Strain, Diet, and Gender Influence the Role of miR155 in Diabetes Mellitus

Sir,

An integrated view of genetic background, gender, and the tissues studied is essential to decipher the role of miR155 in diabetes mellitus.

MicroRNAs (miRNAs) are increasingly being discovered to mediate several physiological and pathological processes. miRNAs are secreted in vesicles in exosomes and are thought to have paracrine or endocrine effects by suppressing the expression of genes in different tissues. One of the miRNAs, namely miR155, has been extensively studied in immunological and metabolic diseases. miR155 has been shown to be expressed in immune cells and other tissues including adipose tissue and are thought to be involved in several diseases including diabetes mellitus.[1-3] miR155 regulates a number of genes involved in adipogenesis and those involved in carbohydrate and lipid metabolism.[2] Adipocyte-derived miR155 has been demonstrated to take part in the polarization of M1 macrophages and influence diet-induced obesity.[4] In this article, we analyze the role of miR155 in mediating insulin resistance, nonalcoholic steatohepatitis, and diabetes in studies done in mice. Two studies have analyzed the role of miR155 in diet-induced obesity and hepatic steatosis in C57BL/6 strain.[5,6] Miller *et al*. found that miR155 knockout mice in C57BL/6 background developed increased hepatic steatosis in comparison to wild-type mice when they were fed high-fat diet.[5] This study was done only in male mice. Another study by Gaudet *et al*. reported that miR155 knockout female mice in C57BL/6 background were protected from high-fat diet-induced obesity but not male mice.[6] In addition, they also showed that there was less increase in white adipose tissue weight in both male and female mice fed high-fat diet. With respect to glucose metabolism, it was found that female mice with miR155 knockout had improved responses. There was no such improvement noticed in male mice with miR155 knockout in both these studies. It can be summarized from these two studies that in C57BL/6 strain, knockout of miR155 in female mice is associated with protection from obesity and dysfunctional glucose metabolism, a decrease in adipose tissue weight in both male and female miR155 knockout mice, and increased liver steatosis in male miR155 knockout mice. These findings highlight the differential role of miR155 in different gender and tissues analyzed in this particular strain. Similar results have been reported in another recent study done in this strain.[7]

In another recent study, Ying *et al*. explored the miRNAs secreted by adipose tissue macrophages and found that miR155 expression was higher in exosomes from obese mice in comparison to lean mice.[8] They further demonstrated that administration of exosomes from obese mice to lean mice made them insulin resistant by affecting the signaling in muscle, liver, and adipose tissue. In contrast, exosomes from lean mice were protective when administered to obese mice and improved insulin resistance. The same authors studied the effect of high-fat diet in miR155 knockout animals (in C57BL/6 background) and found that insulin sensitivity was better among these mice compared to control mice fed with high-fat diet. This is in stark contrast to another report where the authors found that the deficiency of miR155 led to hyperglycemia and insulin resistance compared to wild-type

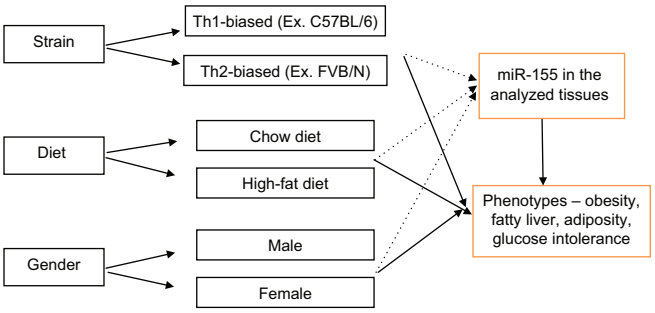

Figure 1: Factors affecting the levels of miR155 in serum and tissues and their role in the causation of insulin resistance and diabetes mellitus can be influenced by a concerted action of strain, diet, and gender. Dotted lines represent the effects mediated through changes in miR155 levels

mice.[9] However, these mice were not fed with high-fat diet. These authors also studied the effects of overexpression of miR155 on insulin resistance and found that global transgenic overexpression of miR155 led to improvement in insulin sensitivity and glucose tolerance. However, this study was done in FVB/N strain which is different in immunological responses as well as susceptibility to diet-induced obesity than C57BL/6 strain. They also found that overexpression of miR155 led to improved insulin signaling in liver, muscle, and adipose tissue, contrary to the findings of Ying *et al*.[8] These findings highlight the importance of the influence of genetic background in metabolic studies.

The comparative analysis of studies reporting on the role of miR155 in metabolic diseases presented in this article suggests the importance of considering the influence of background strain, gender of mice, and the tissues analyzed in various studies.[10] It is, therefore, important that the findings are interpreted by considering these variables [Figure 1] which may influence outcomes in these types of studies to have an impact on translational medicine.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Klöting N, Berthold S, Kovacs P, Schön MR, Fasshauer M, Ruschke K, *et al.* MicroRNA expression in human omental and subcutaneous adipose tissue. PLoS One 2009;4:e4699.
2. Shantikumar S, Caporali A, Emanueli C. Role of microRNAs in diabetes and its cardiovascular complications. Cardiovasc Res 2012;93:583-93.
3. Assar ME, Angulo J, Rodríguez-Mañas L. Diabetes and ageing-induced vascular inflammation. J Physiol 2016;594:2125-46.

4. Zhang Y, Mei H, Chang X, Chen F, Zhu Y, Han X, *et al.* Adipocyte-derived microvesicles from obese mice induce M1 macrophage phenotype through secreted miR-155. J Mol Cell Biol 2016;8:505-17.
5. Miller AM, Gilchrist DS, Nijjar J, Araldi E, Ramirez CM, Lavery CA, *et al.* MiR-155 has a protective role in the development of non-alcoholic hepatosteatosis in mice. PLoS One 2013;8:e72324.
6. Gaudet AD, Fonken LK, Gushchina LV, Aubrecht TG, Maurya SK, Periasamy M, *et al.* MiR-155 deletion in female mice prevents diet-induced obesity. Sci Rep 2016;6:22862.
7. Velázquez KT, Enos RT, Carson MS, Cranford TL, Bader JE, Sougiannis AT, *et al.* MiR155 deficiency aggravates high-fat diet-induced adipose tissue fibrosis in male mice. Physiol Rep 2017;5. pii: e13412.
8. Ying W, Riopel M, Bandyopadhyay G, Dong Y, Birmingham A, Seo JB, *et al.* Adipose tissue macrophage-derived exosomal miRNAs can modulate *in vivo* and *in vitro* insulin sensitivity. Cell 2017;171:372-84.e12.
9. Lin X, Qin Y, Jia J, Lin T, Lin X, Chen L, *et al.* MiR-155 enhances insulin sensitivity by coordinated regulation of multiple genes in mice. PLoS Genet 2016;12:e1006308.
10. Prakash SS. Immune class regulation as an integrated response of factors related to host, stimulus and context. Scand J Immunol 2018;87:e12656.

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