Discovering Conserved Mechanisms of Protection against Ischemia-reperfusion Injury Using a Novel *C. elegans* Behavioral Model

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Ischemia-reperfusion-related disorders (e.g., strokes and heart attacks) are the most common causes of adult deaths. How ischemia-reperfusion causes disease and how organisms protect themselves from ischemia-reperfusion injury are fundamental and unanswered questions. The *C. elegans* gene *egl-9* defines a highly conserved family of O_2-sensing hydroxylases (EGL-9 in *C. elegans* and EGLN2 in mammals) that regulate HIF transcription factors. Exposure to chronic low levels of O_2 (hypoxic preconditioning) or direct inhibition of EGLN2 strongly protects from stroke, heart attack and ischemia-reperfusion injury in mammals.

By quantitatively measuring O_2-modulated behaviors of *C. elegans*, we discovered a robust behavior called the O2-ON response, which is characterized by a transient and rapidly increased locomotion speed triggered by reoxygenation (20% O_2) following brief exposure of animals to anoxia (0% O_2) (Ma et al., 2012). The O2-ON response requires the EGL-9/HIF-1 pathway and models key aspects of mammalian tissue responses to ischemia-reperfusion, as (1) reoxygenation is the major pathological aspect of reperfusion, (2) hypoxic preconditioning can both suppress the O2-ON response in *C. elegans* and protect from reperfusion injury in mammals, and (3) the central regulators (EGL-9/HIF-1) of the O2-ON response and ischemia-reperfusion injury are evolutionarily conserved.

From an *egl-9* suppressor screen, we identified *cyp-13A12*, which encodes a cytochrome P450 oxygenase that acts with the EGL-9/HIF-1 pathway to facilitate the O2-ON response. A *cyp-13A12(gf)* mutation restores the defective O2-ON response of *egl-9* mutants, whereas loss of *cyp-13A12* causes a defective O2-ON response in wild-type animals. CYP-13A12 promotes oxidation of lipids into eicosanoids, inflammatory signaling molecules that in mammals can potently affect ischemia-reperfusion injury responses. We suggest that the molecular pathway from EGL-9/HIF-1 to lipid signaling in regulating the O2-ON response and ischemia-reperfusion is conserved from nematodes to mammals. Further elucidating molecular and neural mechanisms of how the O2-ON response is controlled might help identify new conserved modulators and mechanisms of hypoxia/reperfusion injury.

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