The Ubiquitin-Editing Enzyme A Targets Degradation of SLC7A11 Promoting Ferroptosis to tumour suppression

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Ferroptosis, firstly demonstrated in 2012, is a newly recognized type of iron- and lipid hydroperoxides-dependent regulated cell death, which morphologically, biochemically and genetically distinct from other types of cell death including apoptosis, autophagy, necrosis and pyroptosis. It is involved in various degenerative diseases and represents a targetable susceptibility in certain cancers. The ferroptosis-susceptible cell state can either pre-exist in cells that arise from certain lineages or be acquired during cell-state transitions. A series of strategies have been developed to induce ferroptosis to eliminate cancer cells, including overexpression or knockdown/knockout of ferroptosis-related genes, use of clinical drugs, chemical compounds, and iron-containing nanomaterials. These studies have raised that ferroptosis might be a new option for clinical cancer therapy. The abundance of any protein is determined by the balance between protein synthesis and protein degradation. Regulated protein degradation has emerged as a powerful strategy to precisely control individual protein abundance within cells, which is largely mediated by the ubiquitin-proteasome system (UPS). The hierarchical nature of the UPS provides a rich source of molecular targets for specific intervention and has therefore arisen as a promising approach to innovative anticancer therapies. Here we use DUBs-wide CRISPR–Cas9 suppressor screens to identify Enzyme A as critical contributors to ferroptosis sensitivity in human renal carcinoma cells. Our results show that Enzyme A contribute to ferroptosis by down-regulation the protein level of SLC7A11, a key component of the cystine-glutamate antiporter, which can augment the level of lipid peroxidation within cells leading to the duction of ferroptosis. Carcinoma cells that are initially sensitive to ferroptosis can switch to a ferroptosis-resistant state, which is associated with up-regulation of SLC7A11. We further find that Enzyme A negatively correlates with renal cancer development. Together, our work reveals that a regulatory mechanism of the Enzyme A-SLC7A11 axis in renal cancer cells may be a potential target for treating renal carcinoma.