DANDRITE
Danish Research Institute of Translational Neuroscience
Nordic EMBL Partnership for Molecular Medicine

AARHUS UNIVERSITY

DANDRITE Topical Seminar

Wednesday 26 October 2016
at 14.15 – 15.00

Building 3140, 1st floor, room 114
Gustav Wieds Vej 10, 8000 Aarhus C

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The role of the SERCA Pump in Cell Death and Autophagy

The natural compound Thapsigargin (Tg) specifically blocks the sarco/endoplasmic reticulum Ca2+ ATPase (SERCA), which pumps Ca2+ from the cytosol to ER. Inhibition of SERCA disrupts calcium homeostasis, leading to a rapid block in bulk autophagy (1), ER stress signalling, and eventually cell death.

Tg is an attractive potential anti-tumor drug because it effectively kills both slow and fast proliferating cancer cells. However, since Tg is toxic also to normal cells, it must be targeted towards the cancer cells. Replacing a side chain with a linker connecting the Tg core to a peptide prevents Tg from entering cells. Two different linker-peptide sequences have been introduced in clinically tested Tg prodrugs; one is cleaved by PSA, secreted by prostate cancer cells, and one is cleaved by PSMA, which is secreted by neovascular tissues of a broad range of tumors. The Tg analogs unmasked by the cleavage are able to enter cells and exert their toxic effects. Interestingly, however, in vitro experiments indicate that Tg analogs have different potencies and cellular effects depending on the terminal amino acid residue (2).

Our goal is to elucidate the structural and molecular determinants of the effects a variety of Tg analogs on ER stress, cell death and autophagy. Our results so far suggest that differential toxic effects of Tg analogs are related to their varying abilities to induce sustained ER stress signaling and to upregulate the transcription of genes encoding pro-apoptotic proteins. Furthermore, our preliminary data indicate differential effects of Tg analogs on bulk autophagy.

References

1. Engedal, N., Torgersen, M. L., Guldvik, I. J., Barfeld, S. J., Bakula, D., Saetre, F., Hagen, L. K., Patterson, J. B., Proikas-Cezanne, T., Seglen, P. O., Simonsen, A., and Mills, I. G. (2013) Modulation of intracellular calcium homeostasis blocks autophagosome formation. Autophagy 9, 1475-1490

2. Dubois, C., Vanden Abeele, F., Sehgal, P., Olesen, C., Junker, S., Christensen, S. B., Prevarskaya, N., and Moller, J. V. (2013) Differential effects of thapsigargin analogs on apoptosis of prostate cancer cells: complex regulation by intracellular calcium. The FEBS journal 280, 5430-5440

Host: Group Leader Poul Nissen, DANDRITE, Dept. of Molecular Biology and Genetics, Aarhus University