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May post-translational succination be involved in cardiac arrhythmia? A joint study between (ion mobility) mass spectrometry and molecular dynamics

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During the Krebs cycle, the fumarate is converted into malate by the addition of a molecule of water catalysed by fumarate hydratase. But in some diseases, there is a germline mutation of the fumarase gene resulting in an enzymatic deficiency and therefore an accumulation of fumarate [1]. This molecule can undergo a Michael addition with proteins that present free thiol functions (free cysteines) and this physiologically irreversible reaction is called succination. 2-succinocystein molecules are known to be involved in some pathologies such as diabetes or cardiomyopathies when they are overexpressed [2]. An immunoassay highlighting the reaction products of succination is available. However, no information about the spontaneity of these reactions can be deducted and their efficiency remains relatively controversial in the literature [3]. In this study, an MS-based approach was selected as a potential alternative to the current assay. Indeed, using this technique could increase the knowledge about succination by determining the reaction spontaneity and the maximal number of moieties that can be grafted into the target. The first objective was to verify the existence of spontaneous reactions of succination by MS-based approach. The spontaneity of the succination reaction has been highlighted. Indeed, some peptides/proteins with free cysteines were spontaneously succinated, such as glutathione and SUMO1. SUMO1 is used in the stabilization of some target proteins, including SERCA2, a protein involved in Ca^{2+} regulation during cardiac contraction [4]. Thus, our main objective is to evaluate by Ion Mobility Mass Spectrometry and molecular dynamics whether SUMO1 succination has an impact on its 3D structure and therefore, whether it has an impact on its function and plays a role in cardiac arrhythmia.

References

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