

## Photobiomodulation, Tissue Effects and Bystanders

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**T**HE INTERACTION OF PHOTONS with cells is a necessary and essential condition for photobiomodulation to occur. Absorption and transduction of this energy must occur and it is well known that cellular molecules and structures are capable of absorbing this energy at various wavelengths. It is also known that transmission of some portion of the incident light occurs depending upon the wavelength, the irradiance, the time course of the interaction, and the particular tissue being exposed to the beam.

This interaction is dubbed a “cold” effect because the primary photobiomodulatory event is nonthermal, at least to the extent that the temperature of the target tissue is not elevated or is minimally elevated over baseline. Such measurements are inevitably affected by tissue perfusion and are not easily measured at the level of an individual cell. However, temperature clamping experiments have documented that the biostimulatory effects of 830-nm photoradiation occur if the tissue temperature is held constant.<sup>1</sup> Although it is likely that a number of intracellular molecules are capable of transduction of light energy into a useful form for eukaryotic cells, the cytochrome system is a primary target. Several investigators have documented that photobiomodulation up-regulates ATP production via this system.<sup>2–4</sup> This is the good news. However, the naysayers would point out the fact that cells should “do what they do” and increase activity if more energy is available for cellular machinery. The presumption is that the light exposure should increase activity because the lack of energy is one of the main reasons that cells remain “inactive” or are seemingly bystanders in the response to the photonic stimulus.

It is clear that some cells and tissues remain unresponsive to phototherapy, even when the treatment is provided according to generally accepted and published parameters. Our laboratory demonstrated this phenomenon in a simple tissue model using fetal bovine heart endothelial cells (FBHE). These cells require growth factors for growth and proliferation. They specifically have an absolute dependency on basic fibroblast growth factor (bFGF) for survival in tissue culture.<sup>5</sup> This study demonstrated that 660-nm photoradiation at 2.16J/cm<sup>2</sup> significantly increased cell proliferation and bFGF production in fibroblasts, which in turn increased proliferation of FBHE. Photoirradiation of the FBHE did not result in changes in cell proliferation at the parameters studied.<sup>5</sup> The salient point is that whereas both cell lines possess mitochondria and cytochromes, FBHE still require

bFGF and would otherwise be “refractory” or “unresponsive” to light exposure. Tissues are a complex matrix of cells, which interact with each other and which are also affected by the whole organism and its environment and are communicated and modulated by a number of metabolic processes, tissue perfusion, and neural pathways, among others. It is therefore reasonable to surmise that an intervention at one site or affecting one tissue might have an impact at distant and multiple sites within the organism. One need only to consider vitamin D metabolism as one such studied and accepted example of light interacting with tissues and influencing a cascade of events at multiple sites within the whole organism.

Purschke et al.<sup>6</sup> reported on a phenomenon that they dubbed “the active thermal bystander effect” (ATBE). They point out that the biological definition of “cellular bystander effects” is the induction of biological stress responses in cells that occur as a result of mediation by other cells within the system that are exposed to the stressor, rather than because of a direct response by the bystander cell exposed to the same stress. This is exactly the phenomenon exemplified by the fibroblast and fetal bovine heart endothelial cell model described previously.

Severe stress in the form of modalities such as ionizing radiation, chemical exposure, pH change, and high temperature exposure are well-known inducers of the bystander effect. Purschke’s initial study demonstrated that cells exposed to heat at levels that leave more than 50% of the exposed cells alive induce DNA damage in adjacent, non-heated bystander cells that share the cell culture medium with heat-stressed cells. The authors concluded that the stressed but viable cells generate an unknown mediator that triggers a stress response in non-heated bystander cells.<sup>6,7</sup> They noted that studies of radiation-induced bystander effects demonstrated the involvement of cytokines including interleukin 6, TGF $\beta$ 1, and TNF $\alpha$ , and that other biomolecules such as ROS and serotonin in the culture medium are reported to play a role in generating the bystander effect.<sup>7</sup> This should strike a chord with the phototherapy community as these same mediators have been observed to be modulated when specific wavelengths and parameters are applied to various systems and models.

Purschke et al. subsequently conducted studies that focused on the cell cycle of the receiving bystander cells to assess whether ATBE demonstrates selectivity toward fast-growing cells.<sup>7</sup> They proposed that inducing the ATBE effect might yield a useful clinical approach to target tumors and

other fast-growing cells. Their study demonstrates that the bystander cells must be actively dividing in order for the active thermal bystander effect to occur. This has important ramifications for photobiomodulation as well. It is likely that cell cycle dependency is similarly important in other processes such as wound healing, nerve repair, and the inflammatory response to name a few. This is fertile ground for further investigation. Knowing what the bystanders are doing and being able to sequence treatment modalities accordingly might well make a big difference.

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