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## MicroRNA and the ocular renin-angiotensin system

**Rashidul Haque**
Emory University, USA

Angiotensin (Ang) II, the most physiologically active component of RAS, mediates its effect through two G-protein coupled receptors, Ang II type 1 or type 2 (AT1R and AT2R), having different signal transduction mechanisms. Most of the known cardiovascular effects of Ang II are mediated by AT1R. Prorenin has long been considered as an inactive precursor of renin, without any biological function of its own. However, prorenin binding to a receptor called (pro)renin receptor (PRR) has been recently reported to exert biological effects in the retina. It is also known now that Prorenin is highly elevated in ocular fluid of diabetic patients with proliferative retinopathy, which all suggest that Prorenin and the system RAS are very important in the eye. Using RNA interference tools, we have shown that both the receptors are implicated in hyperglycemia-induced increase of vascular endothelial growth factor (VEGF), VEGFR2, and transforming growth factor beta (TGFβ1). In order to block the effect of Ang II through AT1R and AT2R, in our experiments we inhibited angiotensin converting enzyme (ACE) by perindopril, where Ang II formation is blocked. We have shown that the increased prorenin synthesis due to hyperglycemia has been attributed to the activation of PRR and VEGF by a mechanism involving NADPH oxidase activity, miRNA-21, HIF1-α and NF-κB. Furthermore, we have demonstrated that the downstream targets of miR-21 are three important genes SMAD7, an inhibitor of TGF-β1-induced VEGF expression, PTEN, a negative regulator of PI3 kinase/Akt signaling pathway and SPRY1, a negative regulator of ERK signaling pathway. The PRR-mediated induction of VEGF under hyperglycemic conditions occurs via Rac1 signaling by regulating miR-21 expression. Our studies suggest that hyperglycemia-induced PRR signaling may play a role in the VEGF-induced angiogenesis that may lead to proliferative diabetic retinopathy, wet AMD and other vascular complications in the eye.

rhaque@emory.edu

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