

Could succination be involved in cardiotoxicity?

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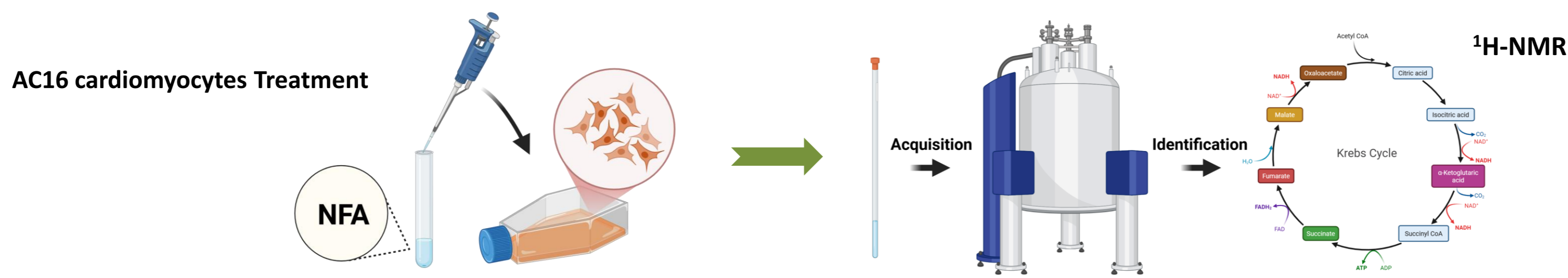
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INTRODUCTION & AIMS

The small ubiquitin-like modifier 1 (SUMO1) is a key regulator of the sarcoplasmic/endoplasmic reticulum Ca²⁺ ATPase 2a (SERCA2a), which facilitates the reuptake of Ca²⁺ in the sarcoplasmic reticulum after contraction. Any change in SUMO1 could affect SERCA2a's activity and stability, hence cause cardiotoxicity. In a previous study, we demonstrated that succination, an irreversible post-translational modification resulting from the spontaneous interaction of fumarate with reactive cysteine thiols, can target SUMO1. This study aims at understanding the impact of SUMO1 succination on SERCA2a SUMOylation, with the hope to better understand heart physiopathology.



METHODS

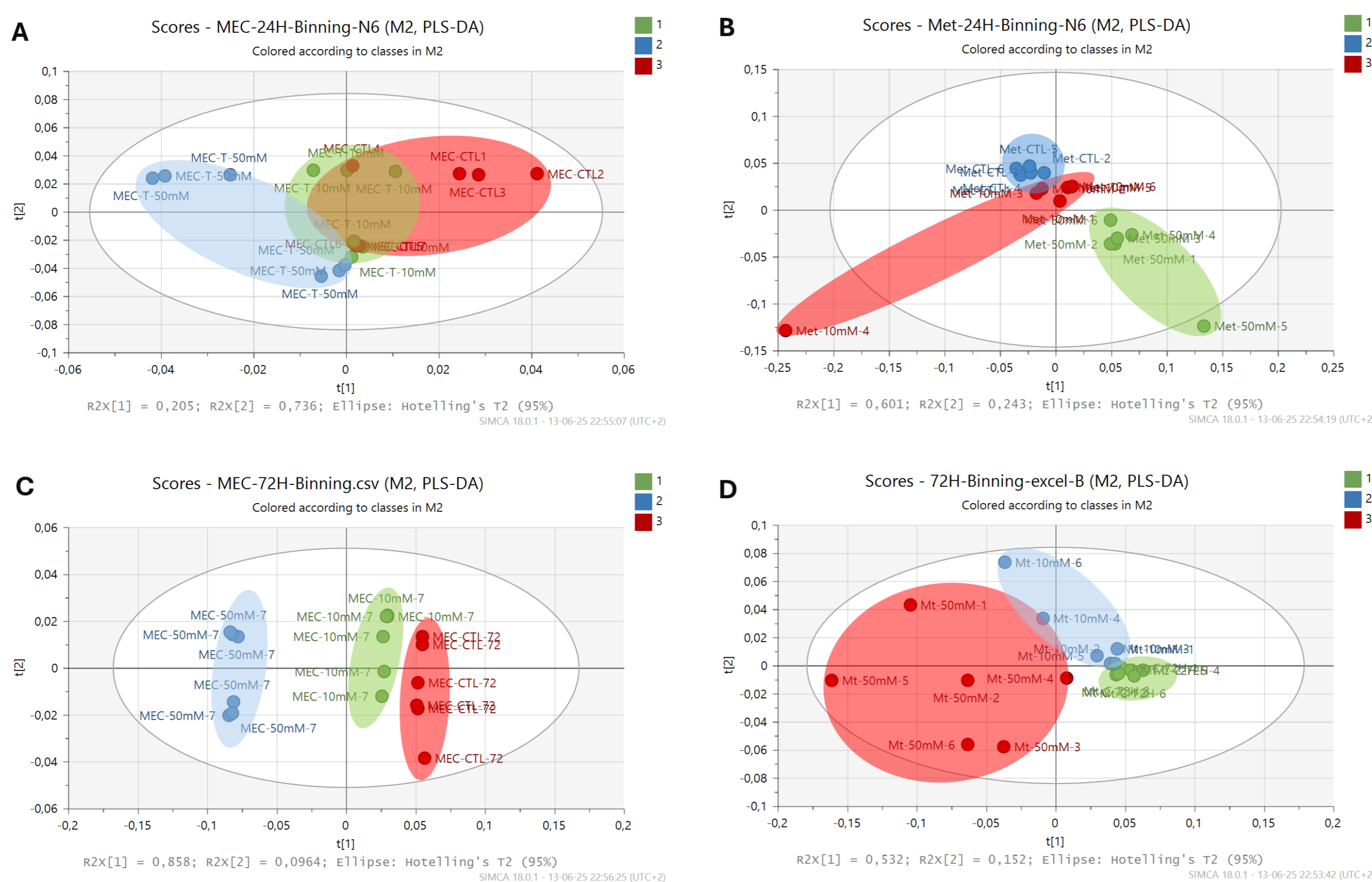


Figure 1: Score plots of PLS-DA. **A.** Results showing the separation between the control group (in red), the 10mM NFA (in green) and the 50mM (in blue) NFA in extracellular media after 24h of treatment. **B.** Results showing the separation between the control group (in blue), the 10mM NFA (in red) and the 50mM (in green) NFA in polar phase after 24h of enrichment. **C.** Results showing the separation between the control group (in red), the 10mM NFA (in green) and the 50mM NFA (in blue) in extracellular media after 72h of enrichment. **D.** Results showing the separation between the control group (in green), the 10mM NFA (in blue) and the 50mM NFA (in green) in polar phase after 72h of enrichment. CV-ANOVA p-value : **A.** 1, **B.** 1, **C.** 0,0025307, **D.** 0,810605.

RESULTS & DISCUSSION

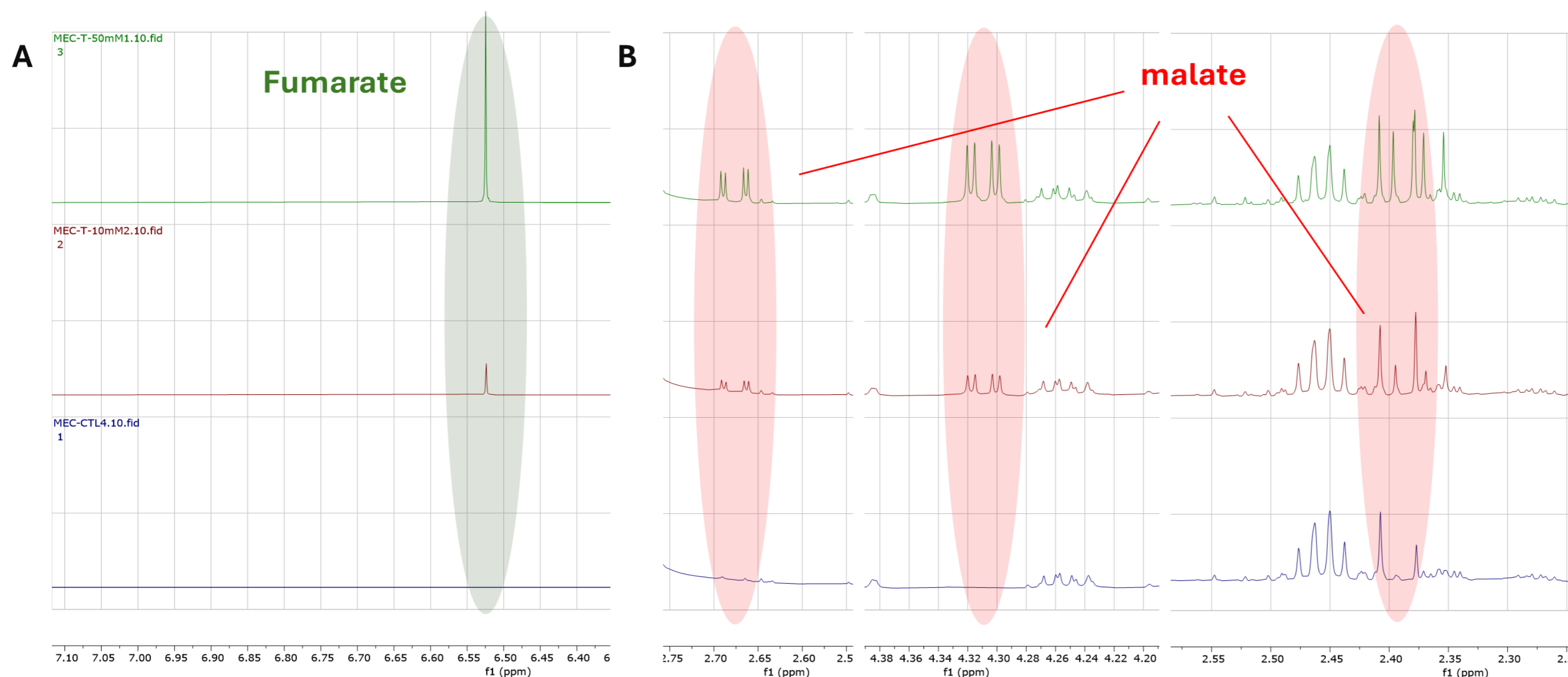


Figure 2: **A.** Extracellular media results showing the increase in Fumarate's concentration following the addition of NFA concentrations 10mM and 50mM in comparison to the untreated control group after 24H. **B.** Extracellular media spectra, showing an elevation in malate metabolite in the treated groups (in red) following the addition of 10mM and 50mM of NFA to the media in comparison to the non-treated groups after 24H.

Preliminary ¹H-NMR results suggest the occurrence of succination in NFA enriched cells starting at a concentration of 10mM of FA. These results are supported by the findings in western blot and calcium assay (not presented), All together, the results suggest that the treatment of NFA induces a modification in the function of SUMO1, leading to a decrease in the intracellular calcium fluxes in the cell. In perspective, it would be interesting to investigate whether SERCA2a's function was affected following SUMO1's potential succination, this could reveal an interesting and novel cardiotoxic mode of action.

CONCLUSION, CURRENT & FUTURE WORK

REFERENCES

- Gu, Y., Fang, Y., Wu, X. et al. The emerging roles of SUMOylation in the tumor microenvironment and therapeutic implications. *Exp Hematol Oncol* 12, 58 (2023). <https://doi.org/10.1186/s40164-023-00420-3>
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