Histone H1.2 regulates autophagy in the development of diabetic retinopathy

Wenjun Wang¹, Ling Zheng¹*

¹College of Life Sciences, Wuhan University, Wuhan, Hubei, P. R. China, 430072

Corresponding author

Ling Zheng, Ph.D.
College of Life Sciences
Wuhan University
lzheng217@hotmail.com
Abstract

Autophagy plays critical and complex roles in a lot of human diseases, including diabetes and its complications. However, the role of autophagy in the development of diabetic retinopathy remains uncertain. It has been reported that core histone modifications were involved in the development of diabetic retinopathy, but little is known about the linker histone variants. Here, we observed increased autophagy and histone H1.2, an important variant of the linker histone H1, in the retinas of type 1 diabetic rodents. Overexpression of histone H1.2 up-regulates SIRT1 and HDAC1 to maintain the deacetylation status of H4K16, which leads to up-regulation of autophagy-related proteins, then promotes autophagy autophagic death in two cultured retinal cell lines. Increased inflammation and cell toxicity was found flowing the overexpression of histone H1.2 in vitro. However, knockdown of histone H1.2 significantly inhibited both the basal autophagy and high glucose induced autophagy/inflammation/cell toxicity. More importantly, overexpression of histone H1.2 in the retinas also enhanced the autophagy level, inflammation, glial activation and neuron loss, which were similar to the pathological changes identified in the early stage of diabetic retinopathy. Furthermore, knockdown of histone H1.2 by siRNA in the retinas of diabetic mice significantly attenuated the diabetes-induced autophagy, inflammation, glial activation and neuron loss. In conclusion, up-regulation of histone H1.2 in the retinas causes deacetylation of H4K16 and promotes autophagy, accompanied with inflammation and cell loss, which contribute to the development of
diabetic retinopathy. These results indicate that histone H1.2 may offer a novel therapeutic target for preventing diabetic retinopathy.

**Key words:** diabetic retinopathy, histone H1.2, autophagy flux, inflammation, cell toxicity