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Turning up the heat: mechanistic insights into thermal photodynamic therapy

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Topical photodynamic therapy (PDT) is commonly used in the treatment of nonmelanoma skin cancer and is favoured for ease of administration, tolerability and excellent cosmetic outcome. Treatment involves topical application of a prodrug, aminolaevulinic acid (ALA) or its methyl ester MAL, which is converted to the photosensitiser protoporphyrin (Pp) IX. Light-activation of PpIX initiates production of reactive oxygen species (ROS) and target cell death primarily via apoptosis.¹ Treatment takes some hours as sufficient time must be given for prodrug penetration and PpIX accumulation, and efficacy is dependent on treatment protocol, type and site of target lesion(s).^{2,3} Application of heat during prodrug incubation has shown promise in improving PDT efficacy. *In vitro*, increased temperature led to greater PpIX accumulation⁴ while a clinical pilot study demonstrated greater clearance of actinic keratosis in heat-treated skin;^{5,6} there are no reports in Bowen's disease or basal cell carcinoma.

In this issue of the *BJD*, Mamalis *et al.*⁷ provide further mechanistic insight into thermal PDT. Using normal human fibroblasts in a series of *in vitro* experiments, they investigated how varying ALA concentration while maintaining constant temperature (36°C), and varying temperature (21-42°C) for a single concentration of ALA, impacted on PDT. Following ALA incubation and light activation, flow cytometry was used to examine for markers of apoptosis and necrosis, and to detect ROS. At 36°C, an ALA concentration-dependent increase in the proportion of apoptosis-positive cells was seen with very few cells undergoing necrosis. This was associated with a similar concentration-dependent increase in production of superoxide species. When a single ALA concentration was used with varying temperature, both the proportion of apoptosis-positive cells and relative amount of superoxide species increased with increasing temperature. This work showed that increasing prodrug concentration or temperature heightened the photodynamic response at the molecular level.

From their human fibroblast model, Mamalis *et al.* conclude that thermal PDT increases production of superoxide and the proportion of apoptotic cells in a temperature-dependent manner, and their data suggested that a temperature of 39°C was optimal. Further *in vitro* studies could explore these mechanisms using keratinocyte tumour cells lines as PDT is used to treat keratinocyte cancers and precancers. The authors speculate that thermal PDT may improve patient compliance and cost-effectiveness through reduced treatment times and increased efficacy. Temperature can be easily controlled *in vitro*, but maintaining a constant, raised temperature at the site of topical prodrug application may prove more challenging, although several methods are available.⁸ Moreover, any advantages gained through the potentially increased efficacy and efficiency of thermal PDT must consider the potential for increased pain and/or other adverse events that may result from a heightened photodynamic reaction, and may have implications for patient acceptability and compliance. The findings of Mamalis *et al.* and others will require translation to well-designed clinical trials to fully assess thermal PDT.

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