A Novel Mechanism for Glucocorticoid-Induced Tightening of Endothelial Barriers

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Blood-retinal barrier dysfunction is a major ophthalmic problem in diabetic retinopathy and ocular inflammatory conditions. Glucocorticoids are used widely in clinical settings to counteract inflammation, including the suppression of vasopermeability. For diabetic macular edema, the utility of glucocorticoids likely is due to a combination of effects, including anti-inflammation and associated reduction of pro-permeability cytokines, including VEGF and TNF-α, as well as a direct effect on enhancing vascular tight junctions. The use of glucocorticoids, however, is limited by potential side effects, including glaucoma and cataract. Glucocorticoids are well-recognized to work through binding to the glucocorticoid receptor (GR), with subsequent modulation of gene expression, including transcriptional activation of multiple anti-inflammatory proteins via binding to glucocorticoid response elements (GREs). Felinski et al. previously identified a GC-responsive cis-promoter element, in the promoter of the tight junction gene occludin, termed the Occludin Enhancer Element (OEE). Interestingly, the OEE was not stimulated directly by activated glucocorticoid receptor (GR).

Keil et al. now identify a heterodimer of transcription factors p54/PSF as OEE binding factors. Furthermore, they perform studies validating the functional role of p54 (also known as NONO) in mediating GC induction of the junctional genes occludin and claudin-5 as well as GC enhancement of endothelial tight junctions. The ability of p54/PSF to bind to the OEE in the promoters of occludin, claudin-5, and cadherin-9 suggests that the OEE can act to coordinate induction of multiple junctional genes in response to glucocorticoids. This constitutes a novel advance in our understanding of glucocorticoid biology, identifying GR-discrete transcriptional activators mediating glucocorticoid effects. Aside from shedding fundamental biologic insights regarding glucocorticoids, this could aid in the development of new therapies for diabetic macular edema targeted specifically toward endothelial tight junctions, therapies that could minimize undesirable side effects.

References