MODULE 6.5
Advanced Glycation End Products

Another part of the cascade of events initiated by hyperglycemia and oxidative stress is the formation of advanced glycation end products (AGEs).[1] AGEs are formed at a slow rate in normal individuals, but in diabetes, because of the increased availability of glucose, their formation is accelerated.[2] Hyperglycemia induces nonenzymatic glycation of proteins to form AGE, possibly contributing to loss of retinal perictyes, formation of microaneurysms, and damage to the vascular endothelium.

The initial product of this nonenzymatic reaction in the extracellular matrix is the formation of a Schiff base, which rearranges itself spontaneously into an Amadori product. Over weeks and months, with further glycation of proteins and lipids, AGEs are generated.[2]

AGEs bind to a number of cell-surface receptors, including the receptor for AGE (RAGE).[2,3] AGE binds to RAGE on endothelial cells, pericytes, and retinal pigment epithelial cells. This interaction initiates cellular pro-oxidant intercellular events that lead to retinal damage in diabetic retinopathy (DR).[2] The primary mechanism by which AGE and RAGE induce oxidative stress is speculated to be activation of nicotinamide adenine dinucleotide phosphate (NAPDH) oxidase, which transduces multiple signals. The eventual result is activation of nuclear transcription factor kappa B (NF-κB), formation of cytokines, and activation of proinflammatory pathways.

Advanced Glycation End Products

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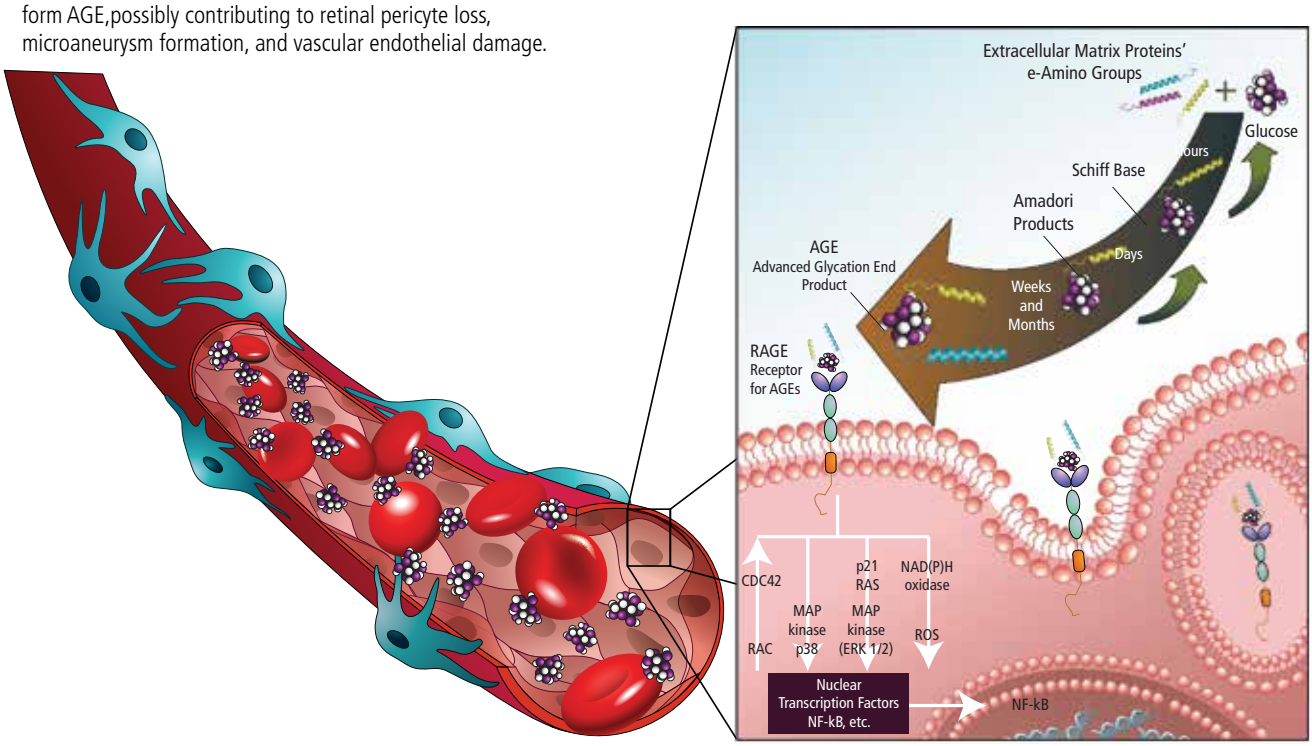

References

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. 2010;376:124-136.

2. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of diabetic retinopathy. *ISRN Ophthalmol.* 2013;2013:343560.

3. Wu Y, Tang L, Chen B. Oxidative stress: implications for the development of diabetic retinopathy and antioxidant therapeutic perspectives. *Oxid Med Cell Longev.* 2014;2014:752387.