

Hyperthermia

- 101 *P53*-independent enhancement of heat-sensitivity by a surface-active agent, Tween 80, in human cancer cells
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We examined heat sensitivity and heat-induced apoptosis of human squamous cell carcinoma (SAS) and *p53*-null lung cancer cells (H1299) transfected with mutant *p53* or a *neo* control vector in the presence of Tween 80 (0.05 %) using colony formation assay and hoechst staining. Further, we examined the effect of Tween 80 on accumulation of heat shock protein using Western blot analysis. Addition of Tween 80 in the medium before heating (44°C) enhanced heat-sensitivity but not X-ray-sensitivity in mutant *p53*-transfected cells as well as the *neo* control cells. These results suggest that Tween 80 enhances heat-sensitivity even in mutant *p53* cancer cells. We can expect Tween 80 as a *p53*-independent hyperthermic sensitizer in cancer therapy. We are now studying about the mechanism of the enhancement of heat-sensitivity by Tween 80.
- 102 Mechanism of enhancement of heat-induced apoptosis by a nitroxide, Tempo.
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A stable membrane-permeable nitroxide Tempo (2,2,6,6-tetramethylpiperidine-1-oxyl) possesses an SOD-like antioxidant activity against a variety of ROS. However, we have observed the Tempo sensitization of heat-induced apoptosis in U937 cells. To elucidate its mechanism, we used a 10 min treatment with 1–5 mM Tempo at 37C or suboptimal heating (44C/10 min), either of which had no effect on the apoptosis in U937 cells. The combined treatment with 5 mM Tempo at 44C for 10 min elicited 90% apoptosis in 6 h, as did the 44C/30 min heating. The enhanced apoptosis was time-dependent, through a mitochondrial dysfunction such as progressive increase in low mitochondrial membrane potential, decrease of superoxide production, early release of cytochrome c and ATP decrease without altered cellular expression of Bcl-2, Bcl-XL and Bax. In early time after the combined treatment, JNK1 was activated moderately, but a JNK inhibitor did not inhibit the apoptosis. Thus, these results indicate a new finding that Tempo sensitizes greatly the heat-induced apoptosis though cytochrome c release and a unique mitochondrial dysfunction.
- 103 Thermosensitization by Inhibition of Gap Junctional Intercellular Communication
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Involvement of gap junctional intercellular communication (GJIC) in cellular response to heat is postulated from the fact that GJIC is impaired in most tumors which are generally more sensitive to heat than normal cells. Here, we investigated the role of GJIC in heat response using a potent GJIC inhibitor, lindane. Cells used were normal human diploid fibroblasts (HE49), which express connexin43, and GJIC-deficient HeLa cells. Influence of lindane on thermosensitivity of HeLa and exponentially growing and confluent HE49 cells was examined by colony formation assay. The confluent HE49 cells were more resistant to heat than exponentially growing HE49 cells. The ratio of heat-treatment time at 10% survival of control to that of lindane-treated cells was 1.28 in HeLa cells, while 1.54 and 2.17 in exponentially growing and confluent HE49 cells, respectively, indicating the involvement of GJIC in cellular response to heat. This result suggests that dysfunction of GJIC as generally seen in tumors potentiates susceptibility to heat.