



Commentary

MicroRNA15a – A Molecule Modulating Multiple Pathologies in Diabetic Retinopathy



Subrata Chakrabarti*

Department of Pathology and Laboratory Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

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In this issue of *EBioMedicine*, Wang and colleagues have demonstrated an important role played by miR15 in diabetic retinopathy (Wang et al., 2016). Using a large number of tools and state of the art technology they showed that in diabetes, miR-15a is reduced both in the bone marrow cells and in the retina. Inhibition of miR-15a upregulated acid sphingomyelinase (ASM), a pro-inflammatory molecule and vascular endothelial growth factor A, an angiogenic molecule expression in the retinal pigment epithelial cells and endothelial cells. Furthermore, migration and retinal vascular repair function was impaired in miR-15a inhibitor-treated circulating angiogenic cells. They further expanded the study to the animal model where they used mice with miR-15a overexpression using Tie-2 promoter. Diabetes induced increased retinal permeability was prevented in these mice. However, such miR-15a overexpression, although reduced ASM and VEGF-A expressions, didn't abolish it completely.

MicroRNAs are increasingly being recognized as molecules with significant modulatory action, in multiple if not all biologic processes (Ghildiyal and Zamore, 2009). Hence, it is highly likely that they are also involved in disease processes and diabetic retinopathy is no exception. Here, this group with longstanding interest and expertise in diabetic retinopathy research demonstrated that miR15 is a potential drug target for the treatment of diabetic retinopathy (add Wang et al. ref.). In keeping with this research, previous studies from several groups including these investigators have demonstrated alterations of multiple microRNAs in chronic diabetic complica-

tions including diabetic retinopathy. The list include miR200b, miR146a, miR195 etc. (Feng et al., 2011; McArthur et al., 2011; Mortuza et al., 2014). However, in most of these publications, investigators used a particular miRNA to target a single mRNA. In this publication, Wang et al. used miR15a to demonstrate that it can be helpful in preventing multiple important biologic processes of significance in diabetic retinopathy, such as increased permeability and angiogenesis (mediated by VEGFA) and inflammatory cytokine production (mediated by ASM) (Penn et al., 2008; Yu et al., 2015). It is of further interest to note that bone marrow derived circulating angiogenic cells (CACs), which normally repairs endothelial injury, are unable to do such repair in diabetes (Kern and Grant, 2013). However miR15a overexpression also corrected these derangements as demonstrated here. Interestingly, although miR15a directly targets VEGFA, it acts on the inflammatory mediators through ASM activation and ceramide production, which allowed it to regulate multiple pro-inflammatory transcripts. In addition, as noted, miR15a also regulates FGF-2. What role FGF-2 played in the context of current pathologies remains to be explored.

There are additional important noteworthy points. Although both retinal pigment epithelial cells (RPE) and endothelial cells showed glucose induced reduction of miR15a and associated alteration, overexpression of miR15a in the endothelial cells (as Tie2 is not expressed in the RPE) prevented diabetes induced changes in the retina, further establishing the notion that retinal endothelial cells are the primary target of tissue damage in diabetes (Khan and Chakrabarti, 2007). However, Tie-2 expressing circulating angiogenic cells (aka endothelial progenitor cells) also contributed to miR15a's preventive effects on the retinal damage in diabetes.

One of the main challenges in the micro RNAs based therapy is that one miRNA has multiple targets and one transcript is regulated post transcriptionally not only by multiple miRNAs, but also by other epigenetic phenomena including other non-coding RNAs, methylation etc. (Ghildiyal and Zamore, 2009; Ruiz et al., 2015). Hence, further investigations related to miR15a's biogenesis and regulations in the context of diabetes are warranted.

In some instances, where alterations of multiple molecules, controlled by one miRNA lead to pathogenesis of a disease, specific miRNA may lend itself to be a potential therapeutic target as shown in this paper. However, a large number of other transcripts are also regulated by miR15a (www.targetscan.org). Hence, other off-target actions may also potentially act as disease modifiers. Furthermore, long term

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* Department of Pathology and Laboratory Medicine, Western University, Rm 4033, Dental Sciences Building, London, Ontario, Canada.

E-mail address: Subrata.Chakrabarti@lhsc.on.ca.

effects of miR15a manipulation in any disease process as well as on other organs are not clear. Hence, long-term studies in larger animal models are needed to broaden our understanding of microRNA based therapy for a chronic disease such as diabetic retinopathy.

Nevertheless the current research is an important step towards developing novel therapeutic approach for the treatment of diabetic retinopathy. From a mechanistic standpoint, it is important to understand these novel molecular regulations aimed towards the development of RNA based therapy for this disease.

Disclosure

The author declared no conflicts of interest.

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