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Influence of photobiomodulation with blue light on the metabolism, proliferation and gene expression of human fibroblasts

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The last decade showed a rapid expansion of photobiomodulation (PBM) for the treatment of a wide variety of ailments in different medical fields. However, its scientific acceptance is still debated: first, due to inconsistent experimental outcomes, caused by variable study designs and irradiation parameters, and second, due to a lack of mechanistic insights into light-triggered signaling. The latter especially applies for blue light, which is, in comparison to red and N(IR) light, rather used for a limited range of medical cutaneous conditions primarily necessitating inhibitory or even cytotoxic effects, like fibrotic skin diseases. However, also stimulatory effects of blue light have rarely been reported in wound healing studies. Thus, the aim of this study was to investigate the biomodulatory potential of different blue light doses on the cellular activity of primary normal human dermal fibroblasts (NHDF), in particular with respect to cell metabolism, proliferation, mitochondrial function and transcriptome changes.

PBM using blue light revealed dose-dependent effects on the metabolism and proliferation of NHDF cells. Whereas 5.4 J/cm^2 led to an increased cell activity, 21.6 J/cm^2 of blue light inhibited the metabolism and proliferation of NHDF cells. Those effects could be enhanced with different irradiation schemes. Also gene expression profiles revealed contrary trends in metabolism, DNA replication and cell cycle regulation. Similarly, both blue light doses induced an immediate ROS burst, accompanied by a fast decrease in ΔΨm indicating metabolic stress. Light effects were identified to rely on retrograde mitochondrial signaling altering the expression of transcription factors like NF-κB or Nrf2 via changes in ΔΨm and ROS. Moreover, *PRKAA1* and *AKT1* coding for primary effectors of metabolic stress, respectively AMPK and AKT, were found significantly expressed exerting antagonistic regulations of *FOXO1* and *MTOR*, which modulate oxidative stress resistance, cell survival and growth. In addition, genes involved in antioxidant defense mechanisms, inter alia transcribed by Nrf2 and AhR, were found up-regulated for both doses, with a higher activation for 21.6 J/cm^2. Cytoprotection was further promoted by affecting pro- and anti-apoptotic genes inducing stress resistance and even a higher proliferative capacity for 5.4 J/cm^2. Prevention of apoptotic signaling was confirmed by viability studies for single treatments, while multiple irradiations with 21.6 J/cm^2 probably led to mitotic catastrophe and finally apoptosis.

In conclusion, blue light irradiation seems to be pro-oxidant in the short term, but anti-oxidant in the long term likely to induce stress resistance, at least following low and controlled amounts of oxidative stress. Driven by metabolic and redox homeostasis, various downstream processes are activated modifying antioxidant defense, survival and proliferation. In addition, the results indicate that an optimal choice of irradiation parameters, particularly the dose, is important for the effectiveness of light treatments, since doses lower or higher than the optimum can lead to ineffective or even negative outcomes. Thus, using cycled irradiation for heat management, the differential effect of varying blue light doses can be exploited for novel concepts in advanced wound care, in particular for chronic wounds showing impaired activity of fibroblasts and fibrotic skin diseases.