THE GRADUATE COLLEGE OF THE

UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Gary Burton O'Mealey

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE

DEPARTMENT OF CELL BIOLOGY

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The Nrf2 Antioxidant Transcription Factor and its Roles in Mitochondrial Dynamics and Proteostasis

COMMITTEE IN CHARGE: Scott M. Plafker, Ph.D., Chair, Leonidas Tsiokas, Ph.D., Gary Gorbsky, Ph.D., James Tomasek, Ph.D., Christopher M. West, Ph.D.

ABSTRACT: The Nrf2 transcription factor is commonly regarded as the master regulator of the cellular antioxidant response. Nrf2 is constitutively degraded by the Ubiquitin Proteasome System, but oxidative stress inhibits this degradation and allows for Nrf2 to enter the nucleus and stimulate the expression of antioxidant genes. Nrf2 has proposed, but unverified roles in proteostatic maintenance as well. Disruptions in proteostasis are characteristic of aging and neurodegenerative disease. We show here that a unique, mitochondria-associated population of Nrf2 coordinates an early response to proteasome inhibition. Proteasome inhibition causes the rapid, perinuclear clustering of mitochondria, and this clustering allows for the release of Nrf2 into the nucleus to

induce the expression of chaperones that drive substrate aggregation.

These aggregates are cleared by autophagy, and this clearance is cytoprotective by replenishing amino acids depleted by proteasome inhibition. We further demonstrate that disruption of this mitochondrial complex of Nrf2, KEAP1, and PGAM5 inhibits mitochondrial clustering. Complex disruption leads neomorphic KEAP1 activity at the mitochondria, and this precipitates degradation of the essential mitochondrial trafficking protein Miro2 through the PINK1/Parkin system. These data collectively demonstrate the necessity for mitochondrial clustering in proteostasis and show that Nrf2 may be linked to the loss of mitochondrial motility that is commonly associated with neurodegenerative disease etiology.