Abstract

Herbal medicines and their bioactive compounds are increasingly being recognized as useful drugs for cancer treatments. The parasitic fungus Cordyceps militaris is an attractive anticancer herbal since it shows very powerful anticancer activity due to its phytocompound cordycepin. We previously discovered and reported that a high amount of xylitol is present in Cordyceps militaris extract, and that xylitol unexpectedly showed anticancer activity in a cancer-selective manner. We thus hypothesized that xylitol could become a useful supplement to help prevent various cancers, if we can clarify the specific machinery by which xylitol induces cancer cell death. It is also unclear whether xylitol acts on cancer suppression *in vivo* as well as *in vitro*. Here we show for the first time that induction of the glutathione-degrading enzyme CHAC1 is the main cause of xylitol-induced apoptotic cell death in cancer cells. The induction of CHAC1 is required for the endoplasmic reticulum (ER) stress that is triggered by xylitol in cancer cells, and is linked to a second induction of oxidative stress in the treated cells, and eventually leads to apoptotic cell death. Our *in vivo* approach also demonstrated that an intravenous injection of xylitol had a tumor-suppressing effect in mice, to which the xylitol-triggered ER stress also greatly contributed. We also observed that xylitol efficiently sensitized cancer cells to chemotherapeutic drugs. Based on our findings, a chemotherapeutic strategy combined with xylitol might improve the outcomes of patients facing cancer.