Hypothesis

Demystifying the Biophoton-Induced Cellular Growth: A Simple Model

Abolfazl Alipour

Students Research Committee, School of pharmacy,
Shiraz University of Medical Sciences, Shiraz, Iran

Use your device to scan and read the article online

Corresponding author:
Abolfazl Alipour
Student Research Committee,
School of pharmacy,
Shiraz University of Medical Sciences, Shiraz, Iran
alipour.abolfazl@yahoo.com

Received: 01.12.2015
Revised: 23.12.2015
Accepted: 26.12.2015

Keywords: None-Chemical Distant Cellular Interactions (NCDCI), Biophoton, Cryptochrome, Cell growth

Abstract

Background: None-Chemical Distant Cellular Interactions (NCDCI) are among the unexplained issues in cell biology. One example of such interactions is the biophoton-induced growth. In this process, photon emissions from one cell can induce mitosis in other cells while they are chemically separated. This effect is evident among many species. **Hypothesis:** It is hypothesized that some simple but universal molecular pathways, which include photoreceptor proteins, modulators of cell cycle and circadian rhythm, can explain this phenomenon. Particularly, existing experimental data has been used to support the hypothesis that exposure of cellular structures to visible light photons deactivates the cryptochrome protein and this deactivation disinhibits cell growth. This disinhibition happens through the influx of Ca^{2+} cations and subsequent activation of the downstream mitogenic pathways. **Conclusion:** While the existing lines of evidence are mixed and equivocal, current hypothesis provides a testable framework for further experimental investigation. The present model and its predictions can be used as a well-documented platform to address the mechanisms of None-Chemical Distant Cellular Interactions in biological systems.

https://doi.org/10.18869/nrip.jamsat.1.2.112

Ultra-weak photon emission in biological objects

In 1920's, A. G. Gurwitsch was the first cell biologist who discovered the phenomenon of the ultra-weak photon emission (UPE) during the period of the cell division of onion root tips (1). This phenomenon is also known as mitogenetic radiation, dark luminescence, low level chemoluminescence and biophoton emission (2). The emission of mitogenic radiations are often attributed to de-excitation of the free radicals in biological objects. This mechanism has been supported by experimental evidence such as increased biophoton emission through addition of hydrogen peroxides to the tissue (3) or increased biophoton emission by reducing the antioxidants in tissue (4). This relationship has been supported by several lines of evidence over recent years. Table 1 presents an outline of such supporting evidence.

None-Chemical Distant Cellular Interaction, an explanatory gap

Along with the discovery of biophoton emissions, several studies suggested the "intercellular communication" as the biological role of the biophoton emission. In fact, Gurwitsch himself was the first one to report that the onion roots can induce mitosis in each other only by emitting biophotons (1). This early discovery was followed by a load of subsequent studies demonstrating the

Table 1. A short list of evidence establishing the relationship between free radicals and biophoton emission

Finding	Year
Direct relationship between the intensity of biophotons and neural metabolic activity in rat hippocampal slices (5).	1995
Association between spontaneous biophoton emission from rat's brain and cerebral energy metabolism and oxidative stress (6,7).	1999
Use of Biophoton emission based imaging to measure oxidative stress(8n).	2006
Biophoton emission as an indicator of dehydration induced oxidative stress (10n).	2008

same effect in yeast cells (10), pig's neutrophils (11), developing tissues (12) and paramecium (13). A short list of similar reports is presented in Table 2 while a comprehensive review has been provided in (14). Although mechanism for biophoton emission is well documented, plausible models for biophonic communication are still lacking. In particular, biophoton-induced mitosis is among unexplained issues. Therefore, the main aim of the present work is to propose a simple model to possibly explain the mechanism of "biophoton-induced mitosis".

The hypothesis

Literally, the term "biophoton" indicates the source of a photon and these photons do not seem to have fundamental differences with other photons emitted from different sources. Considering this, the present paper tries to suggest possible cellular pathways which may underpin the photon-induced growth. It is hypothesized that biophoton emissions from one cell can deactivate a flavin-binding photoreceptor in the other. This deactivation will result in an influx of Ca^{2+} ions which induce mitosis thorough Ca^{2+}-Calmodulin-related cascades in the receiver cell. Figure 1 is a schematic representation of this hypothesis.

Photons can induce growth, regardless of their origin

Photon induced growth is ubiquitous among living organism, especially in plant tissues. Early observations of this phenomenon in plants belong to the last decades of the 19th century (20). In the upcoming years of the 20th century, the similar observation was made in animal cells and was reffered to as LASER wound-healing (21). The nature photoreceptor proteins mediating this effect in plants was not explained until 1993 (22). These proteins are phototropines (23), photoactivated adenylyl cyclase (24) and cryptochromes (25). However, the counterpart proteins in the animal cells which mediate the same effect have remained unknown.

Mediators of light-induced growth, cryptochrome pathway, cell and circadian cycle

Among all above photoreceptor proteins, cryptochrome (Cry) is a particularly interesting. Cry protein highly similar to photolyase proteins which repair DNA by breaking the UV-induced pyrimidine dimers through a light-induced process. Both Cry and Photolyase proteins use Flavin Adenine Dinucleotide (FAD) as their cofactor. However, Cry proteins -except the DASH Cry in some species- do not have the capability of DNA repair. Since the knockdown of Cry in mouse completely abolishes the circadian clock (26, 27), the main function of Cry proteins is assumed to be the regulation of the circadian clock. It is remarkable that Cry regulates the circadian rhythms in a "light independent" manner. This fact questions the benefit of conserving the photoreception capability of Cry in evolution and the answer to this question is still unknown. Hence, there might be other conceivable functions for Cry. To identify possible roles of photoreception capability in Cry, inspecting the intertwined relationship between the circadian cycle and cell cycle seems warranted (28).

Possible pathway for biophoton-induced growth: cryptochrome

As mentioned above, Cry proteins are the major regulators of the circadian rhythm while they can also affect the cell cycle. Cry proteins inhibit cAMP production (29, 30) which is a secondary messenger allowing Ca^{2+} channels opening. Therefore, it is conceivable that Cry protein can suppress the inward flow of Ca^{2+} but the pivotal interaction that bridges the gap in the cycle is the interaction between Cry proteins and photons.

It is known that light emission causes ubiquitnation and subsequent proteolytic degradation of Cry in drosophila (31, 32) and this

Table 2. Several samples of the light-growth interactions in biological systems.

Finding	Year
Biophoton emission changed protein secretion, lipid peroxidation and ultra-weak photon emission in detector cells of mammary gland tissue (15)	1993
Decreased adhesive capability of pseudomonas fluorescens cells through biophotonic communication (16)	2000
Increased growth rate in *Escherichia coli* bacterial colonies through vis-IR photons (17)	2003
Germinating Fucus-zygotes direct their growth with biophoton emissions (18)	2005
Proliferation induction with electromagnetic emission between osteoblast cells (19)	2007

degradation is stopped by turning off the exposing light (33). In other words, light degrades Cry and causes mitosis through disinhibition of the Ca^{2+} inward flow and subsequent formation of Ca^{2+}-Calmodulin complex. Consequently, biophoton/photon emission "disinhibits" cell growth.

Discussion and Conclusion

It is hypothesized that photon emission, regardless of its origin (biological/non-biological) can affect the cell growth through Cry proteins. Some other characteristics of Cry can be used to support the current hypothesis. First, any mechanism which mediates the biophoton/photon induced growth should exist in a wide variety of species. Cry proteins are expressed in animal cells, plants, fungi (34), and even some bacterial species (35, 36). Therefore, it fulfills the first criterion. Secondly, the gene expression profile of the Cry protein in human and mouse shows that it is being expressed in all investigated tissues (37). Hence, ubiquity of Cry protein makes it a possible candidate for mediation of a ubiquitous process. However, these evidences cannot guarantee that the Cry mediates all existing biophotonic communications. In Arabidopsis thaliana, Cry knock-out mutants show the light induced Ca^{2+} influx while phototropin knock-out mutants cannot demonstrate this effect (38). Consequently, it seems that the light-dependent Ca^{2+} influx is mediated through the phototropin proteins rather than cryptochromes in this plant. Thus it is possible that biophotonic communication in some plants happens through other proteins. Additionally, the interaction between Cry protein and cell cycle is another complicated issue that should be considered. The main interaction site between Cry and cell cycle is the G2/M transition check-point. It is reported that Cry proteins promote G2/M transition through inhibition of wee1 gene expression (39). On the other hand, Cry proteins cause degradation of Bmal proteins. Bmal proteins enhance the expression of the wee1 gene and act against Cry by inhibiting the cell proliferation. Based on such evidence, Cry can promote cell proliferation which turns to be completely against the current hypothesis.

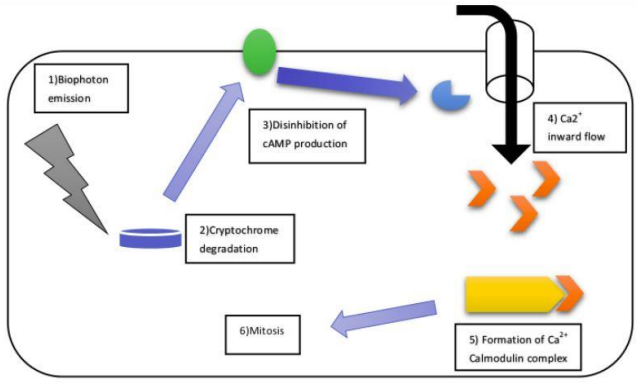

Figure 1. Schematic representation of the hypothesis

Fortunately, since Bmal mutant cell lines do not show a higher proliferation rate or promotion of spontaneous cancer comparing with wild types, the interaction between Cry and cell cycle does not seem to have a significant impact on cell growth. Moreover, both Cry and Bmal mutant cells lead to low proliferative rates which questions the impact of the Cry on cell proliferation again. Therefore, the cell cycle interactions of the Cry seem to be still away from a comprehensive understanding.

In summary, the current hypothesis asserts that a simple photochemical cycle including cryptochrome, cAMP and Ca^{2+} may possibly answer a century-old question. However, only if the predictions of the hypothesis come true, it can be

accounted as plausible. Some predictions of this hypothesis are outlined below:

- There is a positive correlation between photon/biophoton emission and cAMP concentration in the cell.
- Biophoton-induced mitosis should be inhibited by Ca^{2+} channel blockers.
- Knock-down Cry1 and Cry2 cells cannot show the so-called "biophotonic communication".
- Since blue light has the peak absorbance for Cry, blue light photons are the most effective "mitogenic" photons and they can accelerate light-induced wound healing.

It is noteworthy to mention that if the current hypothesis will be confirmed, it will help to determine the types of tissues that phototherapy has its peak efficacy based on the tissue's cry gene expression profile.

Acknowledgment

The author would like to thank Dr. Mohammad Reza Dorvash and Dr. Mohammad Farahmandnia for their useful comments upon the preparation of this hypothesis.

References

1. K A. G. Gurwitsch, Arch Entw Mech Org 1923; 100 (1):11-40
2. F. Grass a, H. Klima B, S. Kasper. Biophotons, microtubules and CNS, is our brain a "Holographic computer"? Med Hypotheses 2004; 62: 169–172
3. Boveris, Alberto, et al. "Organ chemiluminescence: noninvasive assay for oxidative radical reactions." Proc Natl Acad Sci U S A 77.1, 1980: 347-351.
4. Ursini, Fulvio; Barsacchi, Renata; Pelosi, Gualtiero; Benassi, Antonio. Oxidative stress in the rat heart, studies on low-level chemiluminescence. J Biolumin Chemilumin 1989; 4 (1): 241–244.
5. Y. Isojima, T. Isoshima, K. Nagai, K. Kikuchi, H. Nakagawa, Ultraweak biochemiluminescence detected from rat hippocampal slices, NeuroReport, 1995; 6: 658-660
6. M, Kobayashi, M, Takeda, K, Ito, H, Kato, H. Inaba, Two-dimensional photon counting imaging and spatiotemporal characterization of ultra-weak photon emission from a rat's brain in vivo, J Neurosci Methods 93 (1999) 163-168.
7. M. Kobayashi, M. Takeda, T. Sato, Y. Yamazaki, K. Kaneko, K. Ito, H. Kato, H. Inaba, In vivo imaging of spontaneous ultraweak photon emission from a rat's brain correlated with cerebral energy metabolism and oxidative stress, Neurosci Res, 1999; 34:103-113.
8. Michel H, Christian T, Bernard G. Autoluminescence imaging: a non-invasive tool for mapping oxidative stress. Trends Plant Sci, 2006; 11: 480–484
9. Joon-Ho K, Tae-Shik K, Daewoong J, Hoon-Sik L, Sang-Hyuu P, Park, S. H. Effect of dehydration stress on delayed luminescence in plant leaves. J Korean Phys Soc, 2008; 52: 132–136
10. Musumeci F, Scordino A, Triglia A, Blandino G, Milazzo I. Intercellular communication during yeast cell growth. Europhys Lett, 1999; 47: 736–742
11. Shen, Xun, W. Mei, and Xun Xu. Activation of neutrophils by a chemically separated but optically coupled neutrophil population undergoing respiratory burst. Experientia, 1994; 50(10): 963-968
12. Albrecht-Buehler G. Rudimentary form of cellular" vision". Proc Natl Acad Sci U S A 1992; 89(17): 8288-8292.
13. FELS, D. Cellular Communication through Light. PLOS ONE,2009; 4: e5086.
14. Cifra, Michal, Jeremy Z. Fields, Farhadi A. Electromagnetic cellular interactions. PROG BIOPHYS MOL BIO, 2011: 105(3): 223-246
15. Galantsev, V. P. Lipid peroxidation, low-level chemiluminescence and regulation of secretion in the mammary gland. Experientia, 1993; 49(10): 870-875
16. Nikolaev, Yu A. Role of distant interactions in the regulation of the adhesion of pseudomonas fluorescens cells. Microbiology 2000; 69(3): 291-295
17. Trushin, M. V. Culture-to-culture physical interactions causes the alteration in red and infrared light stimulation of Escherichia coli growth rate. J Microbiol Immunol Infect 2003; 36(2): 149-152
18. Jaffe, Lionel F. Marine plants may polarize remote Fucus eggs via luminescence. Biol Bull 2004; 207(2): 160-160 19. Zhang, JianBao, and XiaoJun Zhang. Communication between osteoblasts stimulated by electromagnetic fields." Chinese Sci Bull 2007; 52(1): 98-100
20. Darwin C. The power of movement in plants. Da Capo Press 1881, New York
21. Conlan, MJ., Rapley, J.W., and Cobb, C.M. Biostimulation of wound healing by low-energy laser irradiation. J Clin Periodentol, 1996; 23: 492–496
22. Ahmad, Margaret, Anthony R. Cashmore. HY4 gene of A. thaliana encodes a protein with characteristics of a blue-light photoreceptor. Nature,1993: 162-166
23. Huala, E., P. W. Oeller, E. Liscum, I. S. Han, E. Larsen and W. R. Briggs Arabidopsis NPH1: A protein kinase with a putative redox-sensing domain. Science 1997; 278: 2120–2123
24. Iseki, M., S. Matsunaga, A. Murakami, K. Ohno, K. Shiga, K. Yoshida, M. Sugai, T. Takahashi, T. Hori and M. Watanabe. A blue-light-activated adenylyl cyclase mediates photo- avoidance in Euglena gracilis. Nature, 2002; 415: 1047–1051
25. Ahmad, M. and A. R. Cashmore. HY4 gene of A. thaliana encodes a protein with characteristics of a blue-light photo- receptor. Nature 1993; 366: 162–166
26. Vitaterna, Martha Hotz. Differential regulation of mammalian period genes and circadian rhythmicity by cryptochromes 1 and 2." Proc Natl Acad Sci USA, 1999: 96(21): 12114-12119
27. Van Der Horst, Gijsbertus TJ. Mammalian Cry1 and Cry2 are essential for maintenance of circadian rhythms. Nature, 1999; 398(6728): 627-630
28. Borgs, Laurence. Cell "circadian" cycle. Cell Cycle 2009; 8(6): 832-837
29. Zhang, Eric E. Cryptochrome mediates circadian regulation of cAMP signaling and hepatic gluconeogenesis. Nature Med, 2010; 16(10): 1152-1156
30. Narasimamurthy, Rajesh. Circadian clock protein cryptochrome regulates the expression of proinflammatory cytokines. Proc Natl Acad Sci USA, 2012; 109(31):12662-12667
31. Naidoo N, Song W, Hunter-Ensor M, Sehgal A. A role for the proteasome in the light response of the timeless clock protein. Science, 1999; 285:1737–1741
32. VanVickle-Chavez SJ, Van Gelder RN. Action spectrum of Drosophila crypto-chrome. J Biol Chem 2007; 282:10561–10566
33. Busza, Ania. Roles of the two Drosophila CRYPTOCHROME structural domains in circadian photoreception. Science 2004; 304(5676): 1503-1506
34. Froehlich, A. C., Chen, C. H., Belden, W. J., Madeti, C., Roenneberg, T., Merrow, M., Dunlap, J. C. (2010). Genetic and molecular characterization of a cryptochrome from the filamentous fungus Neurospora crassa. Eukaryot Cell, 9(5), 738-750.
35. Öztürk, N. Structure and function of animal cryptochromes. Cold Spring Harbor Symposia on Quantitative Biology. Vol. 72. Cold Spring Harbor Laboratory Press, 2007
36. Hitomi, Kenichi. Bacterial cryptochrome and photolyase: characterization of two photolyase-like genes of Synechocystis sp. PCC6803. Nucleic Acids Res, 2000; 28(12): 2353-2362
37. Su, Andrew I. A gene atlas of the mouse and human protein-encoding transcriptomes. Proc Natl Acad Sci USA, 2004; 101(16): 6062-6067
38. Stoelzle, Sonja. Blue light activates calcium-permeable channels in Arabidopsis mesophyll cells via the phototropin signaling pathway. Proc Natl Acad Sci USA, 2003; 100(3): 1456-1461
39. Gekakis, Nicholas. Role of the CLOCK protein in the mammalian circadian mechanism. Science 1998; 280 (5369): 1564-1569drug Setarud on cerebral ischemia in male rats. Neural regeneration research. 2012;7(27):2085-91.