Múltiplas funções da citocromo c oxidase em células de mamíferos sob ação de radiação vermelha e perto do infravermelho

Critical Review

Multiple roles of cytochrome *c* oxidase in mammalian cells under action of red and IR-A radiation

Authors

- **Tiina I. Karu ;** IUBMB Life, 62(8): 607–610, 2010

  Corresponding author

  - E-mail address: tkaru@isan.troitsk.ru
  2. Laboratory of Laser Biology and Medicine, Institute of Laser and Information Technologies, Russian Academy of Sciences, Troitsk, Moscow Region, Russian Federation
  - Tiina I. Karu, Institute of Laser and Information Technologies of the Russian Academy of Sciences, 142190 Troitsk, Moscow Region, Russian Federation. Tel: +7-496-751-02-33. Fax: +7-496-751-0886

Abstract

This article reviews the current knowledge in photobiology and photomedicine about the influence of monochromatic, quasimonochromatic, and bread-band radiation of red-to-near infrared (IR-A) part on solar spectrum upon mammalian cells and human skin. The role of cytochrome *c* oxidase as the photoacceptor and photosignal transducer is underlined and its photosensitivity at certain circumstances is discussed. The role of ATP as a critical signaling molecule is discussed. © 2010 IUBMB IUBMB Life, 62(8): 607–610, 2010.

INTRODUCTION

Studies into mechanisms of damaging effects of UV radiation in wavelength range 290–400 nm (UV part of solar radiation reaching the earth surface) have been the major topic in dermatological and photobiological research for years. At the same time, it was believed by researches that other components of solar radiation reaching earth surface (visible light, 400–760 nm, and IR radiation in range 760–3000 nm) do not influence

the metabolism of mammalian cells (1). The main reason for this attitude was the low intensity of IR-A radiation (760–1440 nm) from the solar spectrum. It is limited in central Europe, for example, in summer to about 200 W/m^2 (2). Also, suitable photoacceptors in mammalian cells for this particular spectral region were not known.

At the same time, in second half of 20th century, the action of radiation in red and IR-A regions upon tissues and cells was studied by physicians using recently advented lasers of low intensity (e.g., He–Ne laser) and later, light emitting diodes. These new devices were used to treat in a nondestructive and non-thermal fashion various inflammatory conditions and ulcers (latest reviews (3–5)). Nowadays the dermatologists and environmental photobiologists are interested in effects of IR-A radiation on human skin as well. It was found that this range of solar radiation could not be considered as totally non-active and innocuous but rather participating in effects of solar radiation upon human skin (6–10).

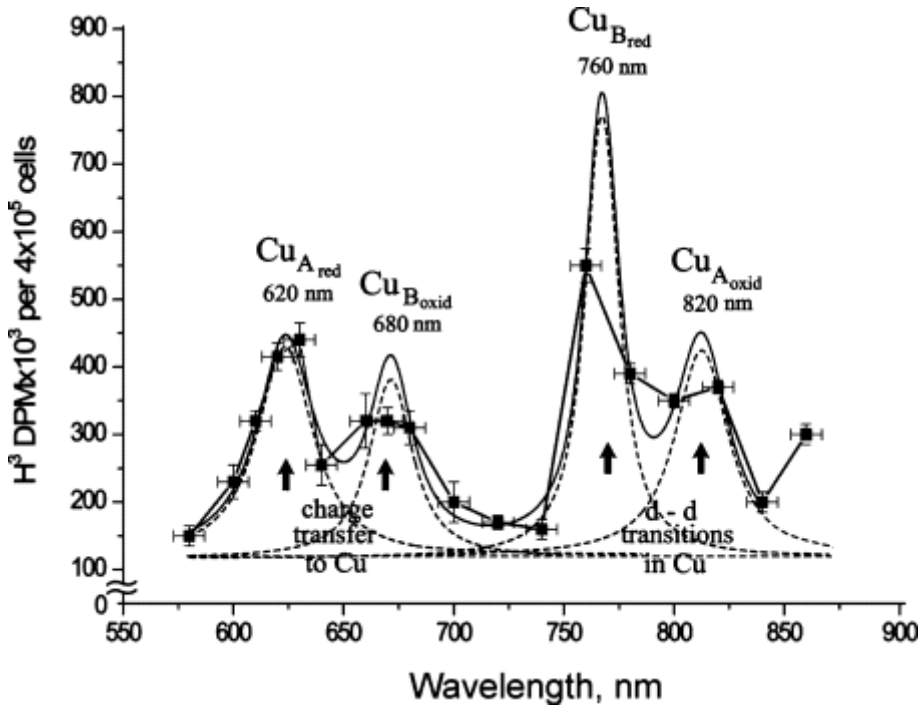
The aim of this review is to give a short overview about photobiological and dermatological research into visible and IR-A radiation effects. First, this is still not a topic of mainstream biology and medicine. Second, it may be surprising that cytochrome *c* oxidase, which is responsible for energy production in mammalian cells, fulfill in cellular metabolism other roles as well.

THE POSSIBLE PHOTOACCEPTOR IN MAMMALIAN CELLS FOR VISIBLE AND IR-A-OPTICAL REGION IS CYTOCHROME *C* OXIDASE

Cytochrome *c* oxidase is the terminal enzyme of the respiratory chain in eukaryotic cells mediating the transfer of electrons from cytochrome *c* to molecular oxygen. It is also considered as the photoacceptor and photosignal transducer in the region of visible and IR-A region (4). This reactivity is due to four redox active metal centers: the binuclear Cu_A, Cu_B, heme a, and heme a_3, all of which have absorbency in the red to IR-A range. This is a short conclusion of a long row of investigations for last decades. The interested reader is guided to reviews (4, 5, 11), which summarize this work. For identifying cytochrome *c* oxidase as the photoacceptor, absorption, and action spectroscopy of living cells were used as well as experimental approaches like dichromatic irradiation of cells and modifying cellular metabolism with various chemicals (11).

Red-to-IR-A part of one typical action spectrum is presented in Fig. 1. Recall that the action spectrum is the dependence of a cellular response on the wavelength used for the irradiation and can be recorded for different biochemical reactions in living cells. In ideal case, the action spectrum resembles the absorption spectrum of the photoacceptor molecule. Insofar as the action spectrum resembles the absorption spectrum of the molecule absorbing the light (the photoacceptor), the bands in various action spectra in visible-to-near IR radiation in living cells were identified by analogy with the metal-ligand systems absorption spectra characteristic in this spectral range (12). This analysis allowed to conclude that all bands in various rather similar by peak positions action spectra (one maximum at 400 nm with the edge of the envelope near 450 nm and two series of doublet bands in the range 620–680 nm and 760–895 nm with well-pronounced maxima at 620, 680, 760, and 825 nm) may be related to the cytochrome *c* oxidase (5, 11, 12, 37).

Figure 1.



The action spectrum for stimulation of DNA synthesis rate on cellular level. Suggested absorbing chromophores of the photoacceptor, cytochrome *c* oxidase, are marked (12, 37). Original curve (-▪-), curve fitting (▁), and Lorentzian fitting (− −) are shown.

Figure 1 presents only the red to IR-A part of the action spectrum of increase of DNA synthesis. Suggested absorbing chromophores of cytochrome *c* oxidase in this region are also shown in Fig. 1. It was suggested that the photoacceptor is one of the intermediate forms of cytochrome *c* oxidase redox cycle. In the red-to-near IR-A region, the 820 nm band is believed belonging mainly to the relatively oxidized Cu_A chromophore of cytochrome *c* oxidase, the 760 nm band to the relatively reduced Cu_B, the 680 nm band to the relatively oxidized Cu_B, and the 620 nm band to the relatively reduced Cu_A (5, 11, 12).

The Cu_A→ heme a → [heme a_3—Cu_B] → O_2 electron transfer within cytochrome *c* oxidase proceeds rapidly (in microsecond time scale) between Cu_A and heme a and between the catalytic center [heme a_3—Cu_B] and dioxygen. The only rate-limiting stage in the turnover appears to be the internal electron transfer between heme a and the [heme a_3—Cu_B] pair. The reduction of the [a_3 — Cu_B] binuclear heme site by the reduced heme a occurs in millisecond time scale (14). One can speculate that irradiation intensifies exactly this electron transfer stage within the enzyme. It is quite possible that irradiation makes more electrons available for the reduction of dioxygen in the catalytic center of cytochrome *c* oxidase (heme a_3 — Cu_B site). It has long been known that

electronic excitation by light stimulates redox processes in organic dyes to intensify electron transfer (15). This is also true of cytochrome *c* oxidase (13). The increase of the availability of electrons can be the crucial result of irradiation in situations when all the four electrons are unavailable for the reduction of dioxygen. Comparison between the absorption and action spectra provided evidence that all bands present in the action spectra were present in the absorption spectra of living cell monolayer as well (12). Dermatologists and photobiologists as the photoacceptor now consider cytochrome *c* oxidase when human skin is irradiated by IR-A radiation (7). Therapy with lasers and light emitting diodes are considered as phototherapy (16).

MITOCHONDRIAL RETROGRADE SIGNALING IN IRRADIATED CELLS

In Fig. 1, the action spectrum of the event occurring in the nucleus (DNA synthesis) is presented. But the photoacceptor, which is responsible to this result, is located in mitochondria. It means that a cellular signaling pathway should exist between mitochondrial respiratory chain and the nucleus. That signaling pathway is activated by irradiation of red and IR-A radiation. The existing experimental data about this putatively mitochondrial retrograde signaling pathway were reviewed recently (17). It was concluded by Schroeder et al. (7) that IR-A radiation, in contrast to UV, elicits a retrograde response in normal human skin fibroblasts. Let us emphasize here that the irradiation of human fibroblasts with red light ($\lambda = 628$ nm) causes not only increase in DNA and RNA synthesis rate (11) but also the upregulation of 111 genes of 10 function categories (18). Figure 2 illustrates this putative mitochondrial signaling pathway, studied until yet only fragmentary (17).

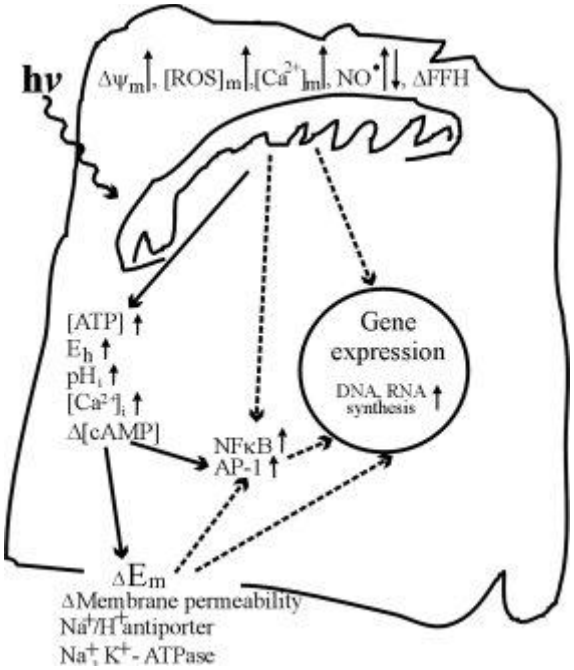


Figure 2.

A schematic explaining putative mitochondrial retrograde signaling pathways after absorption visible and IR-A radiation (marked *hv*) by the photoacceptor, cytochrome *c* oxidase. Arrows ↑ and ↓ mark increase or decrease of the values, brackets [] mark

concentration; ΔFFH: changes in mitochondrial fusion-fission homeostasis; AP-1: activator protein-1; NF-κB: nuclear factor kappa B. Experimentally proved (→) and theoretically suggested (----->) pathways are shown. Adapted from (17).

RADIATION IN RED AND IR-A REGION IS PROTECTIVE AGAINST HARMFUL EFFECTS OF γ AND UV RADIATION AND REVERSES THE TOXIC EFFECTS OF NEURO- AND RETINOTOXINS

The next question arising is the following. If the UV radiation can have damaging effects upon human cells, and the red-to- IR-A part of solar spectrum can have stimulating effects, then what could be the summary effects on the human skin? Menezes and coworkers (19) have suggested that preirradiation with IR light (e.g., during sunrise) is a natural process whereby cells are protected against the solar UV radiation, which was acquired and preserved through evolutional selection and plays an important role in life support. They found that visible-to-near-IR radiation at 400–2000 nm protected human dermal fibroblasts from UV-A and UV-B cytotoxity (19). It was also found in this work that the protection was independent of the protein synthesis. Denno et al. found that IR radiation suppresses UV-B induced sunburn (20).

At the present-day level of knowledge, one can suggest that the stimulating action of visible-to-near IR region of the optical spectrum on cytochrome *c* oxidase may perform, under certain circumstances, a protective function on cells against the harmful effects of γ-rays (21–23) or environmental pollution (e.g., various chemicals, (11), or else other spectral regions of sunlight, e.g. UV (24–26). It was suggested that radioprotective action of He–Ne laser irradiation before γ-irradiation might occur due to a shift in the cellular redox state by laser preirradiation (11). Recent unifying concept in stress response biology based on metabolic oxidation/reduction reactions and cellular responses to ionizing radiation supports this suggestion (27). This type of photoprotection can be considered as a functional upgrading or activation of the pertinent photoacceptor—cytochrome *c* oxidase—as shown in the case of methanol-induced retinal toxicity or primary neurons functionally inactivated by toxins (28–30).

It was experimentally demonstrated that the irradiation of the retina and optic nerve *in vitro* at λ = 670 nm provided an increase in their survival and functional recovery after an acute injury by formic acid, a mitochondrial toxin, generated in the course of methanol intoxication (28, 31). Primary neurons functionally inactivated by tetrodoxin or potassium cyanide showed a functional recovery of cytochrome *c* oxidase following irradiation at 670 nm (29, 30). These studies are important not only from the standpoint of research into the mechanisms of phototherapy. They open a way for exploring the use of light therapy to improve retinal function in the case of acute methanol intoxication or to reverse the detrimental effects of impulse blockade in intoxicated neurons. The authors also suggest that laser phototherapy may facilitate recovery from retinal injuries and other ocular diseases wherein mitochondrial dysfunction is postulated to play a role.

IRRADIATION IN VISIBLE-TO IR-A REGION CAUSES ATP EXTRASYNTHESIS IN MAMMALIAN CELLS

Last years, a long series of discoveries has demonstrated that ATP is not only an energy currency inside cells, but it is also a critical signaling molecule that allows cells and tissues throughout the body to communicate with one another (32, 33). This new aspect of ATP as an intercellular signaling molecule allows broadening the understanding of universality phenomenon of photosensitivity of cytochrome *c* oxidase. The extrasynthesis of ATP in isolated mitochondria and intact cells of various types under irradiation with monochromatic light of different wavelengths is well documented during decades (34, 11). This effect has been considered for long time as the most useful one from point of view of phototherapy (photobiomodulation) (11).

It is known now that neurons release ATP into muscle, gut, and bladder tissue as a messenger molecule. The specific receptors for ATP as for the signaling molecule (P2 family) and for its final breakdown product, adenosine (P1 family), were found and identified (32, 33). ATP activation of P2 receptors (subtypes P2X and P2Y) can produce different cellular effects. A recent research demonstrated that P2Y2 and P2Y11 receptors were expressed in the irradiated at $\lambda = 810$ nm normal human neural progenitor cells *in vitro* (35). It appeared that the irradiation could be used as a replacement for growth factors. This line of research opens a new understanding of the complicated mechanisms of photobiomodulation. From point of view of the topic of the present article, the role of ATP as a signaling molecule provides a new basis for explaining the versatility of phototherapy effects. The multiple roles of ATP in context of mitochondrial mechanisms of photobiomodulation were discussed in ref. 36.

CONCLUDING REMARKS

The photosensitivity of respiratory chain enzymes has never gained researchers' attention, as has that of functional photoacceptors, such as chlorophyll and rhodopsin. However, the fragmentary knowledge gathered so far forces one to ask whether the photosensitivity of cytochrome *c* oxidase may have a physiological significance in spite of the complete adaptation of living systems to photons as a natural external factor. IR-A radiation penetrates rather deep into the tissues (so called “optical window” of the skin or “near IR window” into the body). This circumstance also supports the hypothesis of a possible specific biological role of radiation between ~600 and 1000 nm.

REFERENCES

- *Smith, K. C. andHanawalt, P. C. (1969) Molecular Photobiology. Inactivation and Recovery. Academic Press, New York, London.*
- 2 *Piazena, H. andKellher, D. (2008) Comments on cellular response to infrared radiation involves retrograde mitochondrial signaling. Free Radic. Biol. Med. 44, 1869.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 4

- 3 *Tuner, J. andHode, L. (2002) Laser Therapy. Prima Books AB, Grängesberg, Sweden.*
    - Web of Science® Times Cited: 2
- 4 *Karu, T. I. (2003) Low power laser therapy. In Biomedical Photonics Handbook. (Tuan, V.-D., ed.).Chapter 48, pp. 48-1–48-25, CRC Press, Boca Raton.*
- 5 *Karu, T. (1999) Primary and secondary mechanisms of action of visible-to-near IR radiation on cells. J. Photochem. Photobiol. B Biol. 49, 1–17.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 241
- 6 *Schieke, S. M.,Schroeder, P., andKrutmann, J. (2003) Cutaneous effects of infrared radiation: from clinical observations to molecular response mechanisms. Photodermatol. Photoimmunol. Photomed. 19, 228–234.*
    - Wiley Online Library |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 39
- 7 *Schroeder, P.,Pohl, C.,Marks, C.,Calles, C.,Wild, S., andKrutmann, J. (2007) Cellular response to infrared radiation involves retrograde mitochondrial signaling. Free Radic. Biol. Med. 43, 128–135.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 26
- 8 *Gebbers, N.,Hirt-Burri, N.,Scaletta, C.,Hoffmann, G., andApplegate, L. A. (2007) Water-filtered infrared A radiation (wIRA) is not implicated in cellular degeneration of human skin. Ger. Med. Sci. 5, 1612–3172.*
- 9 *Jung, T.,Höhn, A.,Piazena, H., andGrune, T. (2010) Effects of water-filtered infrared A irradiation on human fibroblasts. Free Radic. Biol. Med. 48, 153–160.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 1
- 10 *Piazena, H. andKelleher, D. K. (2010) Effects of infrared-A irradiation on skin: discrepancies in published data highlight the need for an exact consideration of physical and photobiological laws and appropriate experimental settings. Photochem. Photobiol. 86, 687–705.*
    - Wiley Online Library |
    - PubMed |
    - CAS |
    - Web of Science®
- 11 *Karu, T. (2007) Ten Lectures on Basic Science of Laser Phototherapy. Prima Books AB, Grängesberg, Sweden.*
- 12 *Karu, T. I.,Pyatibrat, L. V.,Kolyakov, S. F., andAfanasyeva, N. I. (2005) Absorption measurements of a cell monolayer relevant to phototherapy: reduction of cytochrome c oxidase under near IR radiation. J. Photochem. Photobiol. B Biol. 81, 98–106.*

    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 22
- 13 *Marcus, R. A. andSutin, N. (1985) Electron transfer in chemistry and biology. Biochem. Biophys. Acta. 811, 265–322.*
    - CAS |
    - Web of Science® Times Cited: 4936
- 14 *Brunori, M.,Giuffre, A., andSarti, P. (2005) Cytochrome c oxidase, ligands and electrons. J. Inorg. Biochem. 99, 324–336.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 40
- 15 *Terenin, A. N. (1947) Photochemistry of Dyes and Other Organic Compounds. Acad. Sci. Publ., Moscow, Leningrad.*
    - Web of Science® Times Cited: 3
- 16 *Smith, K. C. (2005) Laser (and LED) therapy is phototherapy. Photomed. Laser Surg. 23, 78–80.*
    - CrossRef |
    - PubMed |
    - Web of Science® Times Cited: 5
- 17 *Karu, T. I. (2008) Mitochondrial signaling in mammalian cells activated by red and near IR radiation. Photochem. Photobiol. 84, 1091–1099.*
    - Wiley Online Library |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 12
- 18 *Zang, Y.,Song, S.,Fong, C.-C.,Tsang, C.-H.,Yang, Z., andYang, M. (2003) cDNA microarrary analysis of gene expression proteins in human fibroblast cell after irradiation with red light. J. Invest. Dermatol. 120, 849–857.*
    - CrossRef |
    - PubMed |
    - Web of Science® Times Cited: 49
- 19 *Menezes, S.,Coulomb, B.,Leberton, C., andDuberteret, L. (1998) Non-coherent near infrared radiation protects normal human dermal fibroblasts from solar ultraviolet toxicity. J. Invest. Dermatol. 111, 629–633.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 22
- 20 *Danno, K.,Horio, T., andImamura, S. (1992) Infrared radiation suppresses ultraviolet B-induced sunburn-cell formation. Arch. Dermatol. Res. 284, 92–94.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 16
- 21 *Abdvakhitova, A. K.,Grigorieva, L. N., andParkhomenko, I. M. (1982) Effect of laser radiation on Chinese hamster cells cultured in vitro. Radiobiology (Moscow) 22, 40–43.*

    - CAS
- 22 *Karu, T.,Pyatibrat, L., andKalendo, G. (1994) Irradiation with He-Ne laser can influence the cytotoxic response of HeLa cells to ionizing radiation. Int. J. Radiat. Biol. 65, 691–697.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 19
- 23 *Joyce, K. M.,Downes, C. S., andHannigan, B. M. (1999) Radioadaptation in Indian muntjac fibroblast cells induced by low intensity laser irradiation. Mutat Res. 435, 35–42.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 11
- 24 *Lage, C.,Teixeira, P. C., andLeitao, A. C. (2000) Non-coherent visible and infrared radiation increase survival to UV (254 nm) in Escherichia coli K12. J. Photochem. Photobiol. B Biol. 54, 155–161.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 10
- 25 *Kohli, R. andGupta, P. K. (2003) Irradiance dependence of the He-Ne laser-induced protection against UVC radiation in E. coli strains. J. Photochem. Photobiol. B Biol. 69, 161–167.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 10
- 26 *Dube, A.,Bock, C.,Bauer, E.,Kohli, R.,Gupta, P. K., andGreulich, K. O. (2001) He-Ne laser irradiation protects B-lymphoblasts from UVA-induced DNA damage. Radiat. Environ. Biophys. 40, 77–82.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 5
- 27 *Spitz, D. R.,Azzam, E. I.,Li, J. J., andGius, D. (2004) Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation: a unifying concept in stress response biology. Cancer Metastasis Rev. 23, 311–322.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 88
- 28 *Eells, J. T.,Henry, M. M.,Summerfelt, P.,Wong-Riley, M. T.,Buchmann, E. V.,Kane, M.,Whelan, N. T., andWhelan, H. T. (2003) Therapeutic photobiomodulation for methanol-induced retinal toxicity. Proc. Natl. Acad. Sci. USA 100, 3439–3444.*
    - CrossRef |
    - PubMed |

    - CAS |
    - Web of Science® Times Cited: 61 |
    - ADS
- 29 *Wong-Riley, M. T.,Bai, X.,Buchman, E., andWhelan, H. T. (2001) Light-emitting diode treatment reverses the effect of TTX on cytochrome c oxidase in neurons. Neuroreport 12, 3033–3037.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 37
- 30 *Wong-Riley, M. T.,Liang, H. L.,Eells, J. T.,Chance, B.,Henry, M. M.,Buchmann, E.,Kane, M., andWhelan, H. T. (2005) Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome c oxidase. J. Biol. Chem. 280, 4761–4771.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 66
- 31 *Eells, J.,Wong-Riley, M. T.,VerHoeve, J.,Henry, M.,Buchman, E. V.,Kane, M. P.,Gould, L. J.,Das, R.,Jett, M.,Hodgson, B. D.,Margolis, D., andWhelan, H. T. (2004) Mitochondrial signal introduction in accelerated wound and retinal healing by near-infrared light therapy. Mitochondrion 4, 559–567.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 36
- 32 *Burnstock, G. (2009) Purines and sensory nerves. Exp. Pharmacol. 194, 332–392.*
- 33 *Khakh, B. C. andBurnstock, G. (2009) The double life of ATP. Sci. Am. 12, 84–92.*
    - CrossRef |
    - Web of Science®
- 34 *Karu, T.,Pyatibrat, L., andKalendo, G. (1995) Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. J. Photochem. Photobiol. B Biol. 27, 219–223.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 88
- 35 *Anders, J. J.,Romanczyk, T. B.,Ilev, I. K., andWaynant, R. (2008) Light supports neurite outgrowth of human neural progenitor cells in vitro: the role of P2Y receptors. IEEE J. Sel. Top. Quantum Electron 14, 118–125.*
    - CrossRef |
    - CAS |
    - Web of Science® Times Cited: 3
- 36 *Karu, T. (2010) Mitochondrial mechanisms of photobiomodulation in context of new data about multiple roles of ATP. Photomed Laser Surg 28, 159–160.*
    - CrossRef |
    - PubMed |

    - CAS |
    - Web of Science®
- 37 *Karu, T. I. andKolyakov, S. F. (2005) Exact action spectra for cellular responses relevant to phototherapy. Photomed. Laser Surg. 23, 355–361.*
    - CrossRef |
    - PubMed |
    - CAS |
    - Web of Science® Times Cited: 33