MASTER THESIS TITLE:

Investigation of the protective effect of histone deacetylase (HDAC) inhibitors and proteolysis-targeting chimera (PROTAC) on MNNG-induced parthanatos in vitro model and the involvement of macrophage migration inhibitory factor (MIF)

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SUMMARY

Background: Macrophage migration inhibitory factor (MIF) proved to be a key player in the MIF/AIF (apoptosis-inducing factor) complex, which is a complex that plays a role in parthanatos. This suggests that MIF modulators could prevent this type of cell death. A prior study indicates that MIF is a substrate for deacetylation by HDAC6 and that acetylation of MIF protects neurons from ischemic injury, which indicates that HDAC inhibitors could prevent parthanatos. Here, we aim to explore the potential of HDAC inhibitors with different selectivity profiles to inhibit parthanatic cell death.

Methods: We employed a model for parthanatos cell death by treatment with methylnitronitrosoguanidine (MNNG). Small molecule HDAC modulators were screened for inhibition of parthanatic cell death. MIF knockout cell lines were used as controls. Western blotting and confocal microscopy were used to study the MIF protein levels and the MIF protein localization respectively.

Results: We identified that the HDAC8 inhibitor PCI-34051 protects HEK293 and HeLa cells from MNNG-induced parthanatic cell death. With MIF ablation, the protective effect of PCI-34051 was absent, thus indicating that MIF acetylation might be affected by HDAC8 according to a mechanism similar to HDAC6. Nevertheless, MIF translocation to the nucleus was not obviously affected, while AIF translocation to the nucleus was obviously less pronounced. This provides a basis to explore the connection between HDAC8 inhibition, MIF acetylation and its role in parthanatos further.