

# Identification of the Nterminally truncated Nrf2 isoform with different regulation and indications of novel functions of Nrf2.

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Nuclear factor erythroid 2Related Factor 2 (Nrf2) was identified as one of the transcription factors occupying the enhancer region of  $\beta$ 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 stressactivation. This is how Keap1 was identified as its main negative regulator, anchoring Nrf2 to the Cullin3RING ubiquitin ligase complex (CLR3) and mediating its constitutive degradation under no stress.

We have identified the Nrf2 form that is resistant to Keap1CLR3 degradation, is exceptionally stable and in the SDS-PAGE migrates below the stressactivated 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  $\Delta$ NNrf2. Coimmunoprecipitation and modelling studies showed that this Nterminal deletion disrupts  $\Delta$ NNrf2 binding with Keap1, which impairs  $\Delta$ NNrf2 degradation. Interestingly, contrary to Nrf2,  $\Delta$ NNrf2 does not translocate to the nucleus upon electrophilic stressor tBHQ. 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