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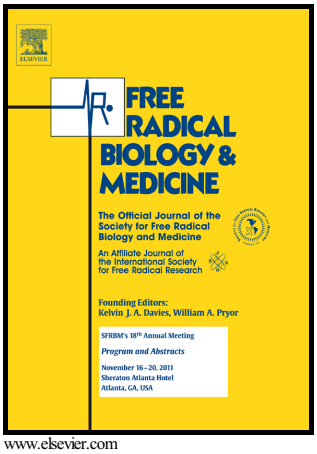

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The antioxidant transcription factor Nrf2 contributes to the protective effect of mild thermotolerance (40°C) against heat shock-induced apoptosis

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Abstract:

The exposure of cells to low doses of stress induces adaptive survival responses that protect cells against subsequent exposure to toxic stress. The ability of cells to resist subsequent toxic stress following exposure to low dose heat stress at 40°C is known as mild thermotolerance. Mild thermotolerance involves increased expression of heat shock proteins and antioxidants, but the initiating factors in this response are not understood. This study aims to understand the role of the Nrf2 antioxidant pathway in acquisition of mild thermotolerance at 40°C, and secondly, whether the Nrf2 pathway could be involved in the protective effect of thermotolerance against heat-shock (42°C)-induced apoptosis. During cell preconditioning at 40°C, protein expression of the Nrf2 transcription factor increased after 15 to 60 min. In addition, levels of the Nrf2 targets MnSOD, catalase, heme oxygenase-1, glutamate cysteine ligase and Hsp70 increased at 40°C. Levels of these Nrf2 targets were enhanced by Nrf2 activator oltipraz and decreased by shRNA targeting Nrf2. Levels of pro-oxidants increased after 30 to 60 min at 40°C. Pro-oxidant levels were decreased by oltipraz and increased by knockdown of Nrf2. Increased Nrf2 expression and catalase activity at 40°C were inhibited by the antioxidant PEG-catalase and by p53 inhibitor pifithrin-α. These results suggest that mild thermotolerance (40°C) increases cellular pro-oxidant levels, which in turn activate Nrf2 and its target genes. Moreover, Nrf2 contributes to the protective effect of thermotolerance against heat-shock (42°C)-induced apoptosis, because Nrf2 activation by oltipraz enhanced