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p75NTR modulation reduces oxidative stress and inflammation in a cell model of Rett syndrome

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INTRODUCTION & AIM

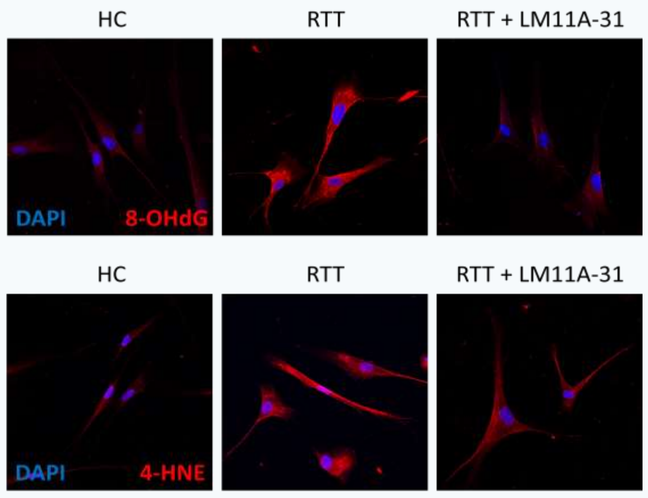
Rett syndrome (RTT, OMIM 312750) is a severe, progressive neurodevelopmental disorder primarily affecting females, leading to cognitive and physical disabilities [1]. It is now recognized as a multisystem syndrome involving redox imbalance and heightened inflammation. Indeed, these derangements appear to play a central role in the pathological manifestations of the disease [2,3]. The low-affinity neurotrophin receptor p75 (p75NTR) is implicated in disorders associated with oxidative stress (OS) and inflammation [4], but its role in RTT remains unexplored. To date, several synthetic compounds have been developed to modulate p75NTR activity, providing new therapeutic opportunities for conditions associated with its dysfunctional signaling of this receptor. This study aimed to assess whether modulating p75NTR with LM11A-31 could mitigate OS and inflammation in RTT. Fibroblast cultures from RTT patients and healthy controls were used as experimental models.

METHOD

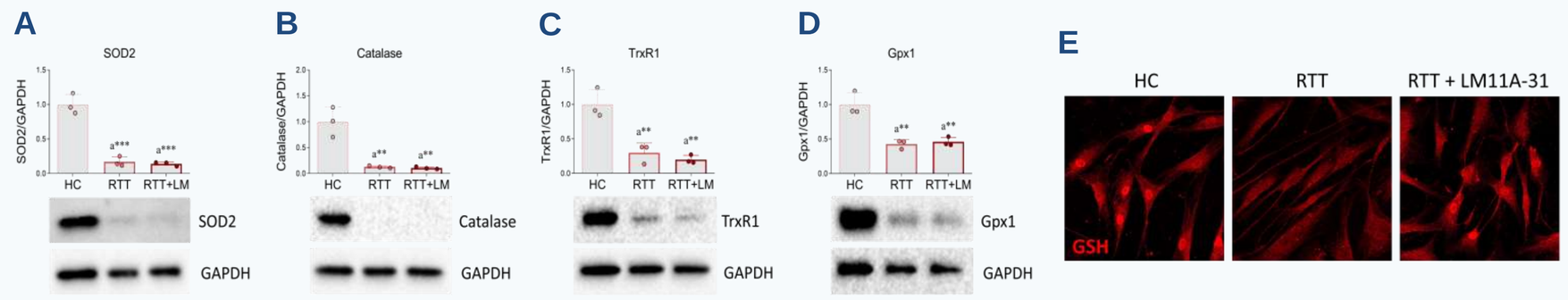
Fibroblasts from healthy donors (HC) and RTT patients (RTT) were cultured at 37°C in a 5% CO_2 atmosphere using DMEM supplemented with 10% FBS. The experimental groups included HC, RTT, and RTT treated with LM11A-31 at a concentration of 0.1 µM for 24 h. Western blot and immunofluorescence analyses were performed to evaluate OS and inflammatory markers. Data represent the mean of at least three biological replicates. Statistical analysis was conducted using one-way ANOVA with Tukey's post-hoc test, considering $P < 0.05$ as statistically significant.

RESULTS & DISCUSSION

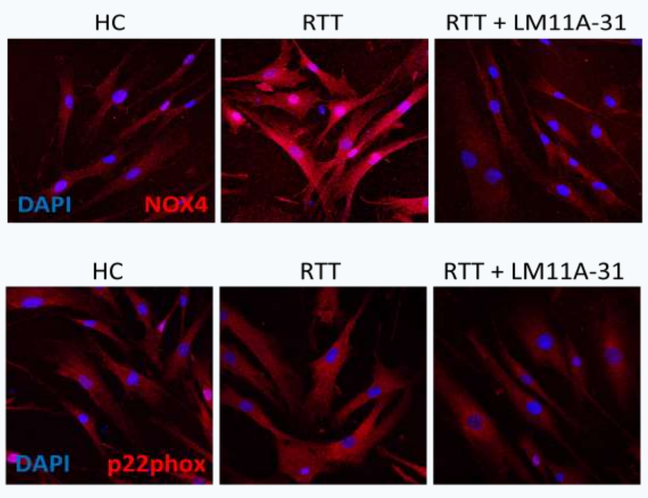
1 LM11A-31 prevents oxidative damage in RTT fibroblasts



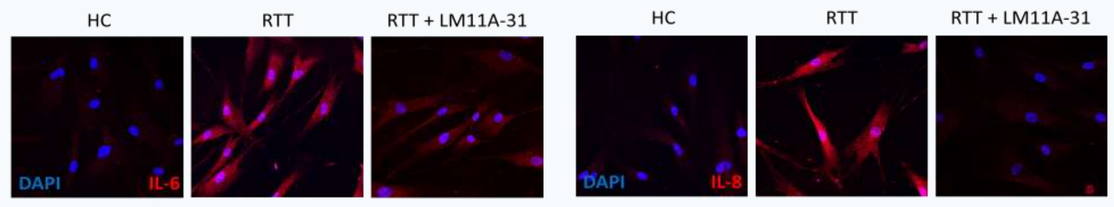
2 LM11A-31 treatment does not modify the altered expression of key anti-oxidant enzymes in RTT patients (A,B,C,D). However, pharmacological modulation of p75NTR restores GSH levels (E)



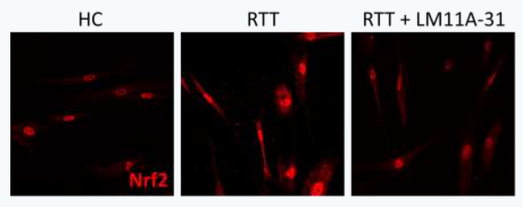
3 LM11A-31 partially counteracts dysregulated subunits expression of the pro-oxidant NADPH oxidase



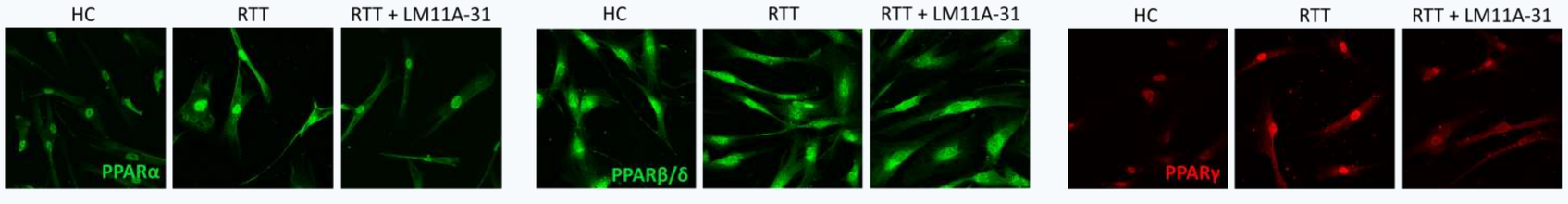
4 p75NTR modulation attenutates the increased expression of inflammatory mediators observed in RTT cells



5 LM11A-31 mitigates Nrf2 dysregulation in RTT



6 p75NTR modulation by LM11A-31 normalizes the expression of PPARs in RTT fibroblasts



CONCLUSION

RTT fibroblasts exhibit disrupted redox balance and elevated inflammatory markers. p75NTR modulation restores GSH levels and normalizes NOX4, mitigating OS. As a compensatory response to oxinflammation, Nrf2 and PPARs are upregulated, but LM11A-31 treatment reverses this effect, suggesting a promising therapeutic strategy.

FUTURE WORK / REFERENCES

Further in vivo studies will be essential to determine whether LM11A-31 can ameliorate the pathological phenotype in RTT, potentially paving the way for novel therapeutic strategies.

[1]Chahrour and Zoghbi, 2007. Neuron.; [2]Pecorelli et al.,2016. Int J Biochem Cell Biol.; [3]Valacchi et al., 2017. Free Radic Biol Med.; [4]Kraemer et al., 2014. J. Biol. Chem.