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Mechanisms of the dichotomous role of lipid peroxidation product 4-hydroxynonenal in stress induced cell signaling

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Stress caused by heat, radiation and chemicals in aerobic organisms invariably leads to the generation of reactive oxygen species (ROS) that may trigger a wide variety of responses. Since membrane lipids are the major target of ROS, oxidation of lipids and fatty acids lead to the formation of a number of highly reactive chemicals including lipid carbonyls such as 4-hydroxynonenal (HNE). Recently, we and others have demonstrated that HNE plays a dichotomous role during oxidative stress in a concentration dependent manner. While at a high concentration HNE causes cell death through activation of signaling for apoptosis and necrosis, at a sub physiological concentrations it induces cell survival and proliferation through induction of cellular defense mechanisms. Based on these studies we have hypothesized that at low levels of HNE generated during initial stages of oxidative stress acts as a sensor of stress to activate the cellular defense mechanisms for negating the deleterious effects of oxidative stress. This hypothesis was tested in various cell types. Results of these studies indicate that the mechanisms induced by HNE include: 1) initiation of cell cycle arrest and repair processes via activation and phosphorylation of H2AX that contribute towards maintaining the genomic integrity during oxidative stress, 2) transcriptional activation of heat shock factors (HSFs) and induction of HSP70, induction of anti-oxidant enzymes via activation of Nrf2, and 3) the activation of Daxx mediated anti-apoptotic mechanisms.

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