

Thymoquinone-induced oxidative stress targets highly aggressive prostate cancers

Researchers at the Tulane University School of Medicine have demonstrated that thymoquinone (TQ), a major component of black seed oil (*Nigella sativa*), can suppress the growth of several aggressive prostate cancer (PCa) cell lines, *in vitro*. Although previous studies have shown the antiproliferative effects of TQ in different types of cancers, the molecular mechanism of this effect of TQ had not been delineated. Since TQ has a structure similar to ubiquinone, a component of the mitochondrial coenzyme-Q complex, the effect of TQ on free oxygen radical production was investigated. These scientists showed exposure to TQ (20–100 $\mu\text{mol/L}$) caused a rapid induction of reactive oxygen species (ROS) generation in both LNCaP and C4-2B cells. A precipitous decrease in the level of glutathione (GSH), an intracellular small molecule antioxidant, was also found to be responsible for the potent anticancer effects of TQ, which could be inhibited by exogenous addition of *N*-acetyl cysteine, a GSH analog. Free oxygen radicals are often used as second messengers for mitogenic signaling in tumor cells where a critical balance in ROS generation, and its rapid inactivation by antioxidants, can dictate cell growth or apoptosis. These investigators showed significant increases in several cell death (apoptosis)-inducing factors, e.g. GAD45 α and AIF-1, in TQ-exposed PCa cells. This study appears on page 751 of this issue of *Experimental Biology and Medicine*.

Dr Mondal stated that, 'Complementary and alternative medicine (CAM) is becoming very important as an adjunct therapy in cancer patients, both to ameliorate the side-effects of chemotherapy as well as to enhance their anti-tumor effects. The low side-effect profiles of natural compounds is also an important aspect in their therapeutic utility as an adjunct to anti-tumor therapy. Indeed, in a

previous publication (*Exp Biol Med*; (2009) Apr; **234**(4):442–53) we had shown that at lower concentrations (<5.0 μM), TQ decreases ROS production and increases GSH levels in pancreatic beta-cells, which restored nelfinavir (an anti-HIV agent) induced deleterious effects on these cells. Our current findings suggest that the ROS-generating effects of high concentrations of TQ (>20 μM) may be of great advantage towards the development of novel anti-cancer therapeutics, especially against hormone-refractory prostate cancers which are much harder to treat'.

The research team led by Dr Krishna C Agrawal (posthumously) included Dr Sandeep Koka, previously a graduate student under Dr Agrawal, and two other faculty members from Tulane University, Dr Asim B Abdel-Mageed and Dr Debasis Mondal. These investigators successfully tested the hypothesis that TQ-induced oxidative stress is responsible for its antiproliferative effects in prostate cancer cells. Since black seed oil has been used in the middle eastern countries for hundreds of years, the investigators postulated that the active component TQ, and possibly the oil itself, can be used effectively, either alone or as an adjunct to chemotherapy, to target highly aggressive prostate cancers.

Dr Steven R Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said 'Koka *et al.* have demonstrated that thymoquinone efficiently killed hormone-dependent and hormone-independent prostate cancer cells. The mechanism appears to be that thymoquinone induces oxidative stress and suppresses GSH levels. This suggests that oxidative stress may lead to decreased tumor growth and increased cell death in highly aggressive forms of prostate cancer'.

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