The Interplay between two PTMs: Succination and SUMOylation

A. FIZAZI[1,2], A-E. DECLEVES[2], J-M. COLET[1].
[1]Human biology and toxicology laboratory, [2]Metabolic and Molecular Biochemistry Laboratory.
University of Mons. Mons, Belgium. A.R.C. Funding
Afaf.FIZAZI@UMONS.ac.be

health risks

Introduction

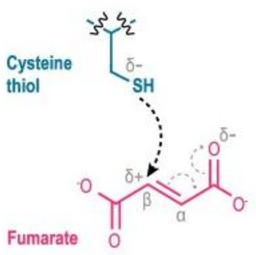
Post-translational modifications (PTMs) are pivotal in controlling a protein's activity and the equilibrium within a cell. Both succination and SUMOlylation have emerged independently as pathways which exacerbate the advancement of tumors by affecting cancer-related genes, cellular metabolism, and stress responses. While SUMOylation can be irreversible and remains subject to tight control, succination is driven by an irreversible modification due to the accumulation of the oncometabolite fumarate. Despite the increasing importance these two modifications hold in cancer research, the possible relationship between the two remains mostly neglected. This research explores the relationship between them in the context of cardiovascular disease (CVD), a field where interest in the role of PTMs is on the rise, by using human AC16 cardiomyocytes treated with fumarate as a model. Our findings suggest that succination may impair SUMOylation activity, offering new insights into calcium regulation and PTM-linked cardiotoxicity.

SUMOylation

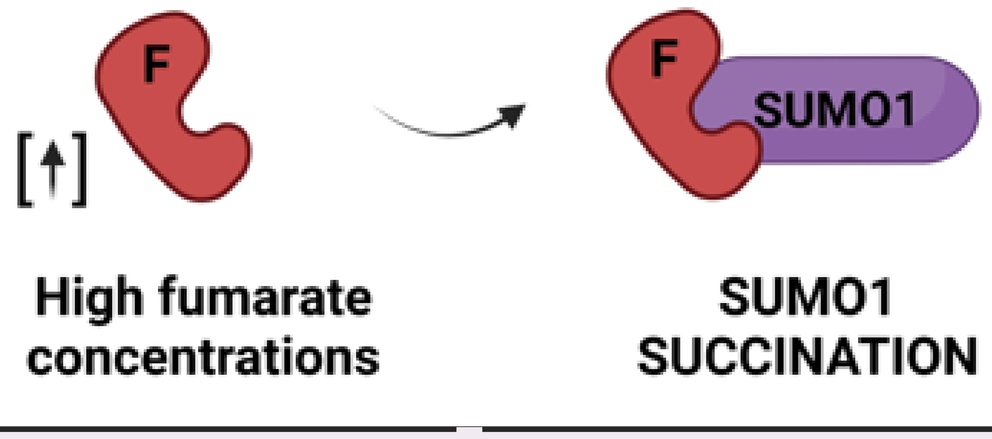
- Affects Tumor Microenvironment
- Epigenetic modification
- Protein function alteration
- Therapeutic Implications

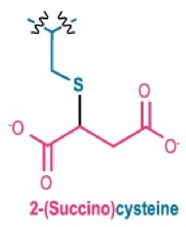
Succination

- Metabolic Reprogramming
- Irreversible modification
- Cancer pathway activation
- Epigenetic Alterations



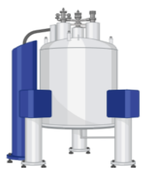
Interplay



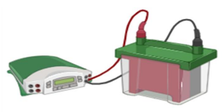


Aims and methods

1. Succination model development using AC16 cardiomyocytes

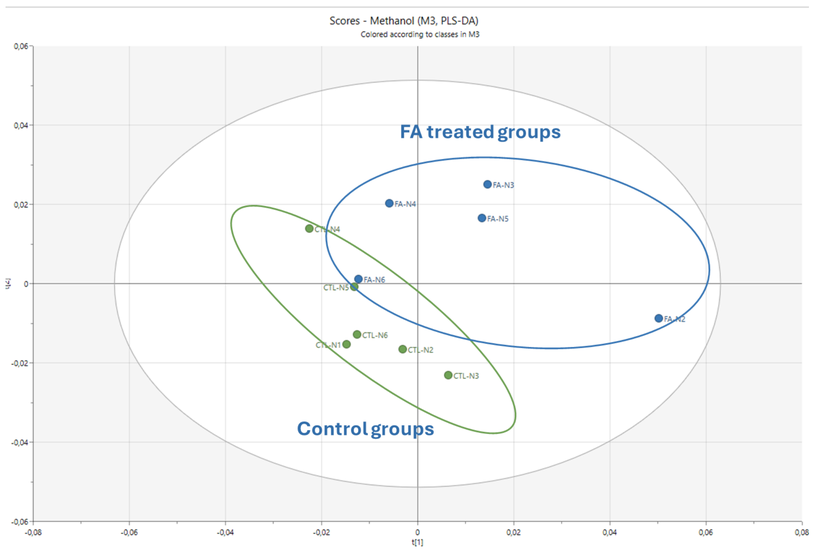


2. Model characterization using ^{1}H-NMR spectrometry



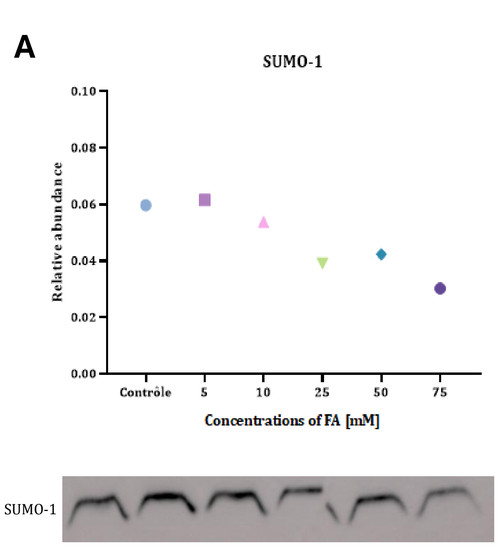
3. Model characterization using Western blotting (on cell extract and on bench assay using a SUMOylation kit)

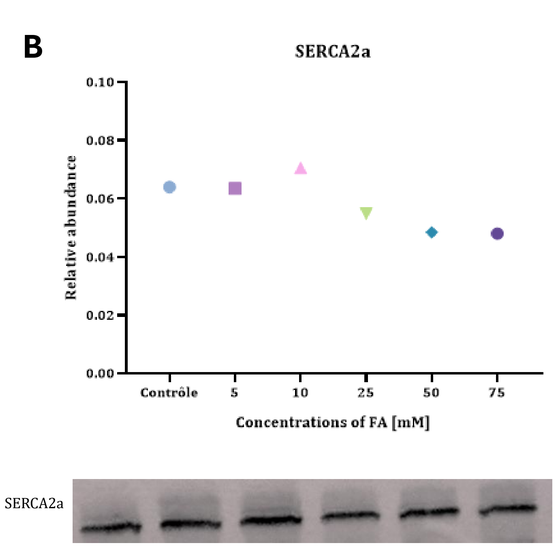
Results

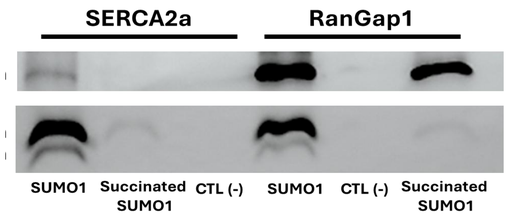


PLS-DA : R2X[1] = 0,462; R2X[2] = 0,181; Ellipse: Hotelling's T2 (95%)

Figure3: Score plot of PLS-DA showing the separation of the treated groups (in blue) from the Control groups (in green).







. Representative immunoblots of SUMOylated vs non-SUMOylated SERCA2a and RanGap1. SERCA2a and RanGap were SUMOylated (following the SUMOylation cycle), with either normal SUMO1 or succinated SUMO1 (with 100x DiethylFumarate for 24H at 37°C).

References

Spinozi L, Tagliatti V, De Winter J, Colet JM. In vitro study of the impact of a metabolic modification on the succinylation/succinylation process in cardiomyocytes. 2021

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

Schmidt C, Sciacovelli M, Frezza C. Fumarate hydratase in cancer: A multifaceted tumour suppressor. Semin Cell Dev Biol. 2020 Feb;98:15-25. doi: 10.1016/j.semcdb.2019.05.002. Epub 2019 May 22. PMID: 31085323; PMCID: PMC6974395.

Figures were created on Biorender.com