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The accumulated acrolein in *akr1a1a* zebrafish mutants promotes insulin resistance leading to hyperglycemia and retina vessels alteration

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Diabetes mellitus is a worldwide disease with increasing prevalence globally. Type 2 diabetes is considered the primary subtype that occupies vast amounts of cases and is characterized by insulin resistance. Therefore, early diagnosis and insulin resistance intervention are more than necessary in treating diabetes and relevant complications. However, up to now, there is still a lack of influential factor for predicting the onset of insulin resistance and molecular mechanisms behind insulin resistance is also far away from clarity.

In my study, by using CRISPR/CAS9 technology, Akr1a1a knockout zebrafish model was generated. A series of experiments were performed regarding the vasculature, glucose homeostasis, and metabolism after Akr1a1a loss. The main discoveries of this dissertation are: *akr1a1a*$^{-/-}$ larvae and adults exhibit impaired ACR detoxification ability and increased internal ACR concentration, which induces the downregulation of *insra/insrb* expression and leads to insulin resistance and hyperglycemia. Impaired glucose homeostasis causes abnormal angiogenesis in retina hyaloid vasculature and can be reversed by L-carnosine and PK11195 application in larvae. Meanwhile, prolonged and impaired glucose homeostasis in *akr1a1a*$^{-/-}$ adults results in angiogenic retina vessels and thickening GBM in the kidney, parallel with an early pathological appearance in diabetic retinopathy and nephropathy.

At last, in my study, a clear connection between acrolein and insulin resistance has been confirmed in zebrafish, suggesting acrolein as a promising candidate to predict insulin resistance in clinics. It also implies that acrolein would be a target for early intervention for insulin resistance. Moreover, since L-carnosine and PK11195 could rescue the vascular effects caused by acrolein, indicating these drugs as hopeful candidates to treat acrolein-induced vascular diseases.

Overall, this dissertation provided patent evidence for the contribution of poor acrolein detoxification and subsequently increased acrolein concentration to the development of hyperglycemia via insulin receptor signaling dysfunction in *akr1a1a* mutants, as a novel direction for future research regarding diabetic pathophysiology and therapy.