

Diabetes and Microvascular Dysfunction

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Microvascular reactivity is an important mechanism that regulates local blood flow and therefore tissue perfusion. The reactivity (vasorelaxation and vasoconstriction) of microvessels is mainly regulated by mechanical factors (shear stress for relaxation and blood pressure for myogenic tone, which is a vasoconstriction of microvessels in response to increase in intraluminal blood pressure) and neuro-hormones. We previously showed that epidermal growth factor receptor tyrosine kinase (EGFRtk) is an important factor in the regulation of myogenic tone in microvessels. In fact, pressure-induced myogenic tone in resistance arteries is regulated by the mechanism that involves metalloproteinases 2 and 9 activation with subsequent Heparin-Binding-EGF release and EGFRtk transactivation [1]. This mechanism appears to be specific to myogenic tone, since the contractions to angiotensin and KCl are independent of EGFRtk transactivation. We previously reported that diabetes is associated with microvascular dysfunction [1,2]. We observed reduced microvascular endothelium-dependent relaxation and aberrant increase in pressure-induced myogenic tone in type 2 diabetes [3,4]. The impairment in microvascular function in type 2 diabetes is, in part, caused by the enhanced EGFRtk activity. In a murine model of type 2 diabetic mice, we found an increase of EGFRtk phosphorylation in microvessels. Interestingly, the inhibition of EGFRtk improves vascular function in type 2 diabetes independently of the diabetes and obesity [4]. We also demonstrated that advanced glycation end products cause microvascular dysfunction in type 2 diabetes through the enhance in oxidative stress [3]. In another study, we demonstrated an increase in poly (ADP-ribose) polymerase 1 (PARP-1) and nuclear factor- κ B activity in microvessels isolated from type 2 diabetic compared to control [2,5,6]. Interestingly, the inhibition of PARP-1 and NF κ B pathways improves microvascular function in type 2 diabetic mice [2,6] indicating that PARP-1 and NF κ B are important factors in microvascular dysfunction in type 2 diabetes. The aberrant increase in PARP-1 and NF κ B activity is caused by the augmented EGFRtk activity [2,7]. Thus, we determined that the inhibition of EGFRtk activity improved microvascular function by PARP-1 and

NF κ B-dependent mechanism [2,7] suggesting that EGFRtk is upstream to PARP-1 and NF κ B signaling. The aberrant increase in NF κ B and PARP-1 activity impairs microvascular function in type 2 diabetes by Sp-1 and COX-2-dependent mechanism. In summary, our studies delineated the mechanism of type 2 diabetes induced microvascular dysfunction. Therefore, the EGFRtk, oxidative stress, NF κ B and PARP-1 pathways could be potential targets for novel therapeutic strategies to overcome diabetes-induced microvascular dysfunction.

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