Protein S-nitrosation as a trigger for DNA leakage from the nucleus: in the quest for a mechanism

DNA is the carrier of genetic information. In animal cells, it is generally confined to the cell nucleus or mitochondria. Its presence in the cytosol is abnormal, as it may indicate pathogen infection or excessive DNA damage. Thus cells containing cytoplasmic DNA shall be instantaneously removed by immune system or should undergo programmed cell death (apoptosis). If those mechanisms fail, cells bearing cytoplasmic DNA should stop to divide to prevent the expansion of infections or loss of genetic stability.

S-nitrosation is a posttranslational modification, which impacts protein functions. Physiological, controlled S-nitrosation is crucial for the maintenance of endothelial cells' homeostasis. Whereas, pathological S-nitrosation may appear in every type of cell, for example during inflammation. Some compounds, which enhance protein S-nitrosation, are present in red meat, the latter often considered as a malignant transformation promoting factor. Protein S-nitrosation is a reversible process and one of denitrosating enzymes is GSNOR. It depletes S-nitrosation from amino acids, which leads to the release of nitric oxide (NO).

Our preliminary data indicate **that depletion of denitrosating enzyme GSNOR from endothelial cells promotes the leakage of DNA into the cytoplasm, which is a biological anomaly. Moreover, cytoplasmic DNA localises in the direct vicinity of protein aggregates, so clusters of dysfunctional, often misfolded proteins. GSNOR lacking cells**, instead of undergoing cell death or at least ceasing the proliferation, **start to divide more intensively**. An analogous situation is observed in case of elderly people-derived endothelial cells, which additionally are characterised by disturbed karyotype (excessive or lacking number of chromosomes). Basing on our preliminary data, we hypothesise that: **protein S-nitrosation perturbs DNA repair and leads to higher nuclear permeability, which promotes the appearance of cytoplasmic DNA.** Moreover, this modification **incapacitates the cells to launch proper signalling pathways,** informing about the danger and permitting the cell self-destruction during apoptosis. As a consequence, there is damage to the genetic material, which poses a threat of onset of oncogenesis.

Using a model of primary human aortic endothelial cells, in which we will manipulate the level of S-nitrosation employing molecular biology tools, we would like to answer four questions:

i) Why does S-nitrosation trigger DNA leakage from the nucleus?
ii) Does protein aggregation play a role in the clearance of cytoplasmic DNA? If so, how?
iii) Why do they not undergo apoptosis or cell cycle arrest?
iv) Do such cells have oncogenic potential?

Recognition of these mechanisms will help, on the one hand, to determine the regulators of the response to cytoplasmic DNA, on the other hand, to understand the possible side effects of S-nitrosation modulators, which are now being introduced in the therapy of asthma.