Identification of the N-terminally truncated Nrf2 isoform with different regulation and indications of novel functions of Nrf2

S. Mikac[I], A. Dziadosz[I], M. Padariya[I], U. Kalathiya[I], R. Fahraeus[I,II], N. Marek-Trzonkowska[I], E. Chrusciel[I], Z. Urban-Wojciuk[I], I. Papak[I], L. Arcimowicz[I], T. Marjanski[III], W. Rzymian[IV], **A. Sznarkowska**[I]

[I]University of Gdansk, International Center for Cancer Vaccine Science, Gdansk, Poland, [II]Inserm UMRS1131, Institut de Génétique Moléculaire, Université Paris 7, Hôpital St. Louis, Paris, France, [III]Department of Medical Immunology, Medical University of Gdansk, Gdansk, Poland, [IV]Department of Thoracic Surgery, Medical University of Gdansk, Gdansk, Poland

Nuclear factor erythroid 2-Related Factor 2 (Nrf2) was identified as one of the transcription factors occupying the enhancer region of β-globin. Nrf2 knockout mice showed a markedly reduced expression of class II detoxification enzymes in response to oxidative stress in comparison to the wild type and heterozygous mice. This discovery directed Nrf2 studies towards toxicology and chemoprevention. Since Nrf2 paved its way as a key regulator of responses to oxidative, xenobiotic and electrophilic stressors, its pathway was studied from the perspective of stress-activation. This is how Keap1 was identified as its main negative regulator, anchoring Nrf2 to the Cullin3-RING ubiquitin ligase complex (CLR3) and mediating its constitutive degradation under no stress.
We have identified the Nrf2 form that is resistant to Keap1-CLR3 degradation, is exceptionally stable and in the SDS-PAGE migrates below the stress-activated form. It is produced from an alternative mRNA variant - transcript 2, which utilizes another AUG for translation initiation, resulting in the Nrf2 form that lacks first 16 amino acids - ΔN-Nrf2. Co-immunoprecipitation and modelling studies showed that this N-terminal deletion disrupts ΔN-Nrf2 binding with Keap1, which impairs ΔN-Nrf2 degradation. Interestingly, contrary to Nrf2, ΔN-Nrf2 does not translocate to the nucleus upon electrophilic stressor t-BHQ. We have also found that Nrf2 might act not only as a transcription factor, but also via direct interactions with proteins and we will show here that direct binding of Nrf2 to Human Leukocyte Antigen type 1 (HLA-I) stabilizes HLA-I in cells. This connects Nrf2 pathway to the antigen presentation pathway.