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Structural Biology 2019: Nrf2, the key transcription factor that regulates the cellular response to oxidative stress, is intrinsically disordered- Nadun Chanaka Karunatilleke- The University of Western Ontario

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Introduction:

Receptive oxygen and nitrogen species (ROS, RNS) are continually produced in the body from interior digestion and outside introduction. In ordinary cells, responsive oxidants are created in a controlled way and some fill helpful needs. Oxidants shaped in light of physiological prompts go about as significant flagging particles to direct such procedures as cell division, aggravation, insusceptible capacity, autophagy, and stress reaction. Uncontrolled creation of oxidants brings about oxidative pressure that impedes cell capacities and adds to the improvement of malignancy, incessant illness, and poisonousness (2–5). From prokaryotes to people, responsive oxidants apparently work as significant controllers of both physiological and pathophysiological results.

The atomic factor erythroid 2 (NFE2)- related factor 2 (Nrf2) is an individual from the top 'n' neckline (CNC) subfamily of essential locale leucine zipper (bZip) record factors. Nrf2 was cloned by goodness of its authoritative to the NFE2-restricting theme, a cis-administrative succession in the β-globin locus control locale vital for erythropoiesis and platelet advancement x. Nrf2 doesn't seem, by all accounts, to be fundamental for platelet separation yet was found to intercede acceptance of a lot of medication processing compounds (DMEs, for example, glutathione S-transferase (GST) and NAD(P) H:quinone oxidoreductase 1 (NQO1), by cancer prevention agents and electrophiles . Acceptance requires a typical DNA grouping called cell reinforcement reaction component (ARE) that looks like the NFE2-restricting theme. Acceptance of the DMEs prompts expanded detoxification and disposal of various exogenous and some endogenous synthetics. In this job, Nrf2 capacities as a xenobiotic-actuated receptor (XAR) to manage the versatile reaction to oxidants and electrophiles.

A major emerging function of Nrf2 from studies over the past decade is its role in resistance to oxidant stress. As follows, knockout of Nrf2 in mice (Nrf2 KO) substantially increased the susceptibility of mice to a broad range of chemical toxicity and disease conditions associated with oxidative pathology. Pharmacological boosting of the Nrf2 activity with chemoprotective agents protected animals from oxidative damage. Genomic-scale search for Nrf2 target genes identified a number of ARE-containing genes involved in the control of oxidant homeostasis in addition to drug metabolism. Molecular and structural analyses of Nrf2 signalling uncovered a “DE depression” regulatory mechanism, wherein Nrf2 is suppressed under a basal condition through Keap1 (Kelch-like erythroid cell-derived protein with CNC homology-associated protein 1)-dependent ubiquitination-proteasomal degradation and is activated by oxidants and electrophiles via modification of critical cysteine thiols of Keap1 and Nrf2. The protective nature of Nrf2 could also be appropriated by cancer cells to create a prosurvival microenvironment for tumour growth and drug resistance. This review focuses on the emerging role and molecular mechanism of action of Nrf2 in the regulation of oxidative stress and associated physiology and toxicity. `

Statement of the Problem: Nuclear factor erythroid 2 - related factor 2 (Nrf2) is the major transcription factor that coordinates the cellular responses to oxidative and environmental stress. Importantly, dysregulation of this protein also linked to tumorigenesis and chemo- resistance, making Nrf2 an attractive therapeutic target for cancer. The transcriptional activity of Nrf2 is tightly regulated by several protein partners. However, the structure of Nrf2 and the molecular details of its interactions with targets are largely unknown. These hinder the development of therapeutics that can target Nrf2 effectively. Methodology & Theoretical Orientation: To close this knowledge gap, we have used a combination of biophysical techniques, including nuclear magnetic resonance (NMR), hydrogen-deuterium exchange mass spectrometry (HDX-MS), and circular dichroism (CD) spectroscopy to extensively characterize the structure of Nrf2. The construct consisting the full-length Nrf2 had been constructed for protein over-expression in E. coli. Purification procedure was optimized based on the existing protocols in the literature. NMR experiments were performed using isotopically labelled full-length Nrf2 and its individual domains. Findings: Our NMR data shows that Nrf2 is partially disordered. Most of the peaks in the 1H-15N HSQC NMR spectrum of full-length Nrf2 are crowded in the region between 7.8 to 8.7 ppm. The lack of peak dispersion is also observed for individual domains of Nrf2. Interestingly, HDX-MS experiments revealed that even though the protein is overall highly exposed to solvent, there are transient structural elements present in Nrf2. This is consistent with the CD result showing that about 13% helicity present in Nrf2 and over 60% is not structured. Conclusion & Significance: Dissecting the structural basis of Nrf2 is crucial in understanding how the Nrf2 activity is modulated in the oxidative stress response. Experimental data suggest that Nrf2 is largely

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disordered and the information is paramount in designing therapeutics against Nrf2 related cancers.

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