Characterisation of the Function and Regulation of Nrf2 Isoform 2

For a cell to survive it is essential to respond to stress in a way to retain homeostasis – ameliorate stress stimuli and adapt to environmental changes. Nrf2 pathway arose to overcome the metabolic toxicity that results from the use of highly reactive molecular oxygen and is dated back to the Great Oxidative Event that took place on earth at 2.45–1.85 billion years (Ga) ago when cyanobacteria and their evolutionary ancestors began utilizing photosynthesis to produce molecular oxygen (O_2) saturating minerals, oceans and in the end – atmosphere. Orthologues of Nrf2 first appeared in fungi around 1.5 Ga when photosynthetic oxygen was being absorbed into the oceans.

Human Nrf2 was identified in 1994 and characterised as a transcription factor that induces responses overcoming oxidative, electrophilic and xenobiotic stress. Later it was shown that Nrf2 regulates also basic metabolic processes and its activity is required during homeostasis. So far it has been accepted that Nrf2 is constantly degraded when no stress stimuli are present. In our studies we have shown that under homeostasis the alternative, truncated Nrf2 version is synthesised, that lacks first 16 aa which impairs its binding with canonical degradation machinery. In this project we will use new techniques to comprehensively characterise this form and understand: (i) which DNA sequences it regulates (CUT&RUN followed by DNA seq); (ii) which proteins it binds to (Mass spectrometry-based proteomics) and (iii) how stress and homeostasis affect its translation (ribosomes purification).