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Lovastatin inhibits Triple - Negative Breast Cancer stem cells through lysine crotonylation and succinylation of ribosomal and cytoskeletal proteins

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Triple-Negative Breast Cancer (TNBC) is the most difficult-to-treat breast cancer subtype. Statins have gained increasing interest as anti-cancer drugs in preclinical investigations. However, clinical trials with statins have yielded inconsistent results. We demonstrated that lovastatin inhibited stemness properties, enhanced chemosensitivity and induced autophagy/apoptosis in Cancer Stem Cells (CSCs) derived from TNBC cells. In a mouse model of orthotopic tumor growth, Lovastatin inhibited tumor burden, CSC markers, angiogenesis and tumor-stromal interaction and induced cell death in TNBC CSCs. Similar results were not observed in non-TNBC cells *in vitro* or *in vivo*. Using TMT labeling followed by high-resolution LC-MS/MS, we performed global profiling of the proteome and lysine acylome in MDA-MB-231 (TNBC) vs. MDA-MB-453 (non-TNBC) CSCs. GO pathway analysis revealed significant enrichment in lysine crotonylome and succinylome but not in the proteome in MDA-MB-231 CSCs treated with lovastatin, suggesting that lysine acylation but not proteomic alteration was the preferred mechanism of lovastatin's inhibitory effects on TNBC CSCs. Specifically, acylation enrichment was found in two functional categories, i.e., ribosomal constituents and cytoskeletal protein binding, both involved in stress response. Enhanced ribosome biogenesis was confirmed by increased staining of the argyrophilic nucleolar organizer region in Lovastatin-treated CSCs. Actin cytoskeleton disruption was confirmed by nuclear/perinuclear translocation of F-actin in Lovastatin-treated CSCs. Our data suggest that Lovastatin-induced lysine acylation mediates stress response which results in disruption of protein homeostasis and eventual cell death of TNBC CSCs. These findings support the use of lovastatin as a candidate targeted drug for the precision therapy of TNBC patients.

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