Uncovering the function of Ferritin heavy chain (FHC) in human embryonic stem cells

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Embryonic stem cells (ESCs) own the ability to differentiate into all cell lineages and are characterized by self-renewal. In this study, we highlighted the cellular profile of human ESCs (hESCs) in response to iron intracellular accumulation after the stable knockdown of ferritin heavy chain (FTH1) gene. FTH1 is known to be the major iron storage of the organism with antioxidant properties and ferroxidase activity. To preserve their morphological and functional integrity, cells promote the activation of detoxifying and repair systems, which are highly operational in ESCs, for restoring their finely modulated redox homeostasis. Here, we investigated the interaction between nuclear factor (erythroid-derived-2)-like 2 (Nrf2) and pentose phosphate pathway (PPP) that play a key role when oxidative stress is particularly abundant in hESCs. We found that FTH1 silencing in hESCs does not induce the rise of reactive oxygen species (ROS) production, confirming that these cells are able to activate efficient mechanisms against oxidative stress-induced cell injuries. Taken together, our results show that FTH1 silencing triggers the activation of NRF2 signaling and PPP. Their crosstalk leads to the activation of hESCs antioxidant cascade events, counteracting the effects caused by FTH1 silencing. To our knowledge, this is the first evidence of an interplay between FTH1 silencing and the activity of NRF2 signaling pathway in ESCs, describing their phenotypic structure under oxidative stress conditions.