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CELL DEATH

Some like it hot

> a conserved mechanism that protects against heatstroke-mediated necrosis

Heat-related pathologies such as heatstroke may lead to acute tissue injury, multi-organ failure and even death, with the survivors of heatstroke often suffering permanent neurological damage. Here, Kourtis *at al.* identify a conserved mechanism that protects against heatstroke-mediated necrosis and neurodegeneration.

In order to gain insight into the molecular mechanisms of heat cytotoxicity, the authors stimulated hyperthermia by exposing *Caenorhabditis elegans* worms to 39 °C for 15 minutes. Exposure to excessive heat resulted in immediate changes in the behaviour of these animals and a large increase in mortality due to widespread cell death, with dying cells showing features of necrosis. Because, paradoxically, pre-exposure to mild stress can result in increased resistance to severe stress, a phenomenon termed 'hormesis', the authors exposed the worms to intermediate, non-lethal temperature before heatstroke. Such preconditioning at 34 °C for 30 minutes enhanced the capacity of the worms to survive and withstand heatstroke.

Interestingly, preconditioning did not increase the survival of mutant worms lacking heat shock transcription factor 1 (HSF-1), indicating that this protein is necessary for protection against heatstroke. HSF-1 induces the expression of heat shock proteins (HSPs), which protect cells from various cytotoxic conditions. Consistent with this, HSP-16.1 and HSP-16.41 were upregulated after preconditioning and, importantly, overexpression of *hsp-16.1* conferred protection and bypassed the requirement for preconditioning to suppress necrosis and increase survival after heatstroke.

Furthermore, the authors found that HSP-16.1 colocalizes with the ATPase PMR-1 in the Golgi, so they asked whether this protein might also have a role in protecting against necrosis. Indeed, worms lacking PMR-1 did not become resistant to heatstroke following preconditioning. As PMR-1 functions in transporting Ca^{2+} (and Mn^{2+}) into the Golgi, these findings indicate that Ca^{2+} homeostasis in the Golgi has a role in mediating protection from heat-related pathologies. Notably, preconditioning suppressed neurodegeneration triggered by hyperactive ion channels, expression of human α-synuclein (an aggregation-prone protein that triggers cell death in the nematode) or hypoxic conditions, suggesting that the HSF-1–HSP-16.1 pathway is able to protect against necrosis caused by diverse stressors.

Finally, the authors examined mouse neurons (either primary cultures or neurons differentiated from mouse embryonic stem cells) to determine whether this protective response is conserved. Consistent with results obtained in worms, preconditioning largely prevented heatstroke-induced death and, furthermore, overexpression of mammalian crystallin αA, a mammalian homologue of the HSP-16 protein family, was sufficient to protect mouse neurons from heat-induced cell death, even in the absence of preconditioning. In contrast, knockdown of PMR1 in mouse cells abolished the protective effect of preconditioning, resulting in widespread necrotic death and axonal degeneration after heatstroke.

Taken together, the findings of this study point to an evolutionarily conserved protective mechanism that operates specifically in the Golgi to defend against a range of necrosis activators that may be relevant to heatstroke and other pathologies involving necrosis in humans.

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ORIGINAL RESEARCH PAPER Kourtis, N., Nikoletopoulou, V. & Tavernarakis, N. Small heat-shock proteins protect from heat-stroke-associated neurodegeneration. *Nature*, 12 Sep 2012 (doi:10.1038/nature11417)