Protein-Fatty Acid Complexes that Exhibit Tumoricidal Activity: From Basic Research to Clinical Trials

K. Hun Mok(mok1@tcd.ie)
Trinity College Dublin

Abstract

HAMLET (Human α-lactalbumin Made Lethal to Tumour cells) and its related partially unfolded protein–fatty acid complexes are novel biomolecular nanoparticles that possess relatively selective cytotoxic activities towards tumour cells [1,2]. Spearheaded by C. Svanborg and her associates - through the utilization of a full arsenal of techniques in cell biology, transcriptomics, proteomics, imaging, and in vivo studies - significant progress has been made to deduce the underlying mechanism(s) of cell death brought about by HAMLET and other related complexes such as BAMLET [3]. From a protein biophysical chemists' / structural biologists' point of view, during the past few years, we have chosen to ask what would be the 'minimal cytotoxic unit' to give rise to this remarkable property [4]. It is now well known that one of the key characteristics is that the protein moiety possesses properties akin to an IDP (intrinsically disordered protein). An unanticipated consequence is that such structural versatility may be endowing native proteins with additional functions in the alternatively folded states.

Experimentally, significant results have confirmed previous suggestions that the fatty acid moiety may be the ultimate cytotoxic agent, and that the protein moiety simply serves as carrier (or 'mule') by increasing its effective critical micelle concentration [4]. Through the examples of other cases, we show that the partially unfolded property of the protein as well as the nature of fatty acid binding is as much as important in determining the cytotoxicity – in other words, there is a delicate balance of structural malleability and related changes in binding affinities that determine the tumoricidal properties. Any efforts to design small-molecule mimics appear to require a better understanding of these structural aspects.

Keywords: *cancer, HAMLET, partially-unfolded protein, protein folding, protein misfolding, protein alternative folding*

References

[1] Min S, Meehan J, Sullivan LM, Harte NP, Xie Y, Davey GP, Svanborg C, Brodkorb A, Mok KH, Biochem Soc Trans 40(4):746-51, 2012.

[2] Xie Y, Min S, Harte NP, Kirk H, O'Brien JE, Voorheis HP, Svanborg C, Mok KH, Proteins: Struc Func Bioinf 81(1): 1-17, 2013.

[3] Ho JCS, Storm P, Rydström A, Bowen B, Alsin F, SullivanL , Ambite I, Mok KH, Northen T, Svanborg C, J Biol Chem 288(24):17460-71, 2013.

[4] Pettersson-Kastberg J, Mossberg AK, Trulsson M, Yong YJ, Min S, Lim Y, O'Brien JE, Svanborg C, Mok KH, J Mol Biol 394(5): 994-1010, 2009.

[5] Nielsen SB, Wilhelm K, Vad B, Schleucher J, Morozova-Roche LA, Otzen D, J Mol Biol 398: 351–361, 2010.

Biography

(1) Associate Professor of Biochemistry at Trinity College Dublin, Ireland
(2) Eurostars Technical Expert
(3) Technical Consultant, HAMLET Pharma AB, Malmö, Sweden (Spin-off company carrying-out Phase I/II clinical trials for bladder cancer and colon cancer.)
(4) Editorial Board member, The Protein Journal (Springer) and BioMed Res Intl
(5) Auditor, Korean Scientists' and Engineers' Assoc in the UK