Lactoferrin selectively triggers apoptosis in highly metastatic breast cancer cells through inhibition of plasmalemal V-H+-ATPase [P7/20]

Cátia S. Pereira [1,2]; Joana P. Guedes [1,2], Marília Gonçalves [1,3], Luís Loureiro [1,3], Lisandra Castro [1], Hernâni Gerós [3], Lígia R. Rodrigues [2], Manuela Côrte-Real [1]

[1] *Centre of Molecular and Environmental Biology (CBMA), Department of Biology, University of Minho, Braga, Portugal*
[2] *Centre of Biological Engineering (CEB), Department of Biological Engineering, University of Minho, Braga, Portugal*
[3] *Centro de Investigação e Tecnologias Agroambientais e Biológicas (CITAB), Department of Biology, University of Minho, Braga, Portugal*

Breast cancer is the most common cancer in women worldwide. Metastatic breast cancer cells are known to display V-H+-ATPase at the plasma membrane, where it is involved in the acquisition of a more metastatic phenotype. Therefore, V-H+-ATPase emerged as a promising candidate for breast cancer therapy, and inhibitors of this pump as potential anticancer drugs. Lactoferrin (Lf) is a natural pro-apoptotic glycoprotein with anticancer activity against various human cancer models. Although Lf can regulate different apoptotic components, the cellular targets of this protein are still unknown. We found that bovine Lf (bLf) is preferentially cytotoxic for highly metastatic breast cancer cells, in comparison with poorly metastatic and non-tumorigenic breast cells. We further demonstrated that this cell-type specific effect against highly metastatic cells is associated with a higher extracellular acidification rate (ECAR) and prominent V-H+-ATPase localization at the plasma membrane. Accordingly, we found that bLf selectively reduces the ECAR and induces intracellular acidification of the highly metastatic cancer cells, and targets V-H+-ATPase inhibiting its proton pumping/hydrolytic activities. In summary, we unveil V-H+-ATPase as a Lf target, which explains its selectivity for highly metastatic breast cancer cells. Thus, our findings may lay the foundation for future *in vivo* studies aiming to exploit the use of this natural protein as a novel V-H+-ATPase inhibitor for the treatment of highly metastatic breast cancers, seemingly with advantages over the toxic V-H+-ATPase inhibitors currently available since it is safe and well-tolerable.

Keywords: Lactoferrin, V-H+-ATPase, breast cancer, V-H+-ATPase inhibitor, extracellular acidification rate

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CBMA – Centro de Biologia Molecular e Ambiental
Universidade do Minho
Departmento de Biologia
Campus de Gualtar
4710 - 057 Braga, Portugal

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