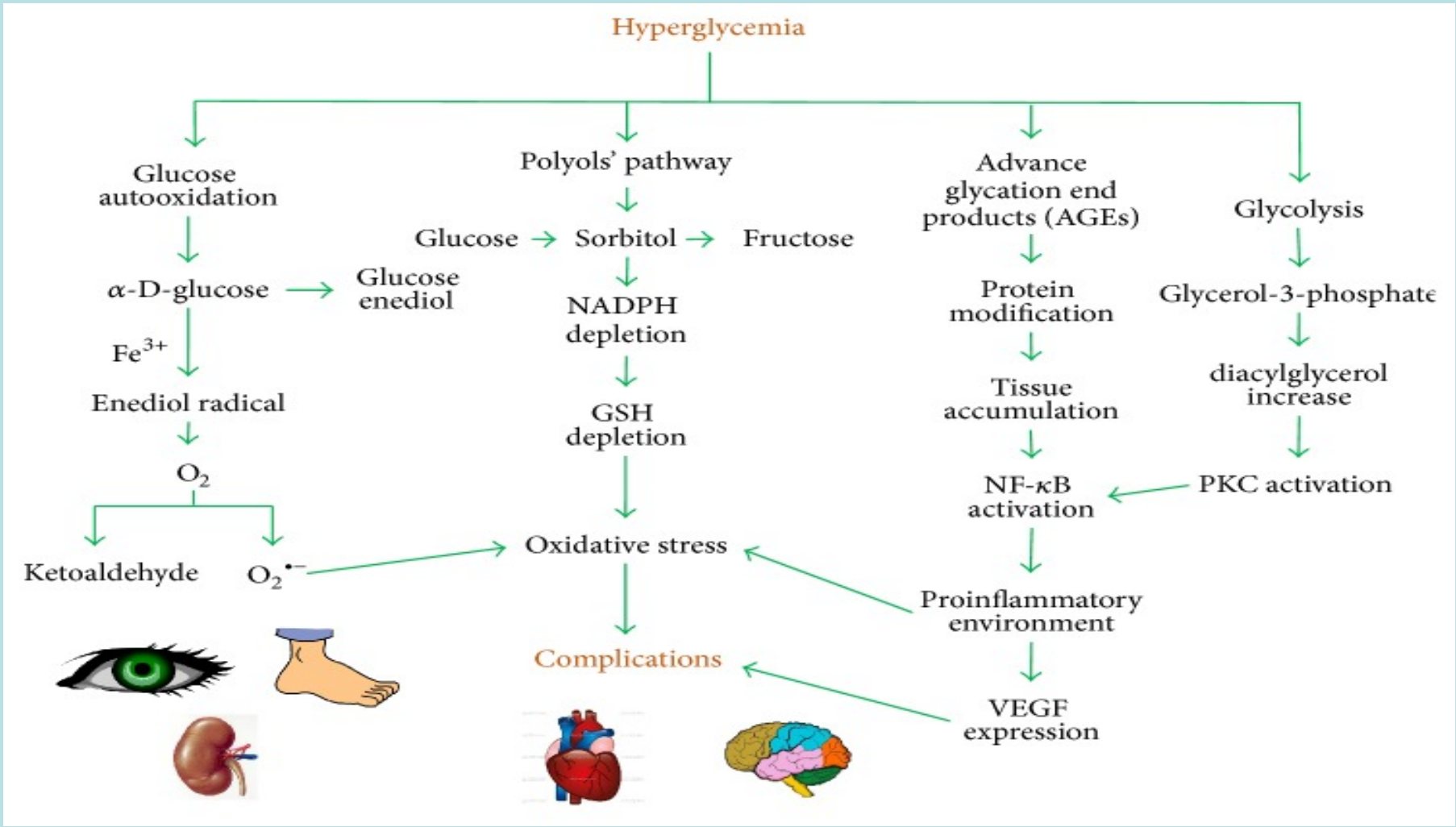
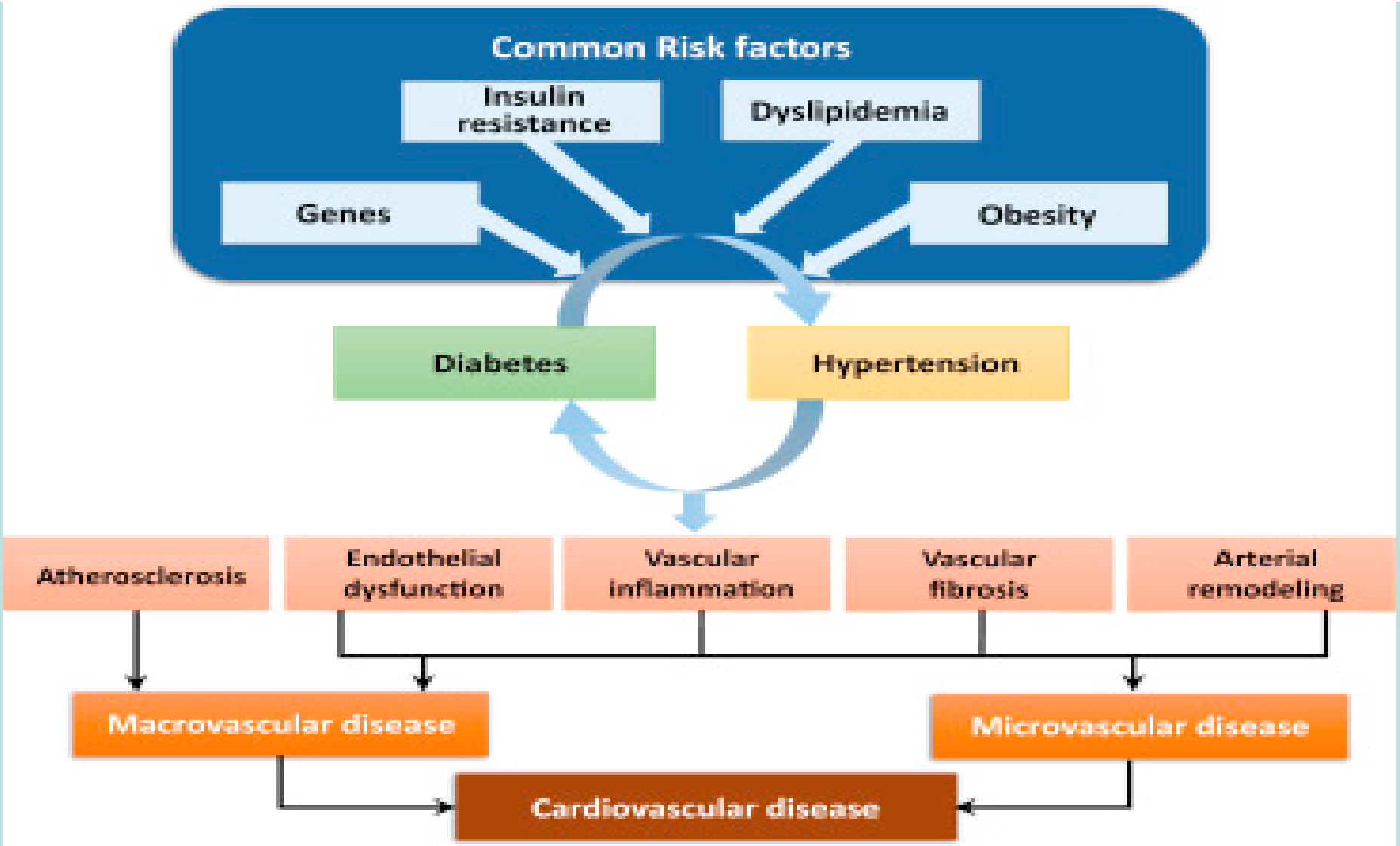
BIOCHEMICAL BASIS OF DIABETIC COMPLICATIONS: AN OVERVIEW

Prof.Dr.Nuray ARI, 2018

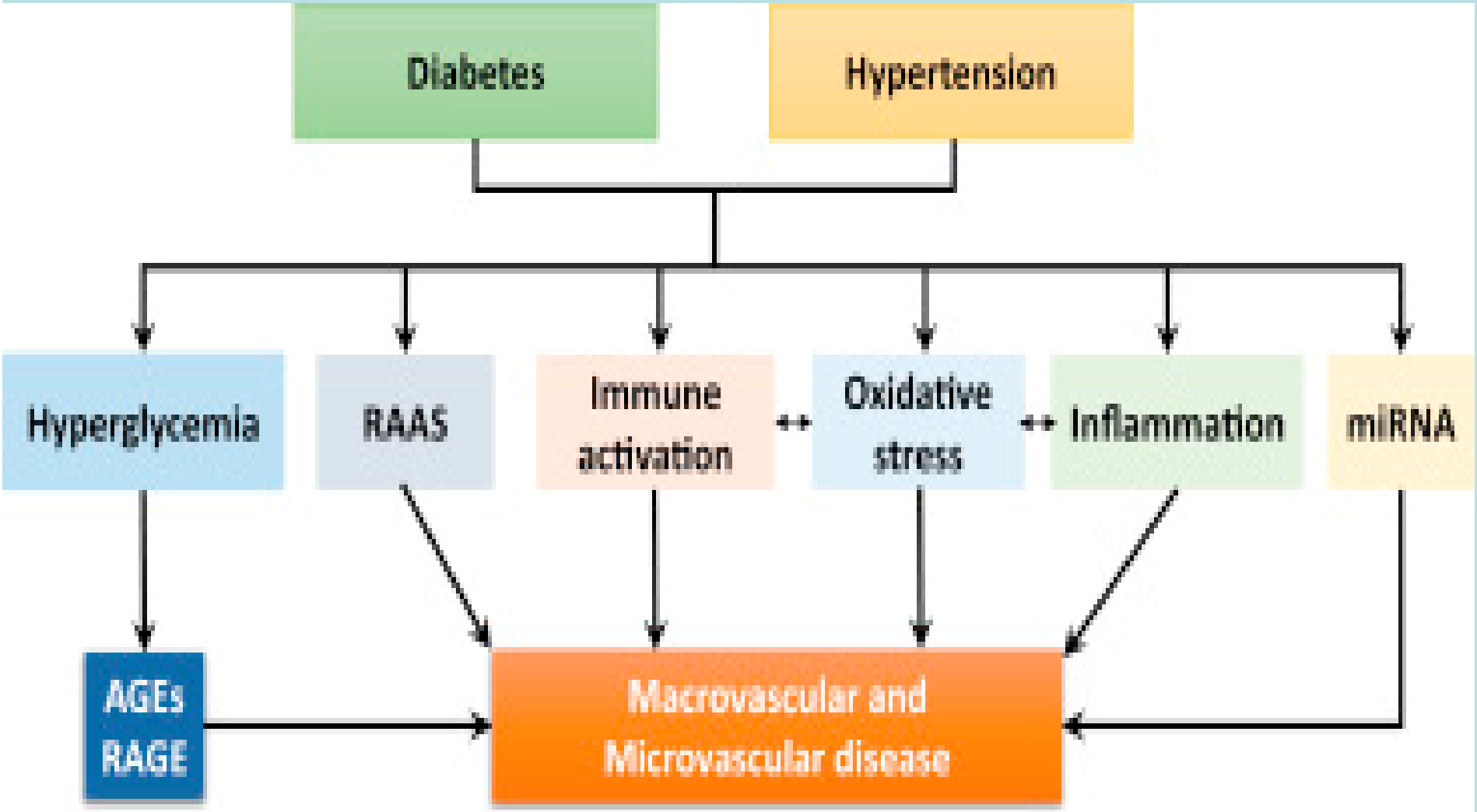


The main pathways triggered by hyperglycemia include glucose autooxidation and constant activation of polyols' pathway and formation of advance glycation end products (AGEs) and excessive glycolysis. With the constant activation of these pathways, living cells and tissues are damaged, mainly by impairment of target protein function, increase in oxidative stress, and activation of signal transduction pathways, leading to the imbalance of normal physiological functions and therefore the development of diabetic complications. **Current Advances in the Biochemical and Physiological Aspects of the Treatment of Type 2 Diabetes Mellitus with Thiazolidinediones. Alemán-González-Duhart D et al.**



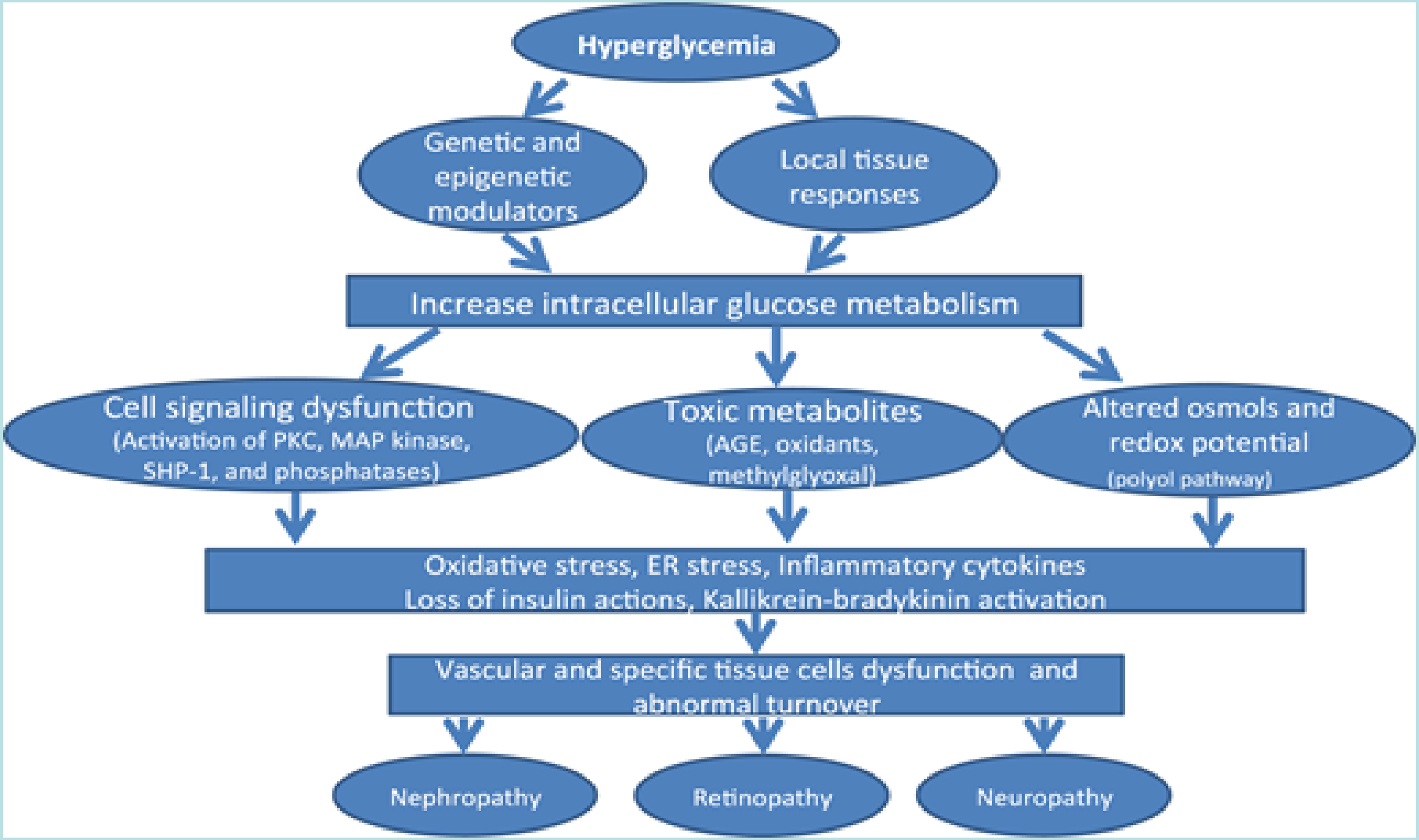
Vascular processes whereby diabetes and hypertension predispose to cardiovascular disease

Can J Cardiol. 2017 Dec 11. pii: S0828-282X(17)31214-X. doi: 10.1016/j.cjca.2017.12.005.[Epub ahead of print] **Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms.**Petrie JR et al.



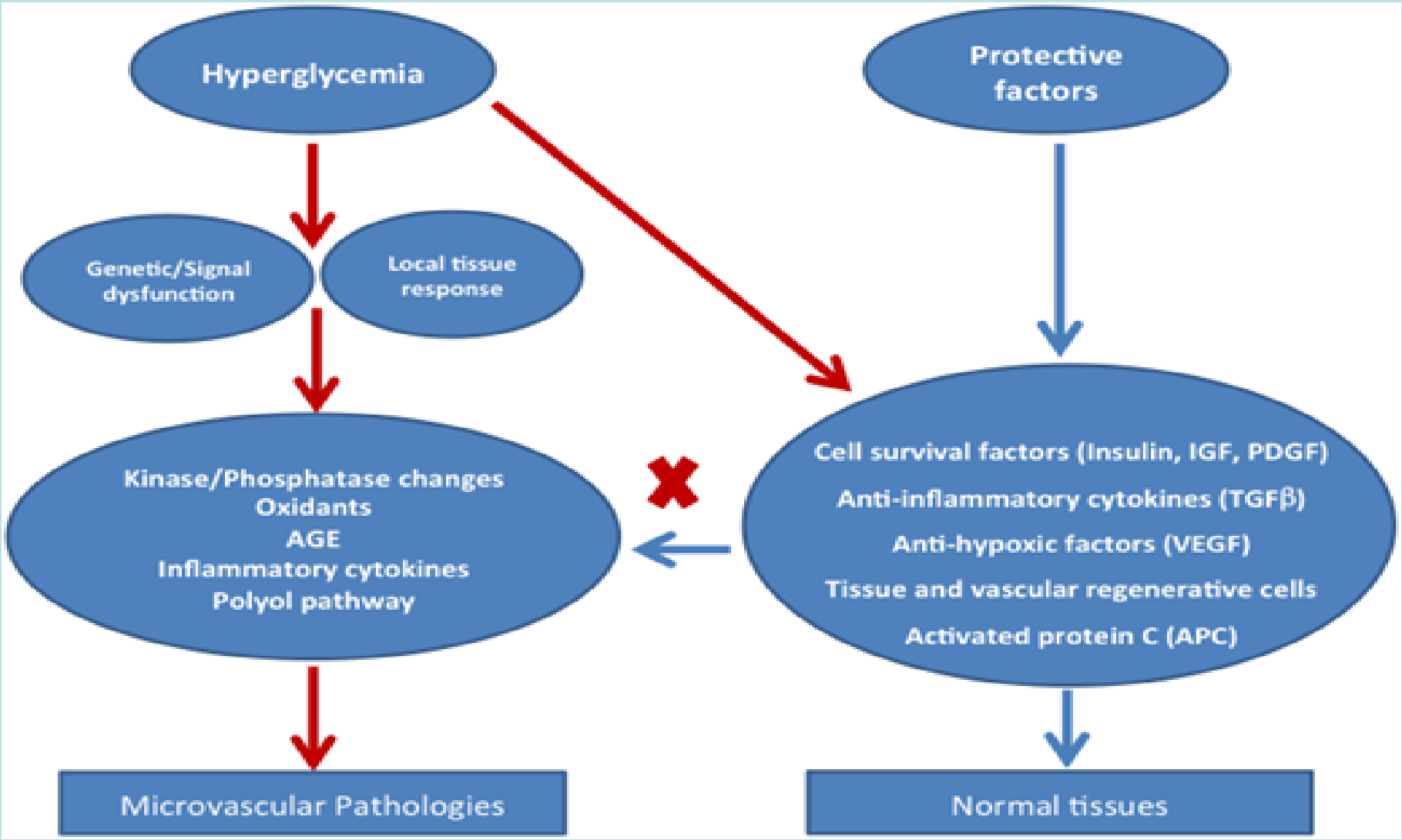
Putative mechanisms whereby diabetes and hypertension cause vascular disease. Immune cell activation and inflammation are mediated through oxidative stress.

Can J Cardiol. 2017 Dec 11. pii: S0828-282X(17)31214-X. doi: 10.1016/j.cjca.2017.12.005.[Epub ahead of print]
Diabetes, Hypertension, and Cardiovascular Disease: Clinical Insights and Vascular Mechanisms. Petrie JR et al.



Schema of hyperglycemia's induced pathways to microvascular complications. MAP, mitogen-activated protein.

J Clin Endocrinol Metab. 2017,102(12):4343-4410. doi: 10.1210/jc.2017-01922. **Diabetic Microvascular Disease: An Endocrine Society Scientific Statement.** Barrett EJ et al.



Interplay of hyperglycemia's toxic mechanisms and tissues' endogenous protective properties. IGF, insulinlike growth factor.

J Clin Endocrinol Metab. 2017 Dec 1;102(12):4343-4410. doi: 10.1210/jc.2017-01922. **Diabetic Microvascular Disease: An Endocrine Society Scientific Statement.** Barrett EJ et al.

Obes Metab. 2018 Feb 8. doi: 10.1111/dom.13247. [Epub ahead of print]

Cardiovascular biomarkers in clinical studies of type 2 diabetes.

Baldassarre MPA, Andersen A, Consoli A, Knop FK, Vilsbøll T.

Abstract

When planning cardiovascular (CV) studies in type 2 diabetes (T2D), selection of CV biomarkers is a complex issue. Because the pathophysiology of CV disease (CVD) in T2D is multifactorial, ideally, the selected CV biomarkers should cover all aspects of the known pathophysiology of the disease. This will allow the researcher to distinguish between effects on different aspects of the pathophysiology. To this end, we discuss a host of biomarkers grouped according to their role in the pathogenesis of CVD, namely: (1) cardiac damage biomarkers; (2) inflammatory biomarkers; and (3) novel biomarkers (oxidative stress and endothelial dysfunction biomarkers). Within each category we present the best currently validated biomarkers, with special focus on the population of interest (people with T2D). For each individual biomarker, we discuss the physiological role, validation in the general population and in people with T2D, analytical methodology, modifying factors, effects of glucose-lowering drugs, and interpretation. This approach will provide clinical researchers with the information necessary for planning, conducting and interpreting results from clinical trials. Furthermore, a systematic approach to selection of CV biomarkers in T2D research will improve the quality of future research.

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Diabetic Microvascular Disease: An Endocrine Society Scientific Statement.

Barrett EJ, Liu Z, et al. J Clin Endocrinol Metab. 2017 Dec 1;102(12):4343-4410. doi: 10.1210/jc.2017-01922

Abstract

Both type 1 and type 2 diabetes adversely affect the microvasculature in multiple organs. Our understanding of the genesis of this injury and of potential interventions to prevent, limit, or reverse injury/dysfunction is continuously evolving. This statement reviews biochemical/cellular pathways involved in facilitating and abrogating microvascular injury. The statement summarizes the types of injury/dysfunction that occur in the three classical diabetes microvascular target tissues, the eye, the kidney, and the peripheral nervous system; the statement also reviews information on the effects of diabetes and insulin resistance on the microvasculature of skin, brain, adipose tissue, and cardiac and skeletal muscle. Despite extensive and intensive research, it is disappointing that microvascular complications of diabetes continue to compromise the quantity and quality of life for patients with diabetes. Hopefully, by understanding and building on current research findings, we will discover new approaches for prevention and treatment that will be effective for future generations.

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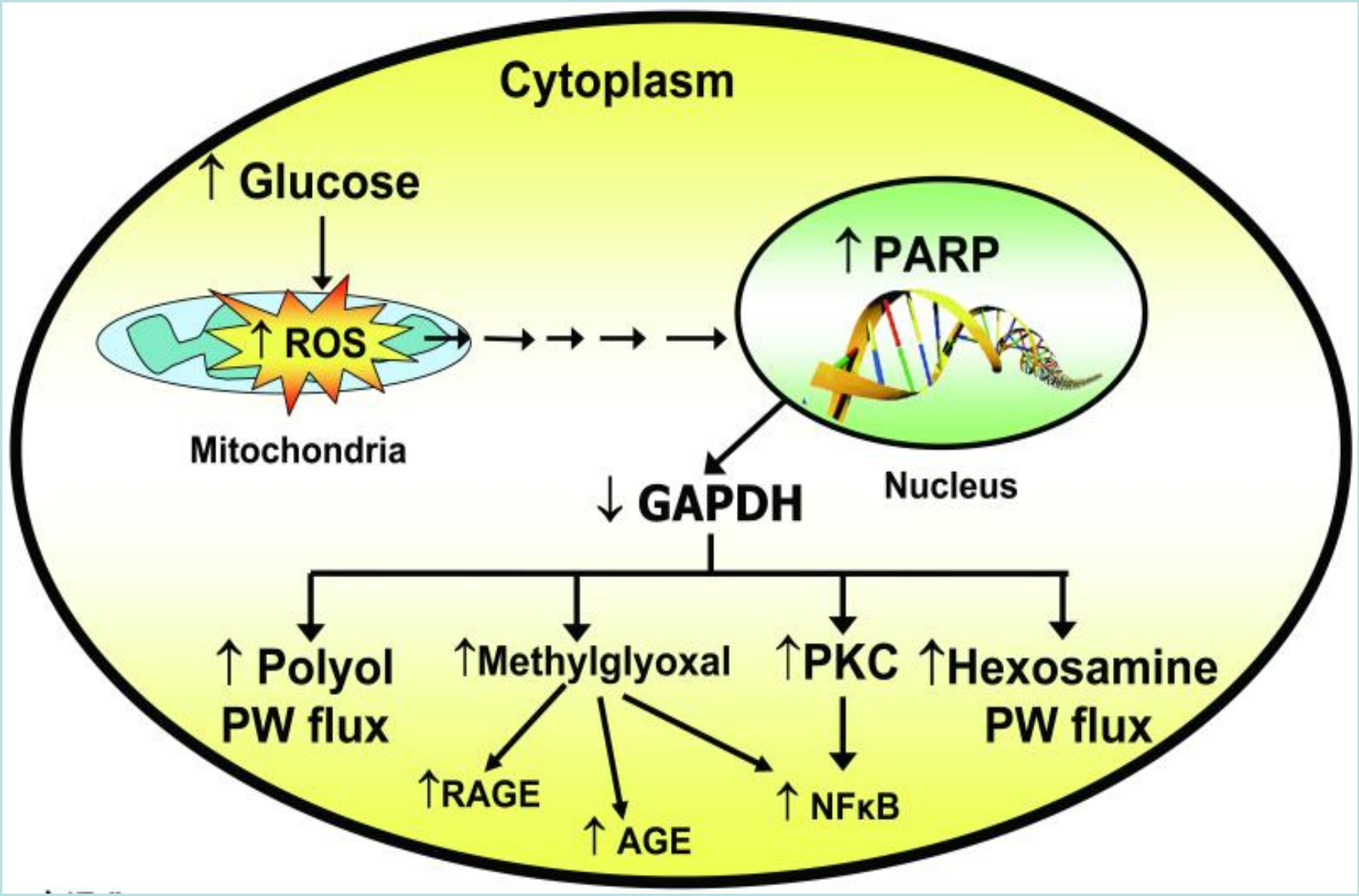
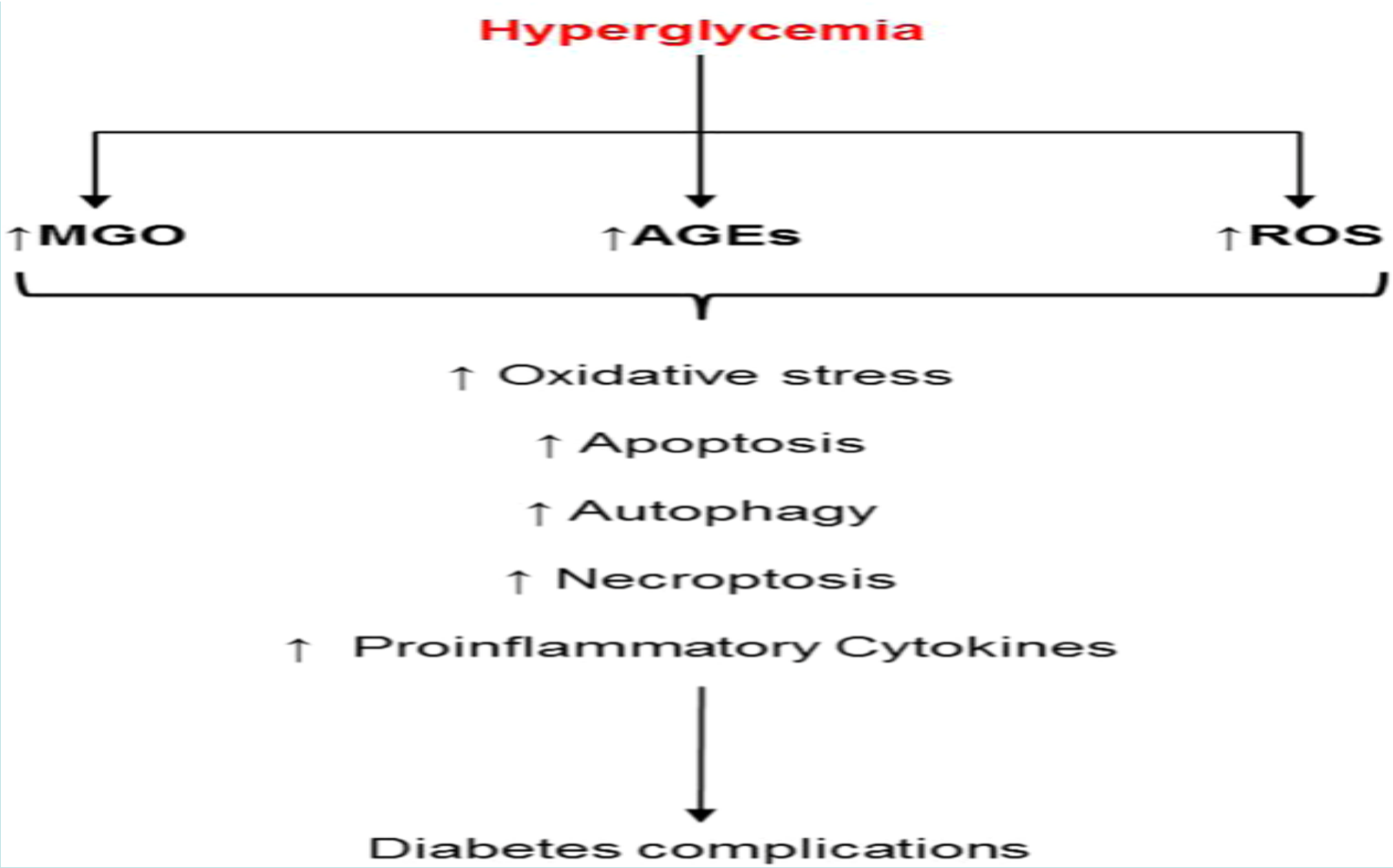
Oxidative stress and diabetic complications. Giacco F, Brownlee M. Circ Res. 2010, 107(9):1058-70..

Oxidative stress plays a pivotal role in the development of diabetes complications, both microvascular and cardiovascular. The metabolic abnormalities of diabetes cause mitochondrial superoxide overproduction in endothelial cells of both large and small vessels, as well as in the myocardium. This increased superoxide production causes the activation of 5 major pathways involved in the pathogenesis of complications: polyol pathway flux, increased formation of AGEs (advanced glycation end products), increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C isoforms, and overactivity of the hexosamine pathway. It also directly inactivates 2 critical antiatherosclerotic enzymes, endothelial nitric oxide synthase and prostacyclin synthase. Through these pathways, increased intracellular reactive oxygen species (ROS) cause defective angiogenesis in response to ischemia, activate a number of proinflammatory pathways, and cause long-lasting epigenetic changes that drive persistent expression of proinflammatory genes after glycemia is normalized ("hyperglycemic memory"). Atherosclerosis and cardiomyopathy in type 2 diabetes are caused in part by pathway-selective insulin resistance, which increases mitochondrial ROS production from free fatty acids and by inactivation of antiatherosclerosis enzymes by ROS. Overexpression of superoxide dismutase in transgenic diabetic mice prevents diabetic retinopathy, nephropathy, and cardiomyopathy. The aim of this review is to highlight advances in understanding the role of metabolite-generated ROS in the development of diabetic complications.

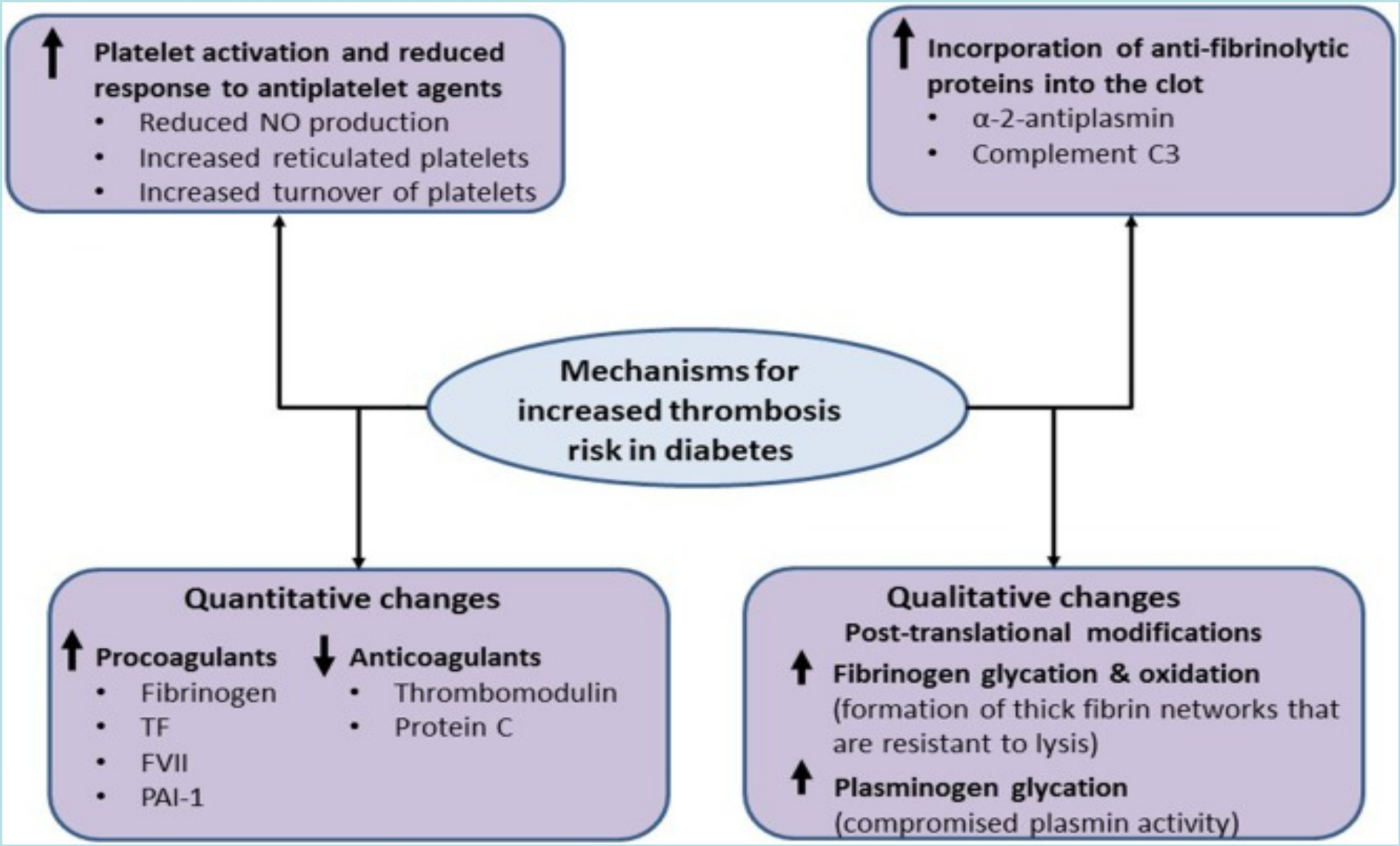


Schematic showing elements of the unifying mechanism of hyperglycemia-induced cellular damage

Res. 2010.107(9):1058–1070. **Oxidative stress and diabetic complications** Giacco F and Brownlee M.

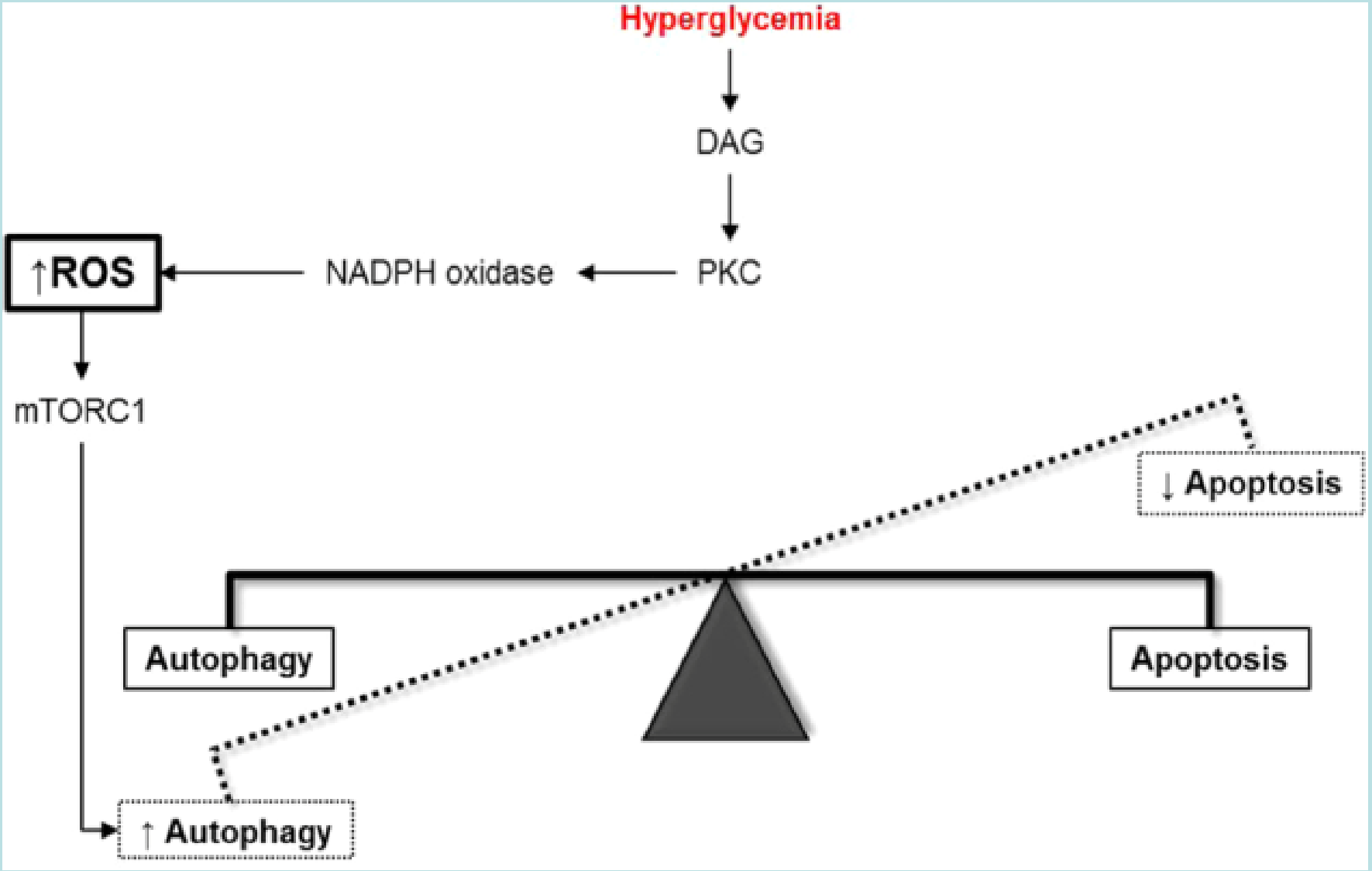


Oxidative stress and cell death: necroptosis, a programmed necrosis of inflammatory cell, and apoptosis can be induced in diabetes by AGEs, ROS, and MGO, leading to diabetes complications (retinopathy, age-related macular etc.)MGO = methylglyoxal, AGEs = advanced glycation end products, ROS = reactive oxygen species.
Cell Death Dis. 2018 25;9(2):119. Volpe CMO et al.



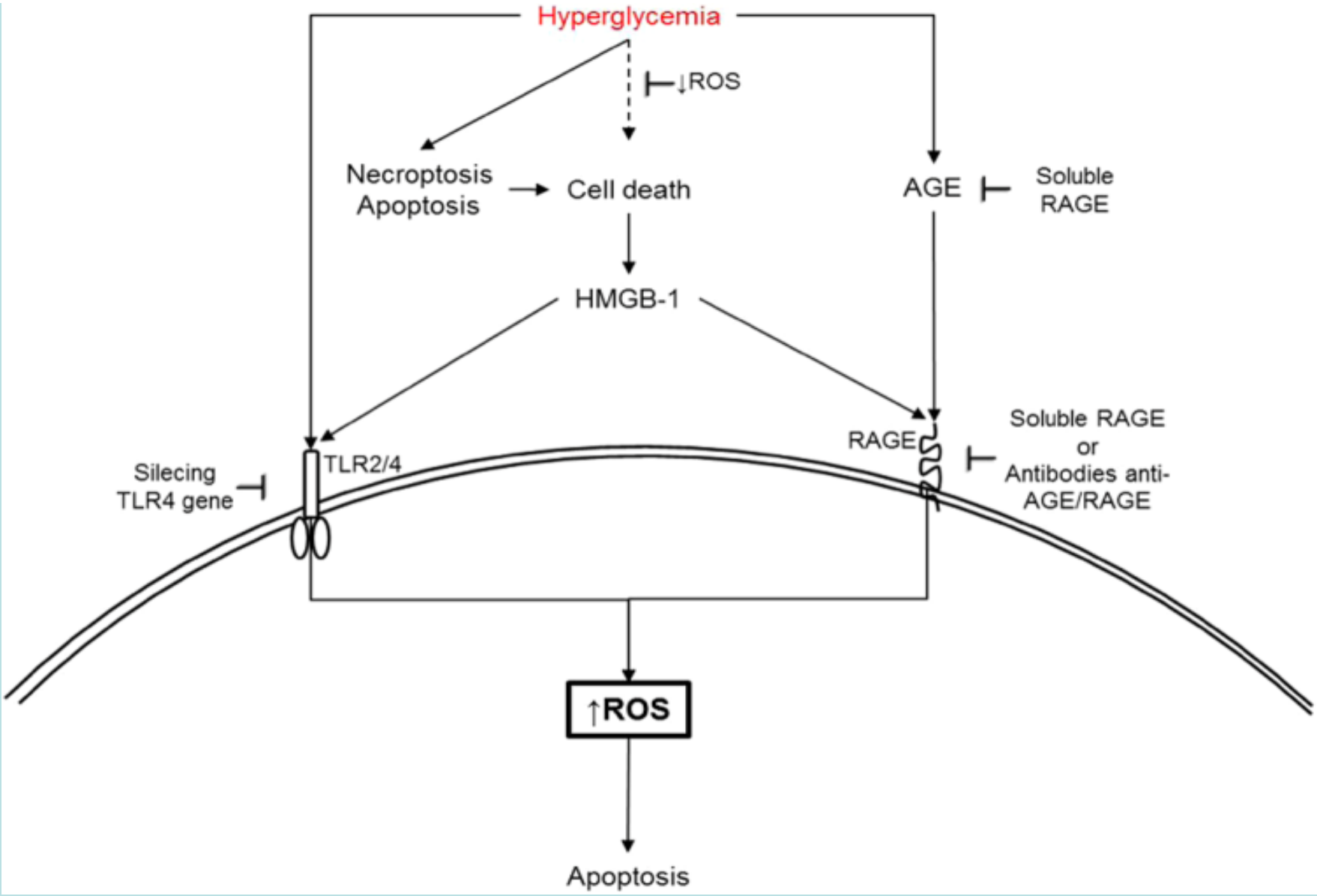
Mechanistic pathways for increased thrombosis risk in diabetes.

Front Cardiovasc Med. 2018; 5: 1. Published online 2018 Jan 19. doi: 10.3389/fcvm.2018.00001
PMCID: PMC5780411**Thrombosis and Vascular Inflammation in Diabetes: Mechanisms and Potential Therapeutic Targets** Pechlivani N and Ajjan[n] RA.

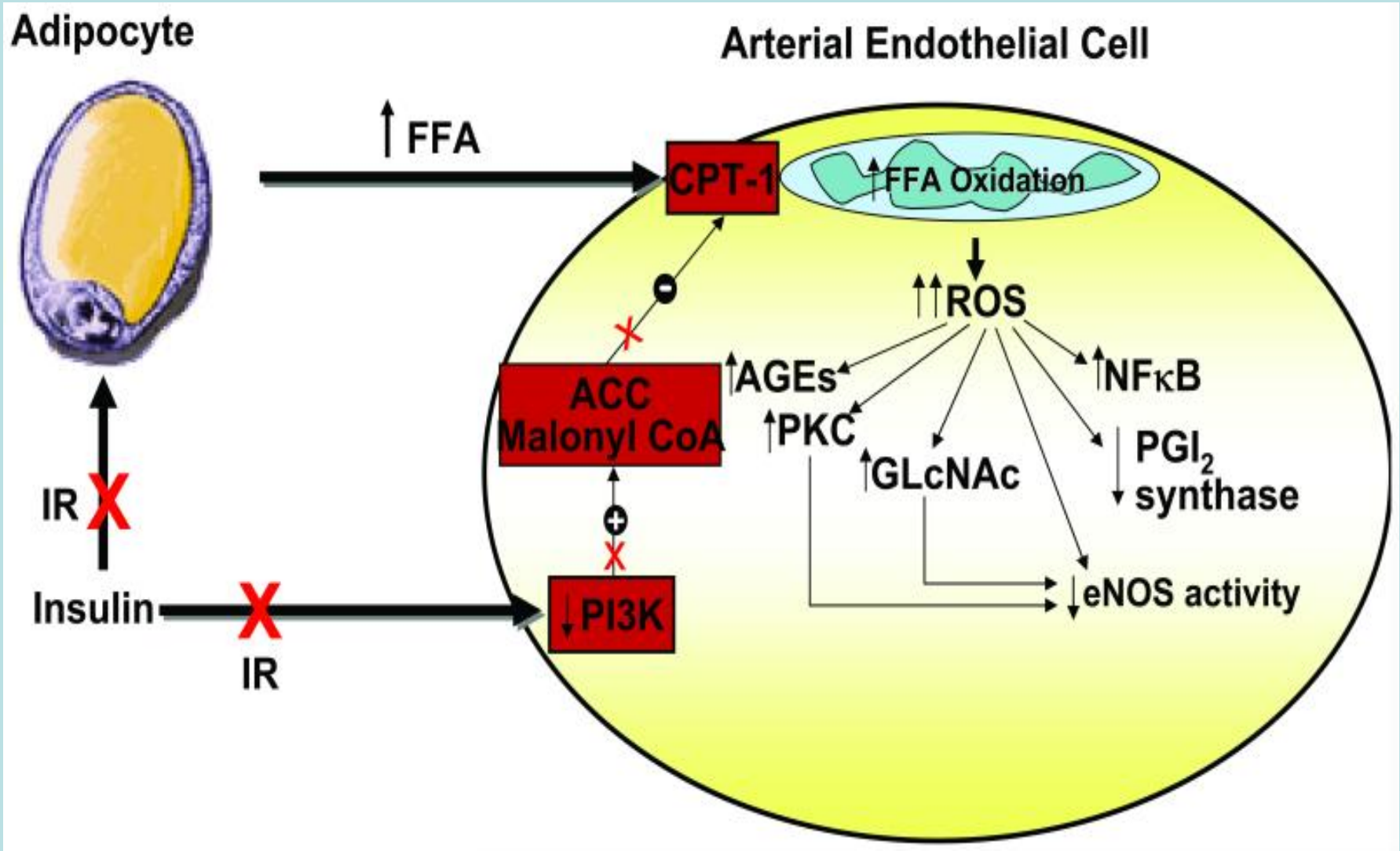


Balance between autophagy and apoptosis: apoptosis is downregulated by activation of mTORC1 depends on PKC, which is activated by DAG. Thus, PKC in conjunction with ROS and mTORC1 pathway are associated in the control of cellular autophagy. Akt/mammalian target of rapamycin complex 1 = mTORC1, ROS reactive oxygen species, PKC = protein kinase C, DAG = diacylglycerol.

Cell Death Dis. 2018 25;9(2):119. Volpe CMO et al.

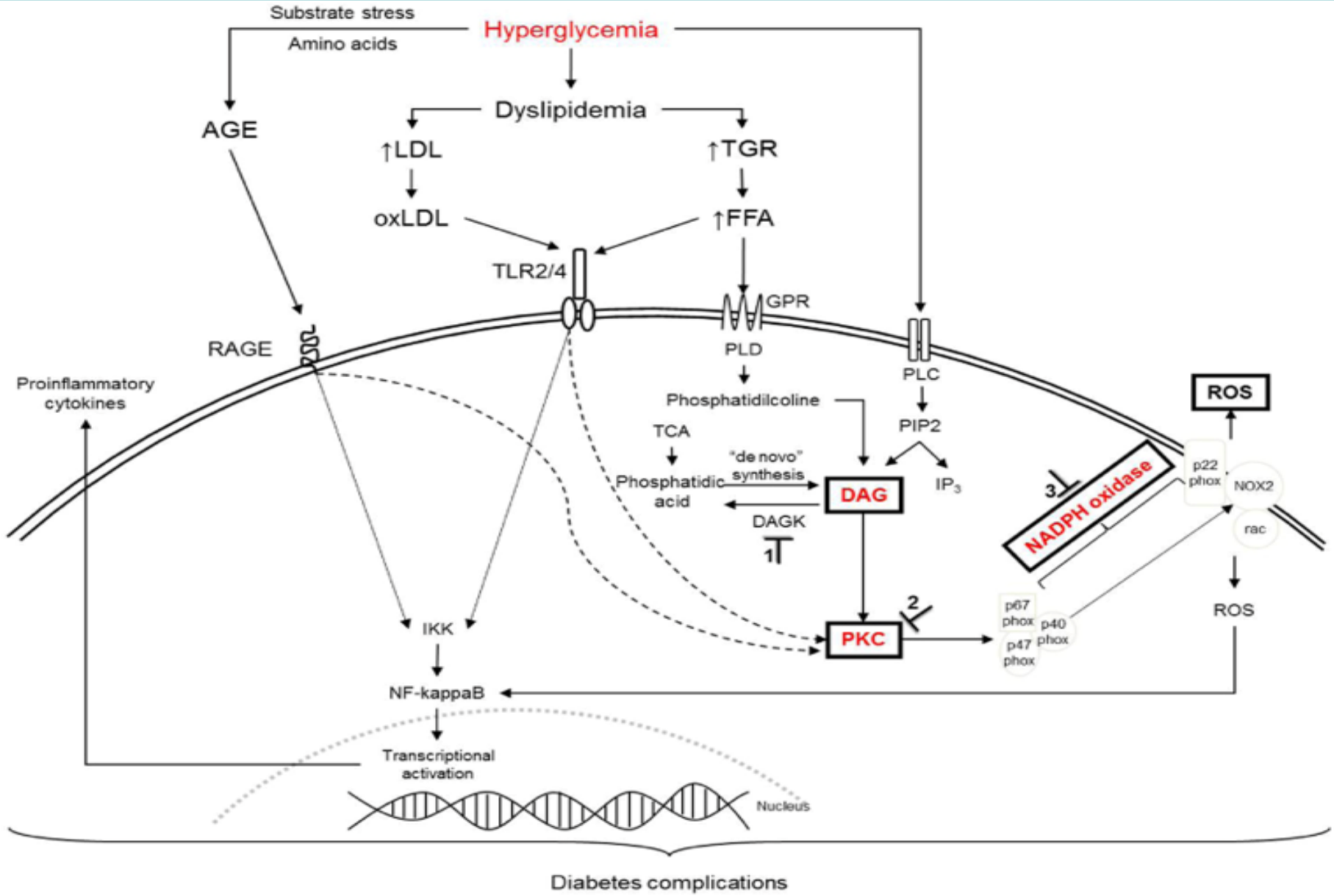


Targets for modulation of cell death: some points may act as modulators of cell death depending on the kind of activation Apoptosis induced by TLR activation has been suggested to be downregulated by silencing of TLR4 gene in experimental model or using soluble RAGE and/or specific antibodies against RAGE. Cell death is a source of HMGB-1, an activator of RAGE. TLR TLR-Toll-like receptors, RAGE receptor for advanced glycation end products. *Cell Death Dis. 2018 25;9(2):119. Volpe CMO et al.*



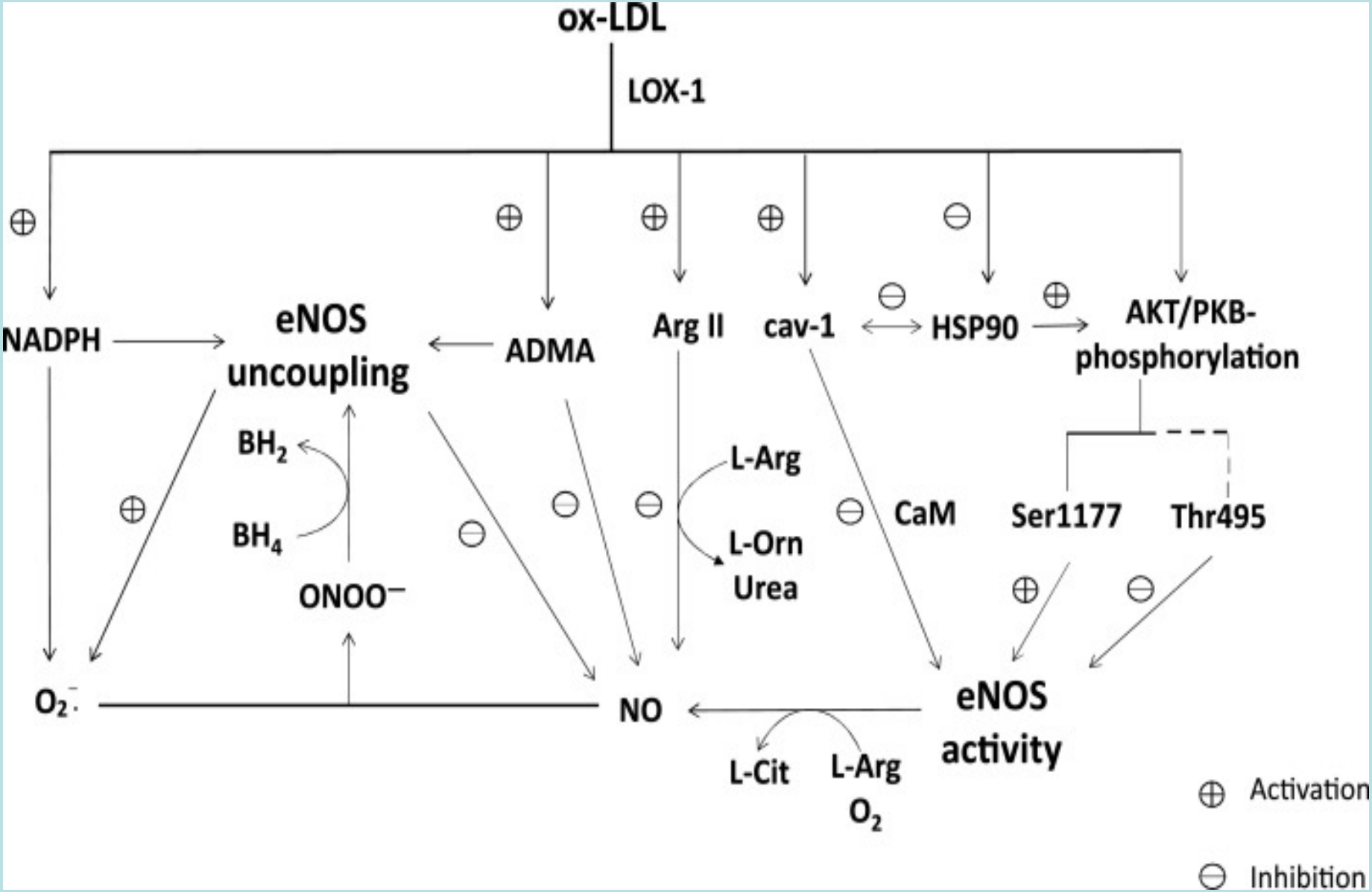
Role of insulin resistance and free fatty acids in macrovascular endothelial cell ROS formation and atherogenesis.

Circ Res. 2010.107(9):1058–1070. **Oxidative stress and diabetic complications** Giacco F and Brownlee M.*

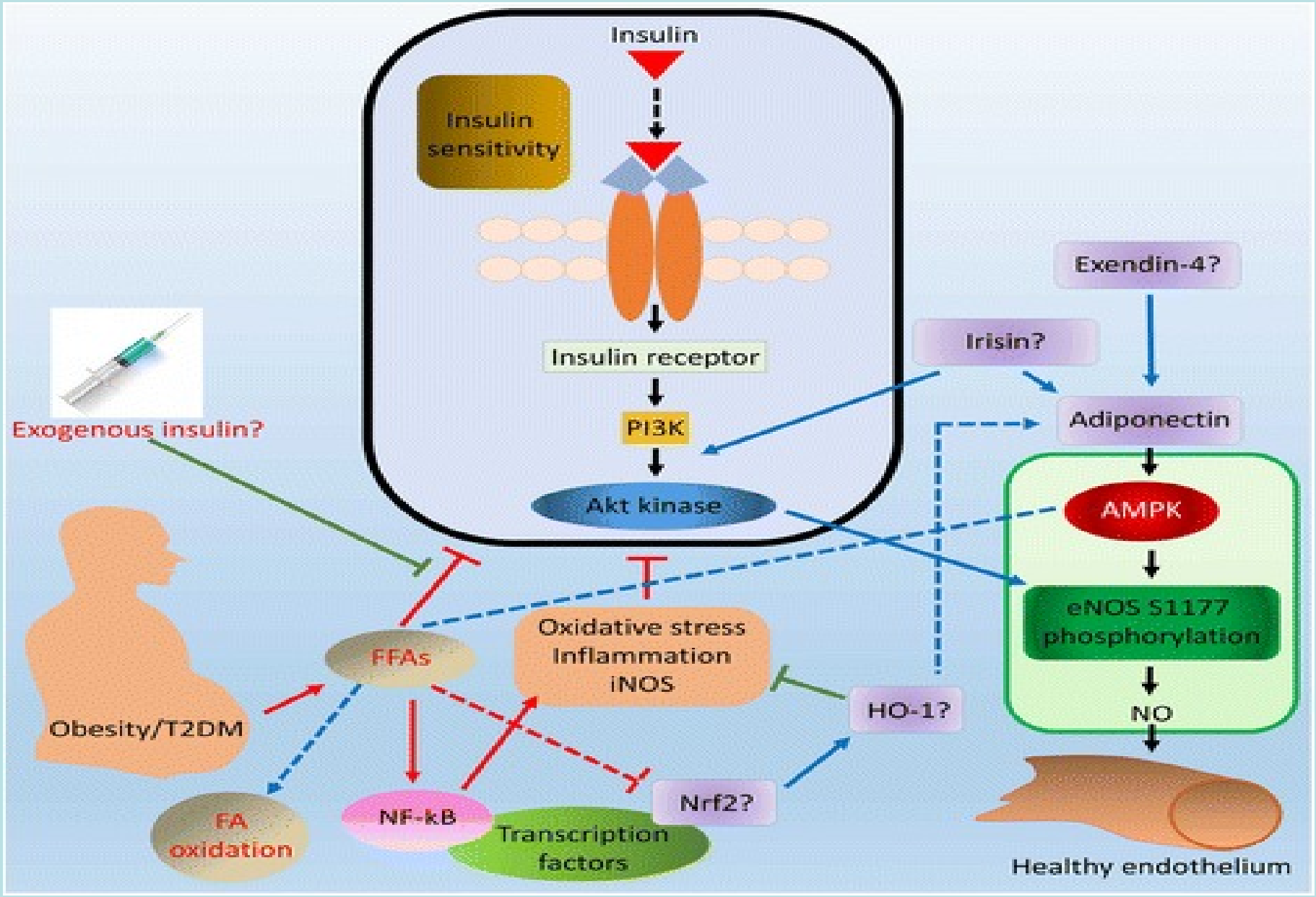


Proposed signaling pathways from hyperglycemia to ROS production and cytokine release leading to diabetes complications

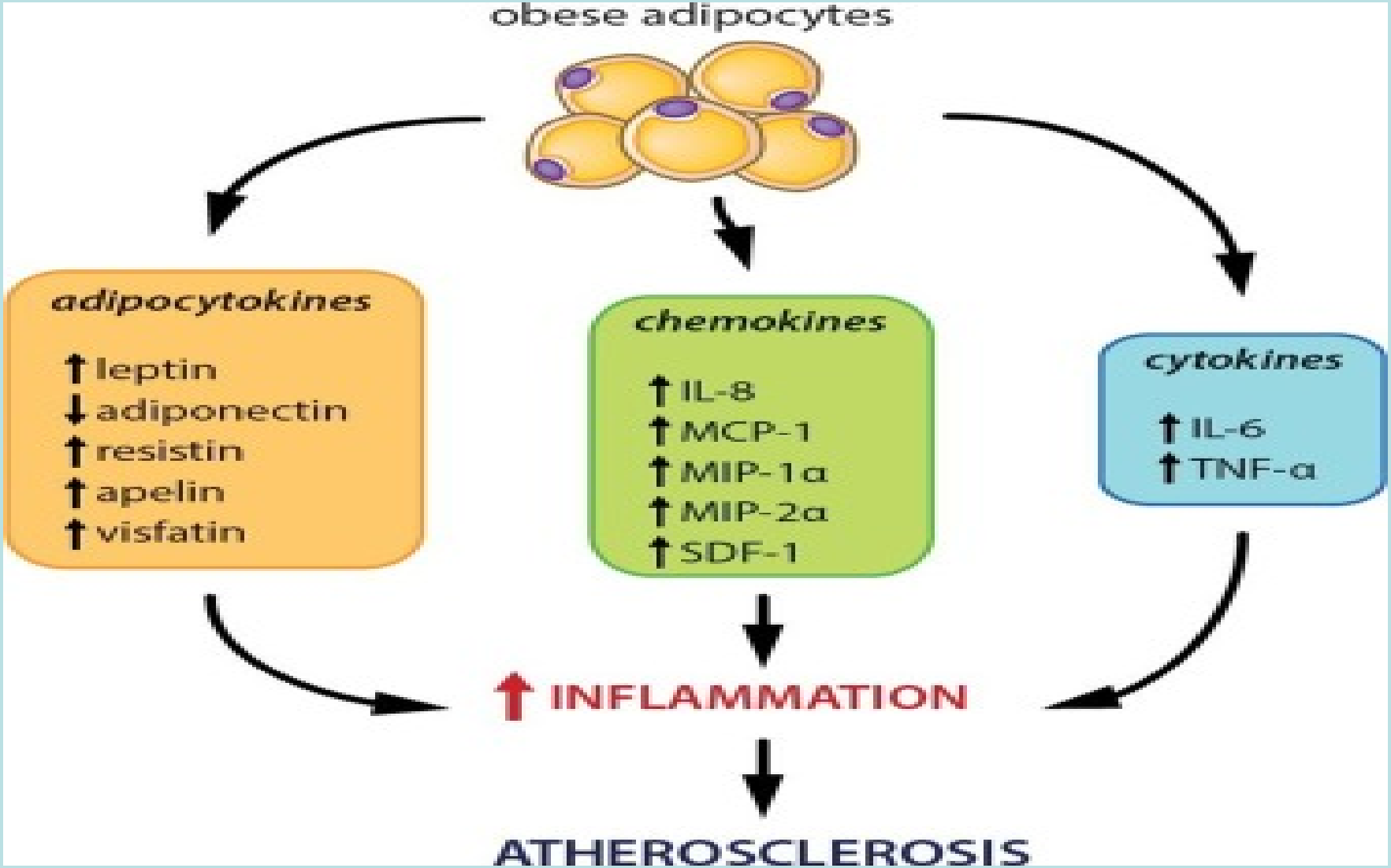
Cell Death Dis. 2018 25;9(2):119. Volpe CMO et al.



Biomed Pharmacother. 2018;97:423-428. Chen JY et al

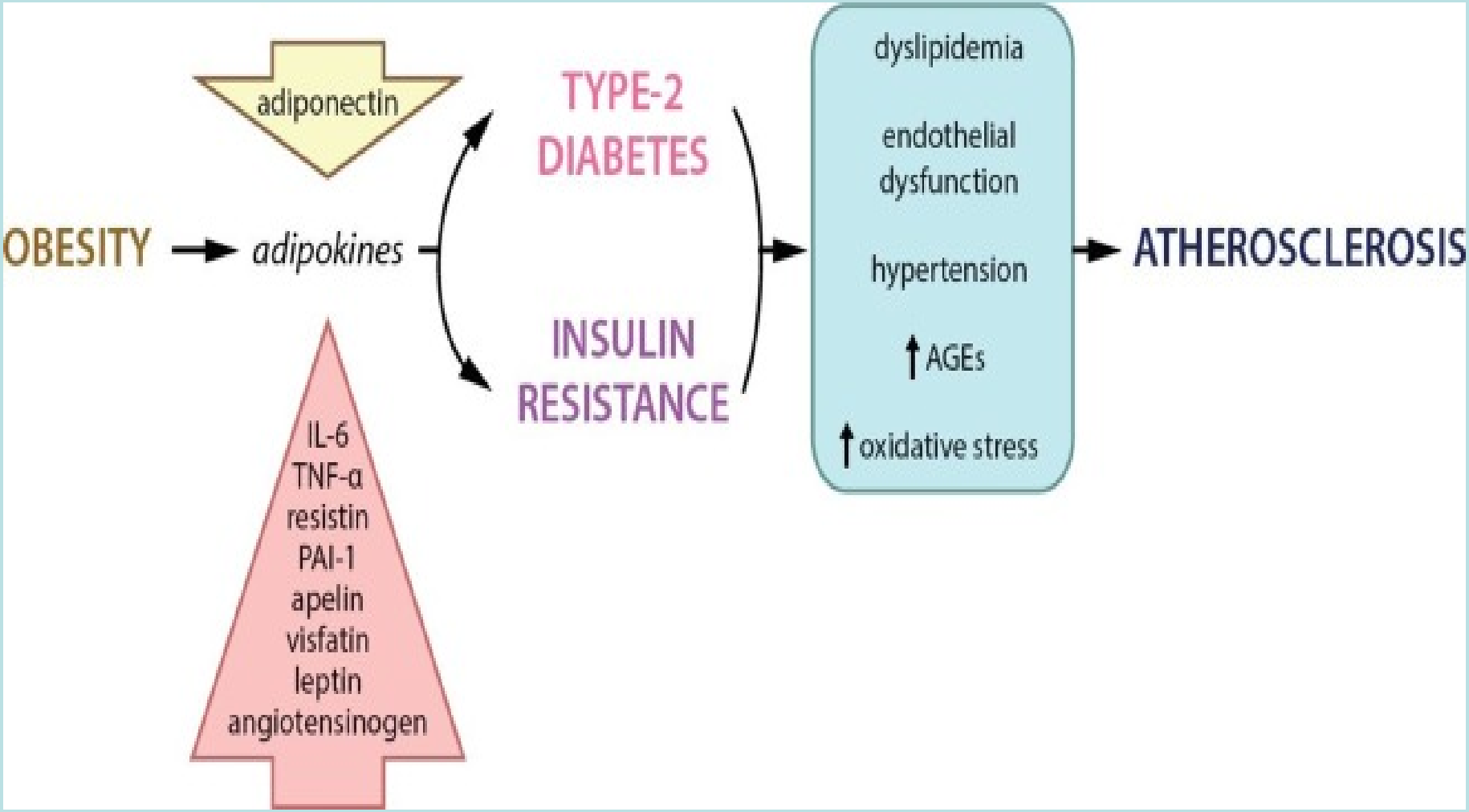


J Biomed Sci. 2017; 24(1):50. **Role of free fatty acids in endothelial dysfunction.** Ghosh A et al



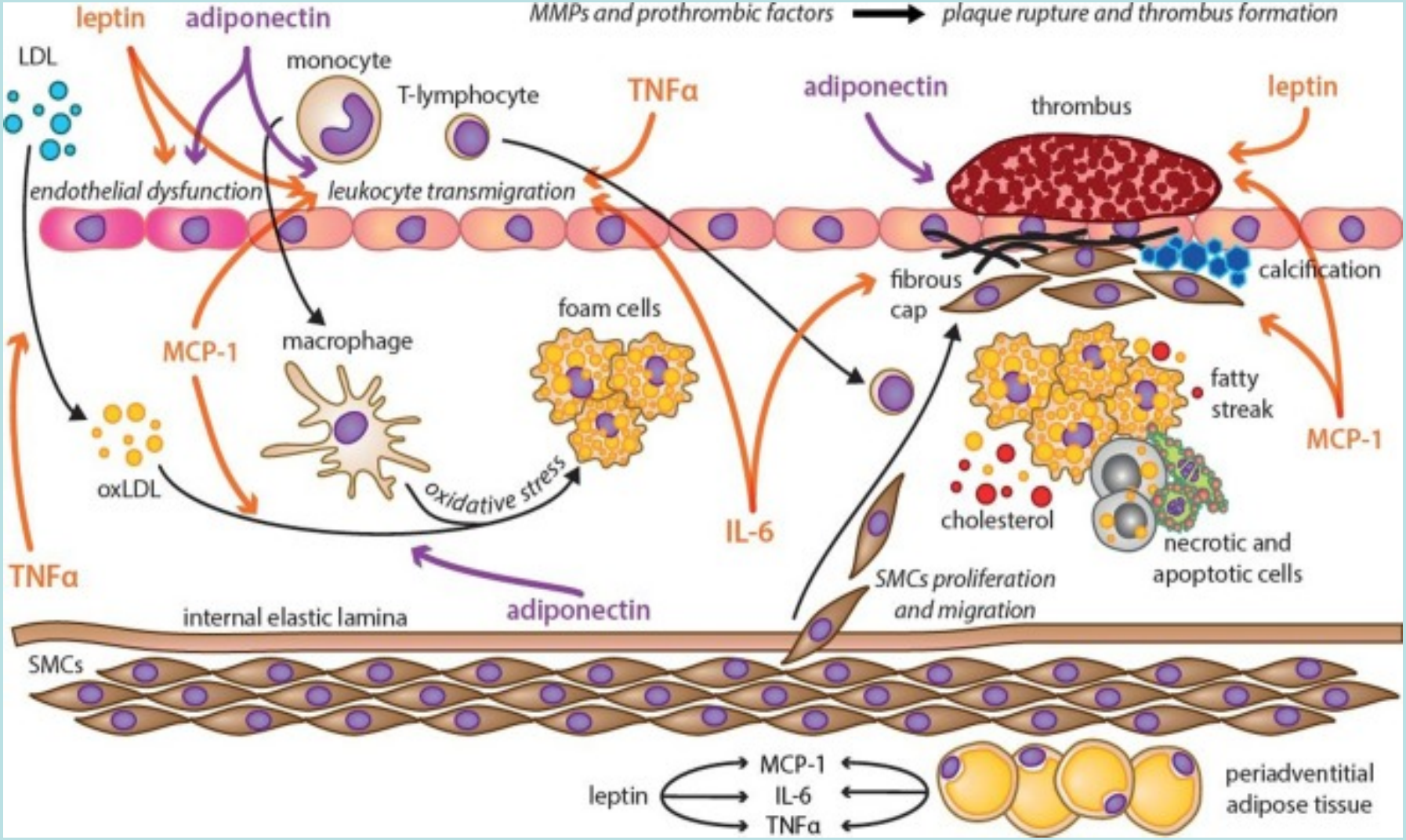
The basic role of adipocyte dysfunction in the pathogenesis of atherosclerosis.

Biomed Pharmacother. 2018 Feb;98:424-432. doi: 10.1016/j.biopha.2017.12.074. Epub 2017 Dec 27. **Adipokines in neurovascular diseases.** Opatrilova R. Et al.



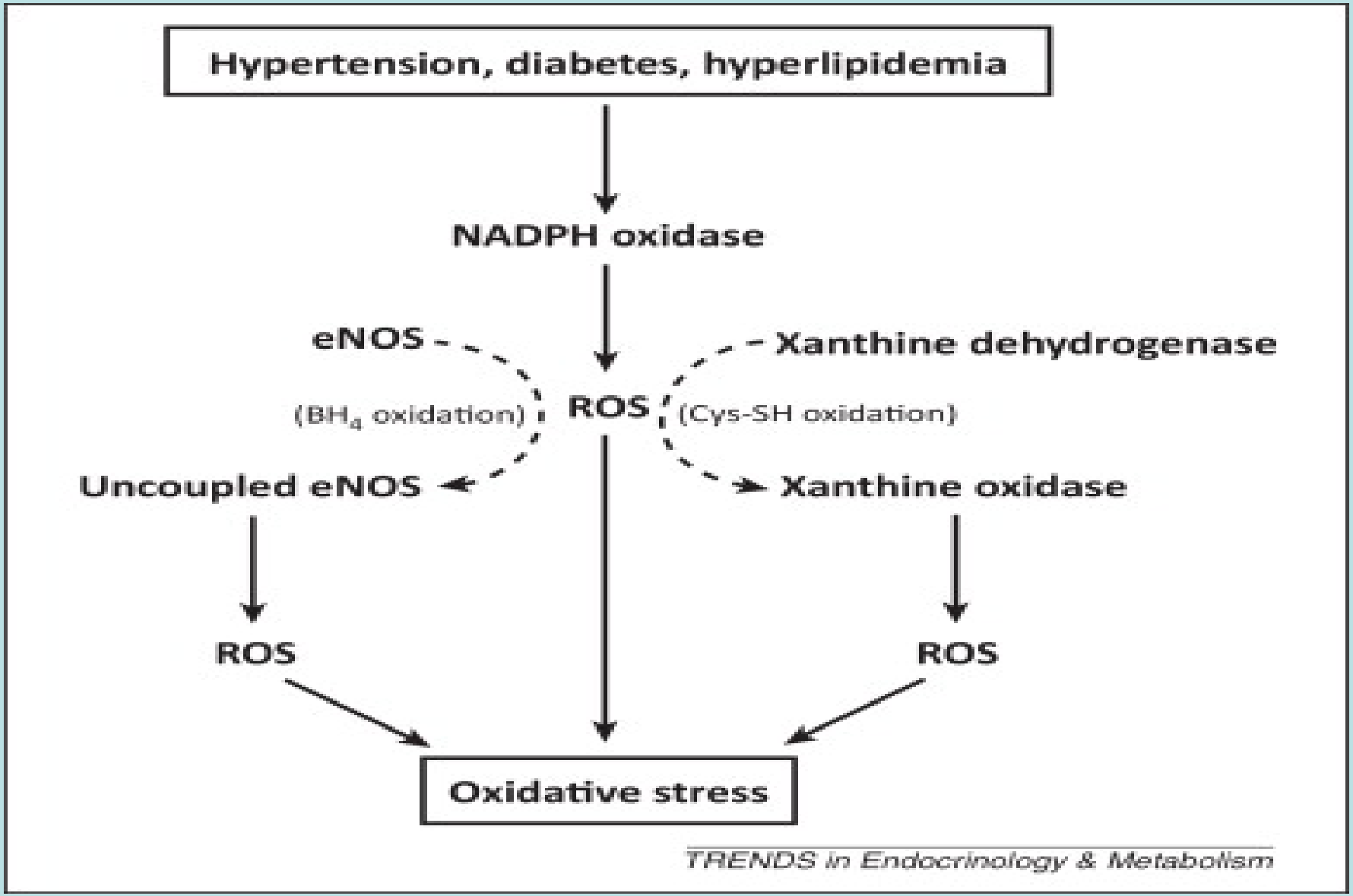
Adipokines as the signal molecules of metabolic syndrome and endothelial dysfunction.

Biomed Pharmacother. 2018 Feb;98:424-432. doi: 10.1016/j.biopha.2017.12.074. Epub 2017 Dec 27. **Adipokines in neurovascular diseases.** Opatrilova R. Et al.

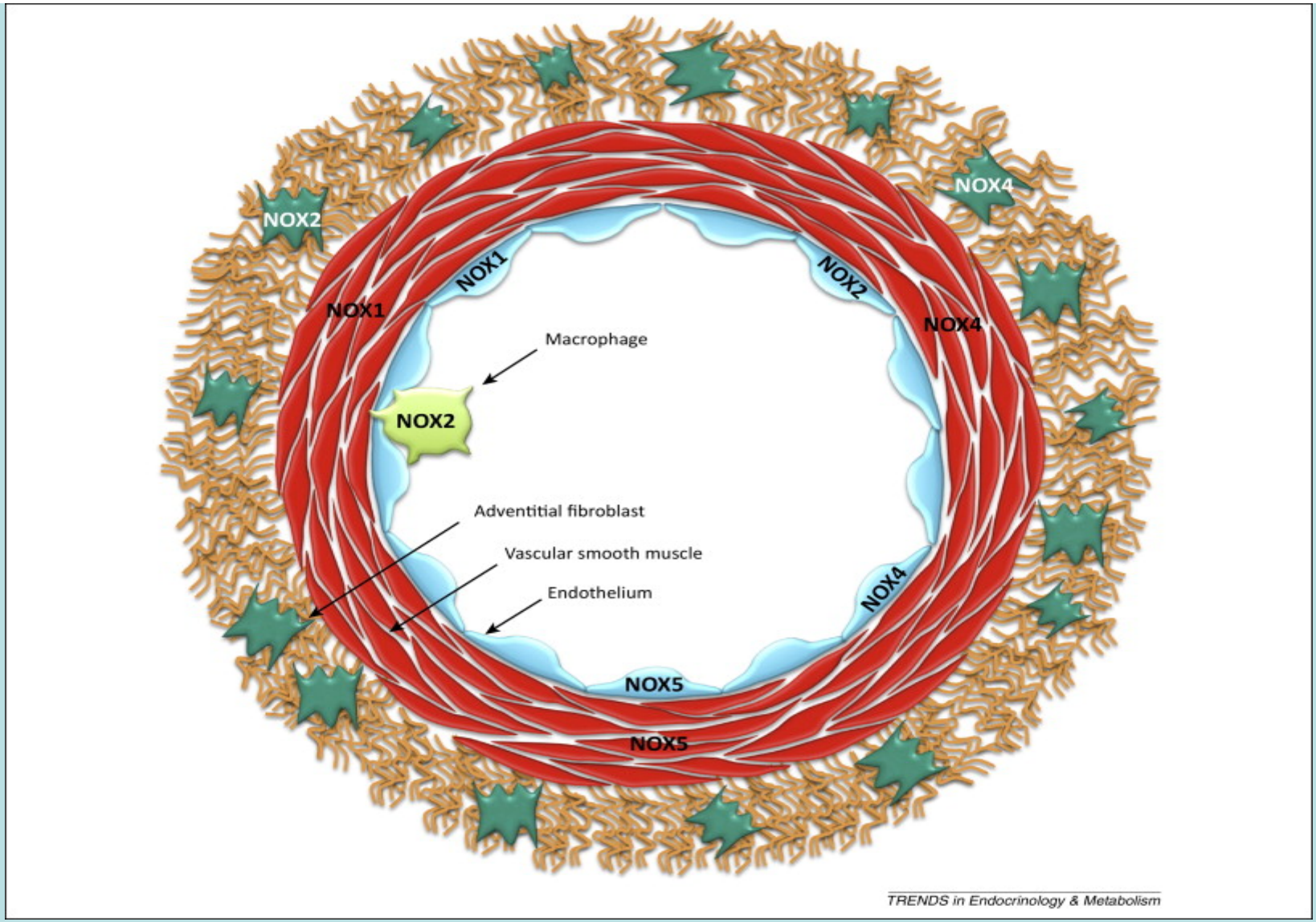


Functions of leptin and adiponectin in the atherogenic process.

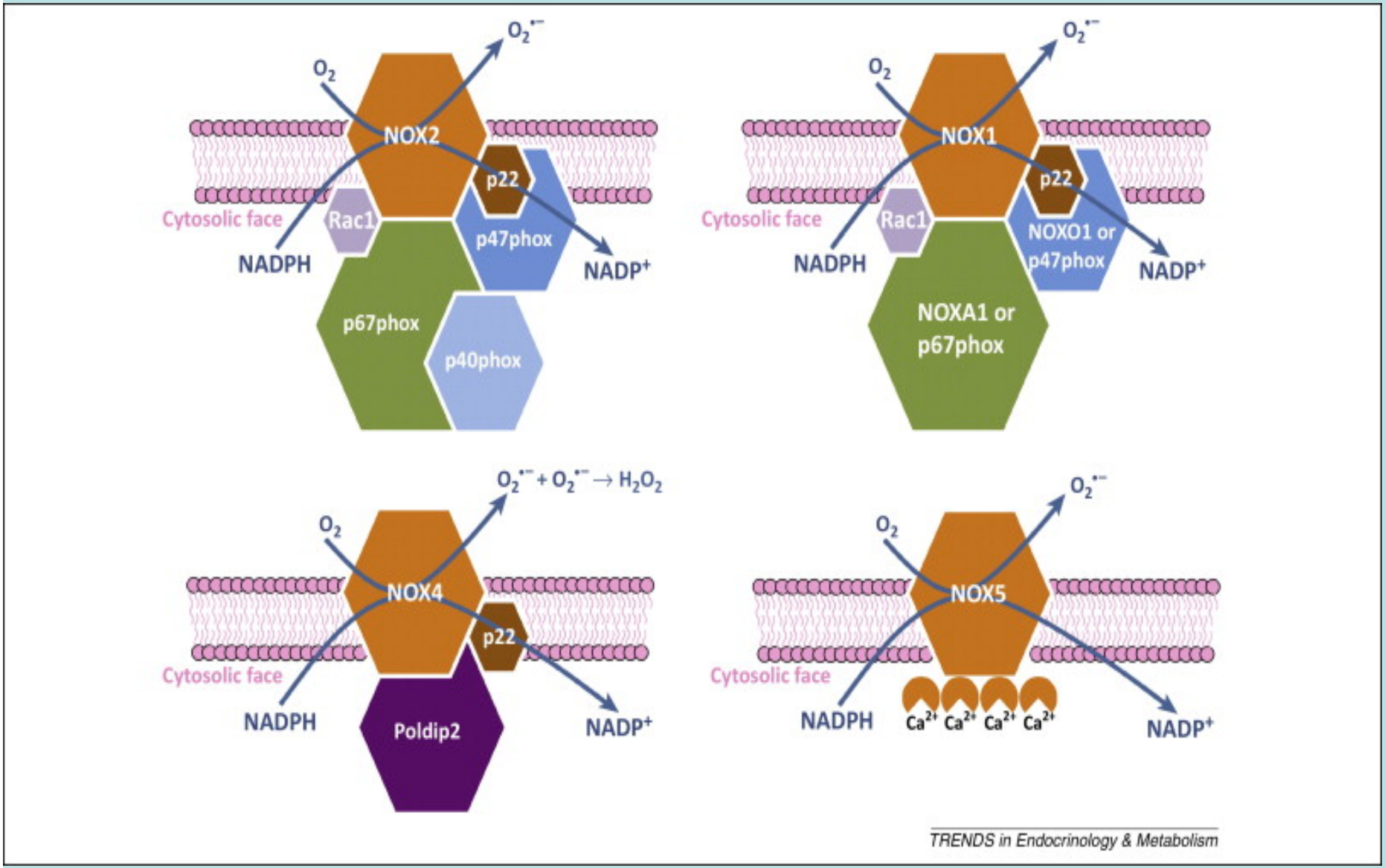
Biomed Pharmacother. 2018;98:424-432. doi: 10.1016/j.biopha.2017.12.074. **Adipokines in neurovascular diseases.** Opatrilova R. et al.



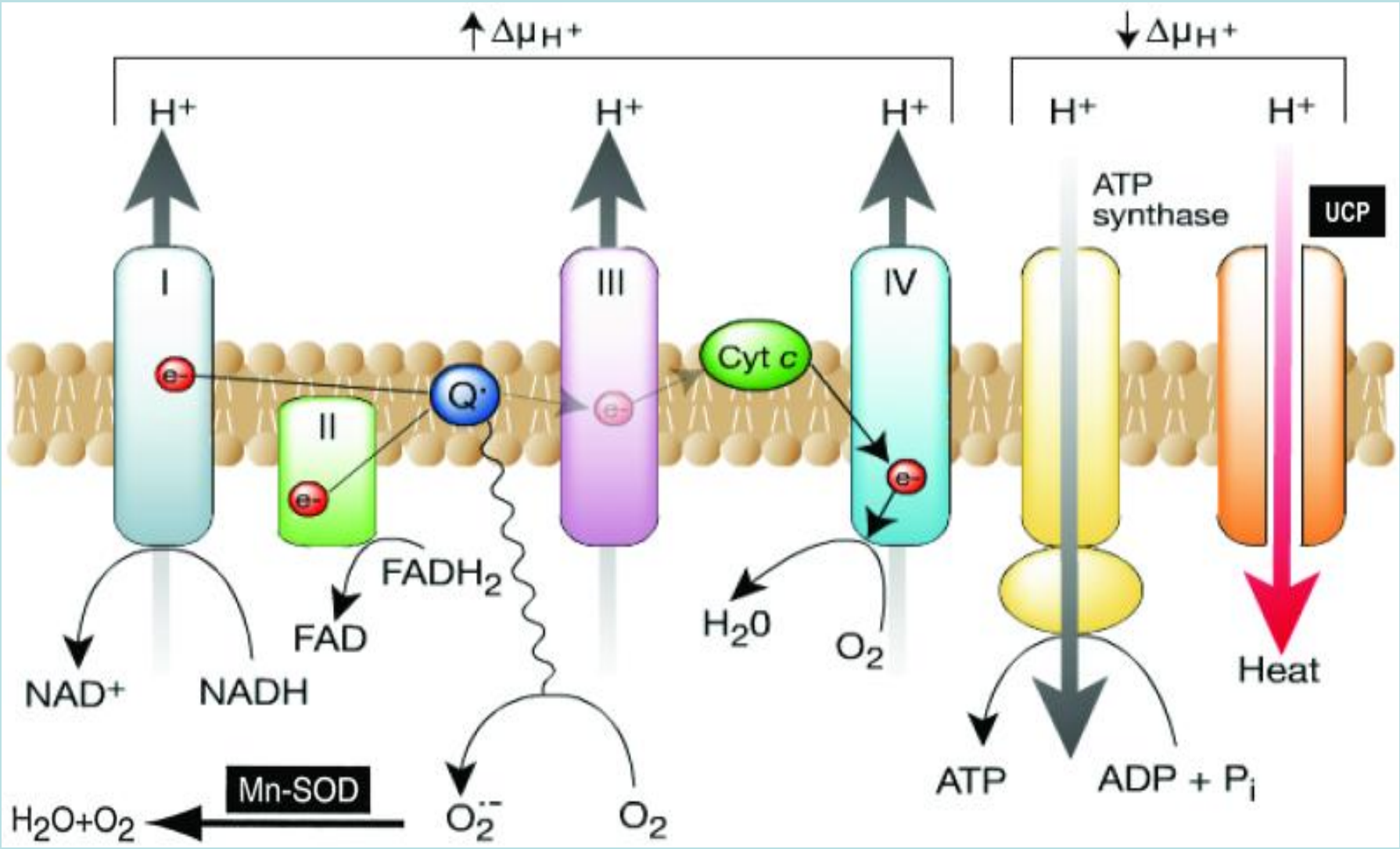
NADPH oxidase (NOX)-derived reactive oxygen species (ROS) elicit ROS production from other enzyme sources. Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



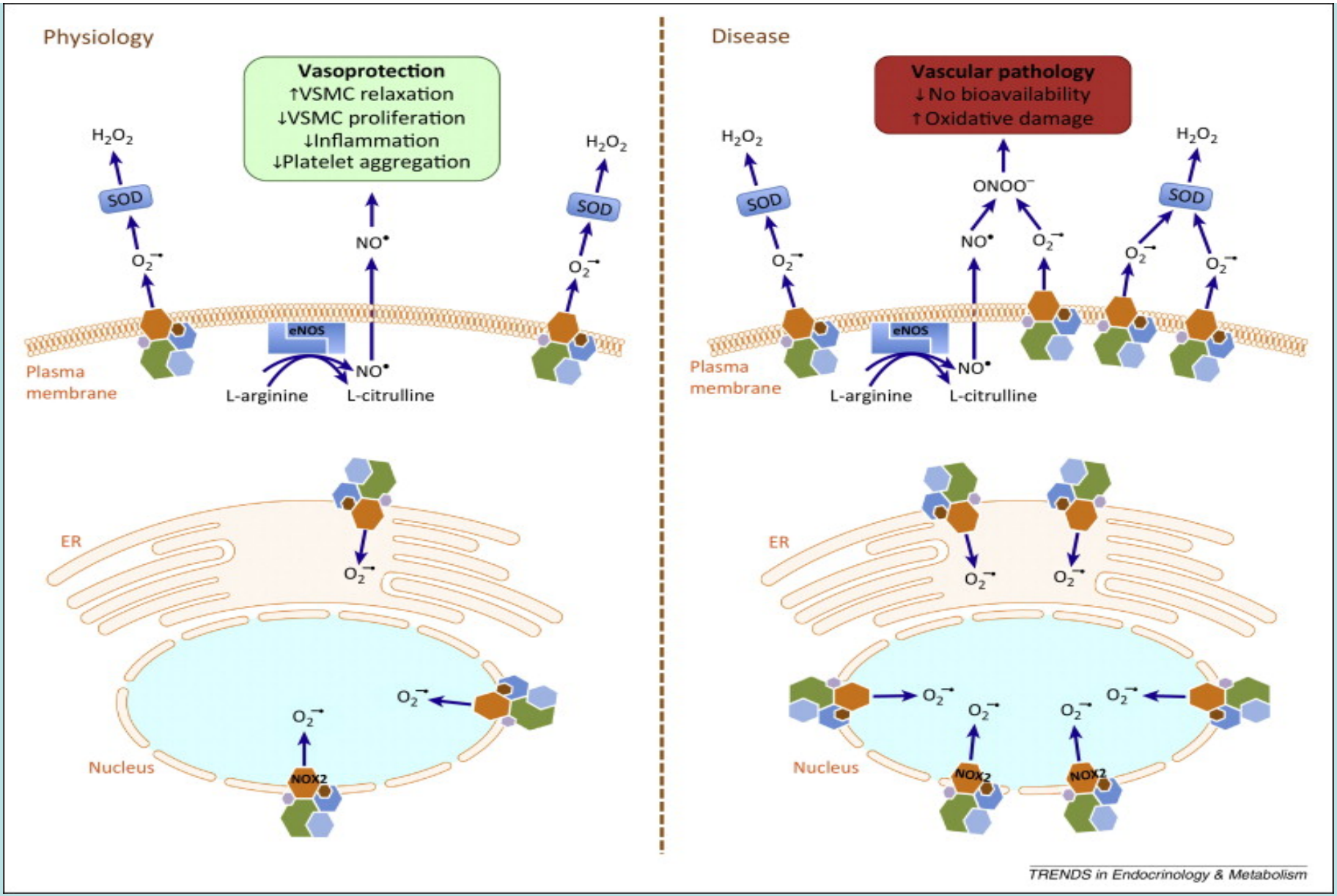
NADPH oxidase (NOX) isoform expression in the various cell types of the blood vessel wall. Four NOX isoforms are expressed in the vascular wall, including NOX1 (in endothelial cells and vascular smooth-muscle cells, VSMCs), NOX2 (in endothelial cells, adventitial fibroblasts, and leukocytes such as monocytes, macrophages, and platelets), NOX4 (in endothelial cells, VSMCs, and adventitial fibroblasts), and NOX5 (in endothelial and VSMCs – not expressed in rodents). Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



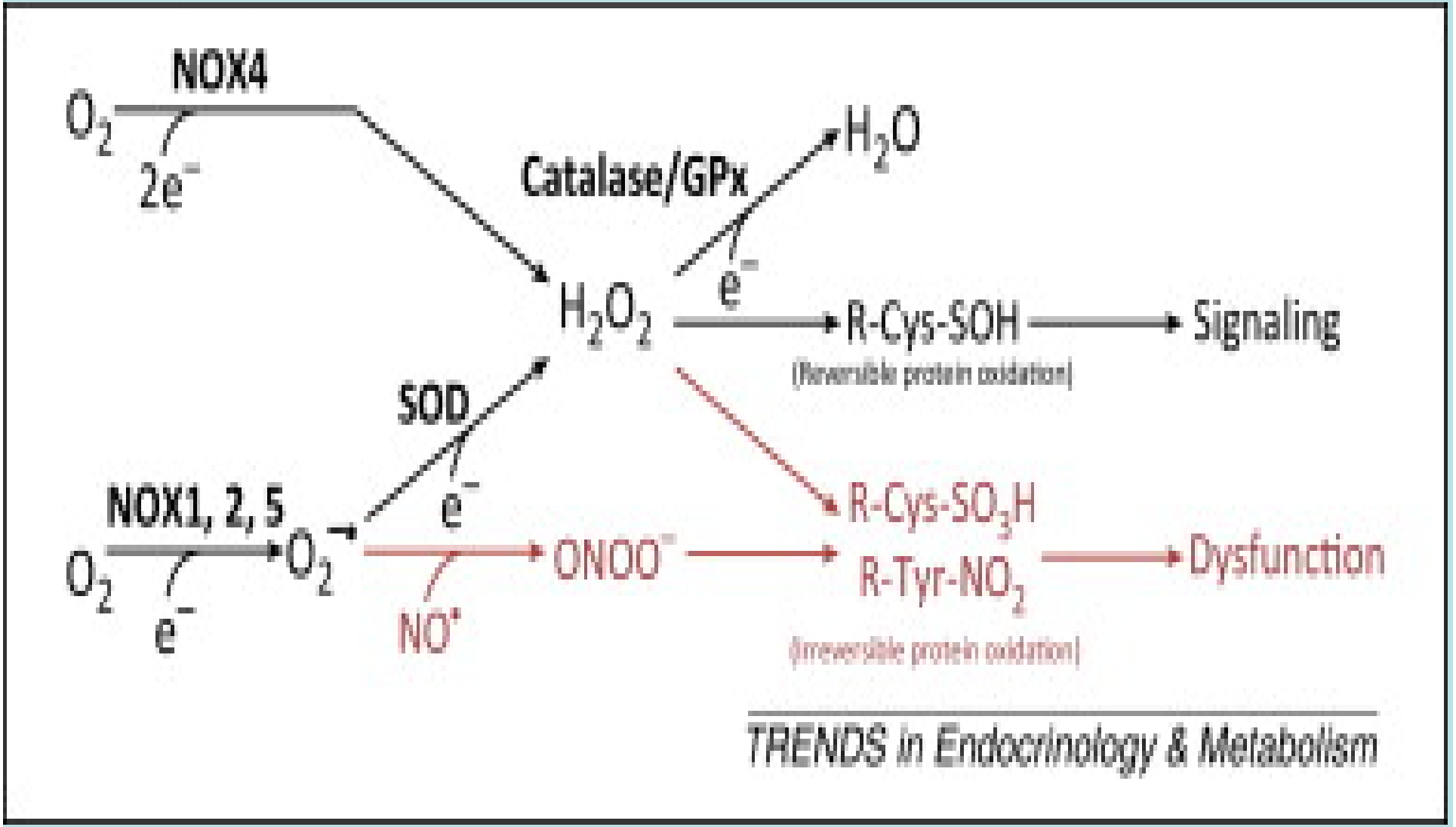
Molecular composition of the endothelial NADPH oxidases ('NOXs') Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



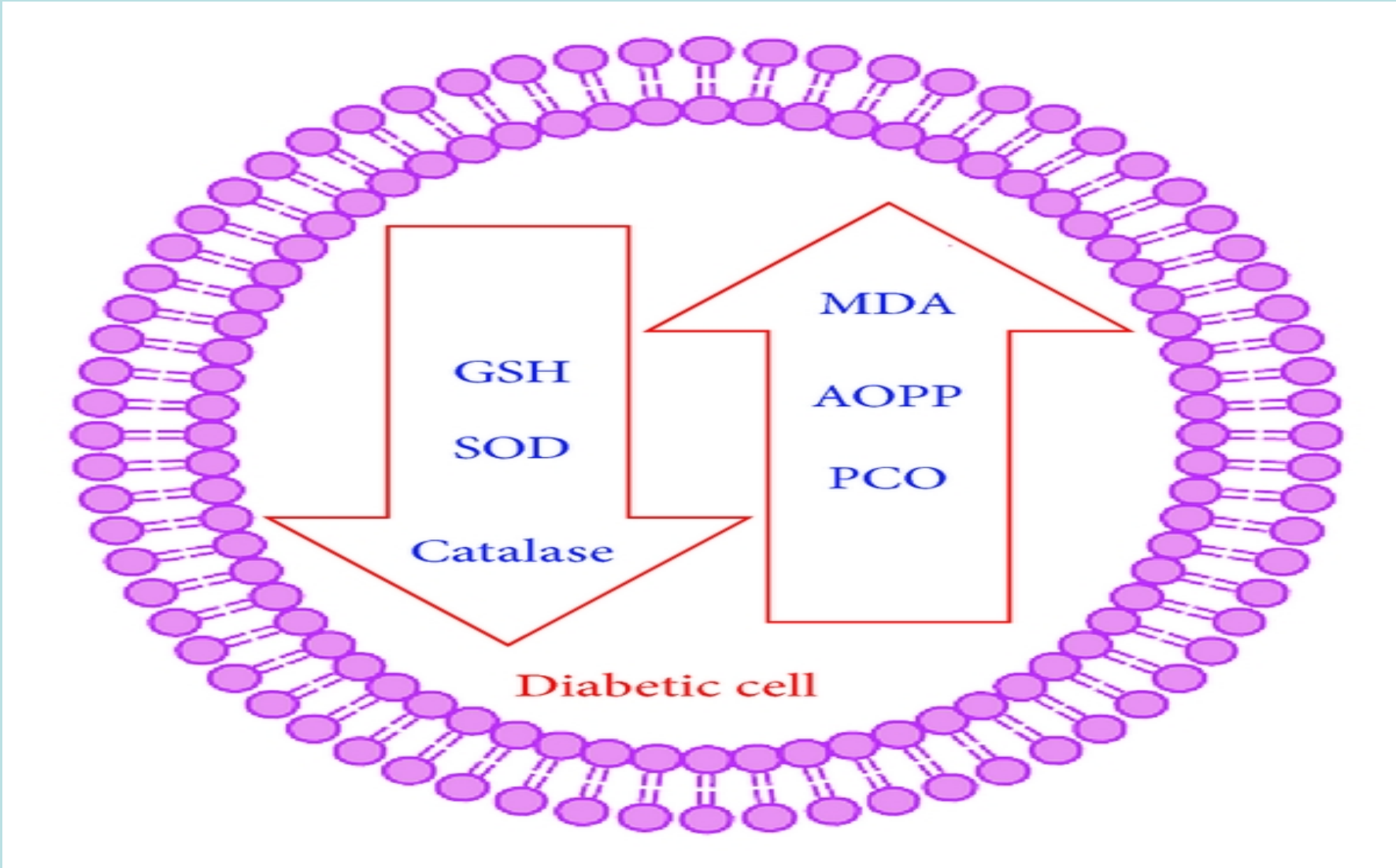
Production of ROS by the mitochondrial electron transport chain. Circ Res. 2010, 107(9):1058–1070. **Oxidative stress and diabetic complications** Giacco F and Brownlee M.



Subcellular compartments into which NADPH oxidase NOX2 generates superoxide in the endothelium in physiology and disease, and the impact on nitric oxide (NO) bioavailability. Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



The chemistries of redox signaling and endothelial dysfunction in endothelial cells. Trends Endocrinol Metab. 2014 25(9):452-63. **Endothelial NADPH oxidases: which NOX to target in vascular disease?** Drummond GR, and Sobey CG.



Schematic representation of the status of oxidative stress markers during diabetes. MDA: malondialdehyde, AOPP: Advanced oxidation protein products, PCO: protein carbonyls, GSH: reduced glutathione, and SOD: superoxide dismutase. Markers of Oxidative Stress during Diabetes Mellitus.Tiwari BTJournal of Biomarkers Volume 2013 (2013), Article ID 378790, 8 pages