MODULE 6.7
Hexosamine Pathway

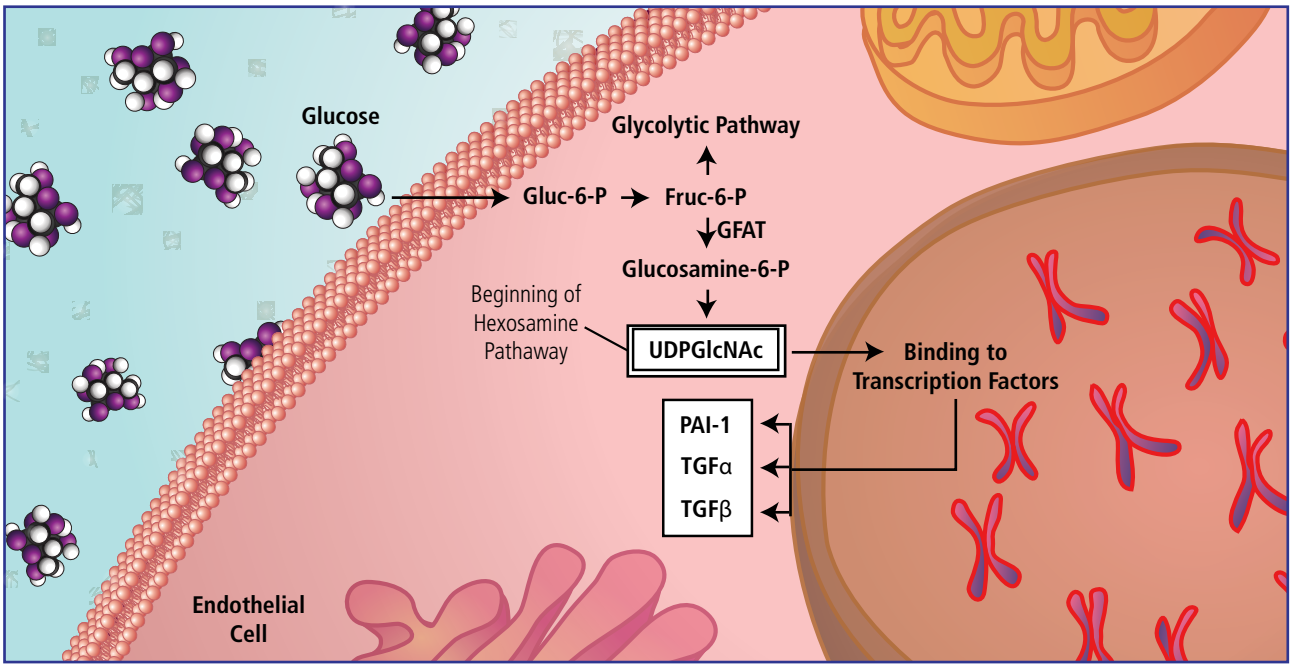
The hexosamine pathway is another downstream consequence of oxidative stress. As described in Module 6.4, Brownlee proposed oxidative stress as a unifying mechanism that links all the damaging biochemical pathways induced in diabetic retinopathy (DR) by hyperglycemia.[1,2] That theory holds that overproduction of reactive oxygen species by mitochondria is the single upstream event that activates four separate metabolic pathways: (1) increased intracellular production of advanced glycation end products (AGEs), activation of protein kinase C (PKC), increased flux in the polyol pathway, and overactivation of the hexosamine pathway.[3]

When glucose is elevated in a cell, most of it is metabolized by glycolysis: first to glucose 6-phosphate, then to fructose 6-phosphate, and then on through the pathway. In hyperglycemia-induced oxidative stress, the flux of fructose 6-phosphate into the hexosamine pathway is increased, diverting it from the glycolytic pathway. Here it is converted by the enzyme glutamine: fructose 6-phosphate amidotransferase (GFAT) into glucosamine 6-phosphate, which is subsequently converted to uridine diphosphate-N-acetylglucosamine (UDPGlcNAc), a hexosamine.[1,3]

UDPGlcNAc then binds to specific serine and threonine residues in transcription factors, leading to pathologic changes in gene expression, such as increases in transcription of transforming growth factor (TGF) α and TGFβ. Increased activation of transcription factor Sp1 through the hexosamine pathway, induced by hyperglycemia, has been shown to lead to the activation of plasminogen activator inhibitor-1 (PAI-1).[1,3] PAI-1 is upregulated by both the PKC and hexosamine pathways, again illustrating how these four separate pathways are interconnected in diabetes.[3]

Hexosamine Pathway in DME

HYPERGLYCEMIA INCREASES FLUX OF HEXOSAMINE PATHWAY



References

1. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54:1615-1625.

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.