Two faces of ER stress-from cancer to neurodegenerative diseases

Piwocka K[1], Kusio-Kobialka M[1], Dudka-Ruszkowska W[1], Brewinska-Olchowik M[1], Krysa W[2], Rakowicz M[2], Stepniak [2]I, Sulek A[2]

[1]Nencki Institute of Experimental Biology, Warsaw, Poland
[2]Institute of Psychiatry and Neurology, Warsaw, Poland

Endoplasmic reticulum (ER) is the site where proteins folding and assembly occurs. A number of stimuli, such as perturbations in calcium homeostasis or redox state, accumulation of misfolded proteins, glucose deprivation, and altered glycosylation disrupts ER homeostasis and induces ER stress. Mild chronic ER stress allows for adaptation and leads to permanent changes in cellular function and activation of pro-survival mechanisms, whereas excessive stress activates cell death execution. The balance between adaptation *versus* cell death has a tremendous physiological importance. The UPR (Unfolded Protein Response) activates three signaling branches participating in regulation between survival and apoptosis upon ER stress. Activation of the ER stress signalling can play an opposite role in cancer and neurodegenerative diseases. In cancer, activation of the UPR response plays predominantly a prosurvival and protective role, but can also correlate with induction of cell death. Previously, the cytoprotective function was mostly correlated with solid tumors. However, we showed that mild ER stress and one of the UPR branches are activated in chronic myeloid leukemia cells, and are connected with the disease progression and resistance to imatinib therapy. Attenuation of this pathway in CML cells led to inhibition of proleukemic signaling, apoptosis and increased sensitivity to imatinib. On the other hand, disturbed levels of endoplasmic reticulum stress (ER) markers were already observed in post-mortem brains, mouse models and cell cultures derived from patients with Alzheimer's (AD), Parkinson's or Huntington's disease (HD), highlighting the role of ER stress in the neurodegeneration. Moreover, targeting the UPR elements seems to be an interesting strategy to prevent loss of neurons. It was also reported that UPR proteins are activated in blood cells of AD patients, suggesting that peripheral cells may serve as a model to study the disease pathophysiology.

In HD mutated huntingtin aggregates provoke ER stress and the UPR. We performed pilot studies to verify the hypothesis that level of some ER stress mediators may serve as a peripheral biomarker in HD patients, correlating to disease stage and number of CAG repetitions in carriers of CAG expansion in *HTT locus.* We assume that pathophysiological processes appear in HD prior to clinical manifestations, and this study was done to look for the biomarkers correlating to the disease progression and indicators of the compensative mechanisms efficiency in asymptomatic subjects. Understanding the complexity of ER stress response in cancer and neurodegeneration is necessary and may help to improve current, and discover novel therapeutic strategies.

This work was supported by grants 2011/01/B/NZ3/02145 and
2013/10/E/NZ3/00673 from the National Science Centre in Poland.