How can a milk protein selectively kill cancer cells? Mechanisms underlying lactoferrin-induced apoptosis

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Lactoferrin (Lf) is an iron-binding protein abundant in milk that has been shown to exhibit anticancer activity. Since Lf is non-toxic to cancer cells (1) and is well tolerated in humans (2), this protein has a huge potential to be used in cancer therapy. However, the targets and mechanisms underlying its selective anticancer activity are poorly elucidated, which limits its clinical exploitation. The recruitment of the proton pump V-ATPase to the plasma membrane, where it mediates the acidification of the tumor microenvironment, is a recognized feature involved in the acquisition of a metastatic phenotype in different cancers, including breast cancer. Therefore, inhibitors of this pump have emerged as promising anticancer drugs. Here we show that bovine lactoferrin (bLf) preferentially inhibits cell proliferation and induces apoptosis in two highly metastatic breast cancer cell lines, which display a prominent localization of V-ATPase at the plasma membrane, but not in a lowly metastatic or a non-tumorigenic cell lines (3). We then characterized the mechanism underlying bLf-induced apoptosis and demonstrated that bLf selective cytotoxicity is caused by the inhibition of extracellular acidification rate and the ensuing intracellular acidification in the highly metastatic breast cancer cells. Accordingly, bLf, like the well-known proton pump inhibitors concanamycin A and bafilomycin A1, inhibits V-ATPase proton pumping and hydrolytic activities in sub-cellular fractions enriched in this proton pump. We recently also demonstrated that bLf preferentially induces apoptosis in other types of highly metastatic cancer cells other than breast (4). Altogether, our data demonstrated for the first time that bLf acts as a V-ATPase inhibitor and established a common mechanism of action of bLf against highly metastatic cancer cell exhibiting this proton pump at the plasma membrane. This study opens promising perspectives for the safer and more rational application of bLf in the therapy of these life-threatening cancers.

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