Beyond Anti-oxidation: Keap1-Nrf2 as metabolic checkpoints for T-cell effector responses

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Kelch-like ECH-associated protein (Keap1) and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) form the antioxidation complex that controls the levels of reactive oxygen species (ROS) to maintain redox balance in the cells. Nrf2 is traditionally known as a regulator of oxidative stress. This seminar will focus on non-traditional and novel functions of Nrf2 as modulator of T-cell metabolism and in turn, T-cell immune functions. T-lymphocytes (T-cells), which are constituted of CD4 and CD8 T-cells, are central players of adaptive immunity. Recent focus has been on the manipulation of metabolism to shape their immune responses. Our lab is currently exploring the usage of Nrf2 as metabolic intervention for treating immune diseases. Using a multidisciplinary approach and mice with T-cell specific deletion of Nrf2 or Keap1 we investigated the role of Keap1 and Nrf2 in T-cell activation, proliferation and cytokine functions. The data reveal that Nrf2 positively regulates activation-driven proliferation of T-cells but negatively regulates expression of inflammatory cytokines like IFN-gamma and IL-17. Further, Nrf2 controls these immune responses by modulating glucose and glutamine metabolism. Overall, our studies identified Nrf2 as a metabolic and temporal modulator of T-cell responses. Ongoing studies are aimed at deciphering the underlying mechanisms and testing the usage of Nrf2 modulators in pre-clinical setting of immune diseases.