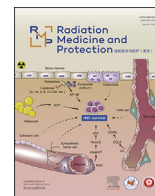




Contents lists available at ScienceDirect

## Radiation Medicine and Protection

journal homepage: [www.radmp.org](http://www.radmp.org)

## Review

## Biophoton signaling in mediation of cell-to-cell communication and radiation-induced bystander effects

Jian Tong

School of Public Health, Soochow University, Suzhou 215123, China

## ARTICLE INFO

## Keywords:

Biophoton  
 Radiation-induced bystander effect  
 Ionizing radiation  
 Cell-to-cell communication  
 Mitochondrion  
 Exosome

## ABSTRACT

This paper presents a comprehensive overview of the historical trajectory and development in biophoton studies over the past 100 years, with a particular focus on the recent progress regarding the pivotal role of biophoton in mediating radiation-induced bystander effects (RIBE). The exploration of biophoton mystery starts from the initial observation of mitogenic radiation and continues to develop to the contemporary science of biophotonics. The properties and underlying mechanisms of biophoton emission are described with illustrative examples from diverse biological systems such as plants, animals and humans. The conclusive evidence of cell-to-cell communication facilitated by biophoton signaling is presented, followed by an elaborate interpretation of potential mechanisms through which biophoton mediates RIBE. The engagement of mitochondria and exosomes in this process is extensively clarified, by highlighting their significant roles in biophoton-mediated RIBE. The advances in biophoton research in respect of bystander response to ionizing radiation may offer profound insights into radiobiology and provide for possible future applications as well in radiation medicine and protection.

## 1. Introduction

Low-dose ionizing radiation (LDIR) responses refer to the reactions or effects observed in biological systems when exposed to ionizing radiation (IR) at low doses (<100 mGy) and low dose rates (<6 mGy/h), which are considered to bring about biological responses involving changes in biological functions, cellular processes, or potential health risks with low-level radiation exposure.<sup>1,2</sup> The classical and contemporary studies on low-dose radiation effects have been illuminated and thoroughly examined, particularly for hormesis<sup>3-6</sup> and adaptive radiation response,<sup>7</sup> along with bystander effects and other non-targeted effects (NTE).<sup>7,8</sup> Notably, these effects were observed to exhibit nonlinearity within the low-dose range of IR. Mechanistic investigations have revealed that crucial cellular processes, such as gene induction,<sup>9,10</sup> gene expression and epigenetic control,<sup>11</sup> protein expression,<sup>12</sup> DNA repair,<sup>13</sup> and intracellular signaling related to cell cycle arrest and apoptosis,<sup>14</sup> all manifest nonlinearity at low doses. Additionally, interconnected intracellular and extracellular signaling processes have also been explored accordingly.<sup>15,16</sup>

A comprehensive series of reviews have delved into and commented on the significance of the bystander effect induced by IR. Initially, these studies focused on the potentially adverse biological effects of LDIR, including cytotoxicity,<sup>15,17-19</sup> mutagenicity,<sup>20-22</sup> genomic

instability,<sup>23-25</sup> carcinogenic effects,<sup>26</sup> and inflammatory responses.<sup>27</sup> These radiation-induced deleterious effects to the organism were later defined as bionegative effects.<sup>7</sup> However, subsequent research provided deeper insights, revealing that the bystander effects could also bring about positive biological outcomes<sup>7,28-30</sup> in extended dose ranges. These biopositive effects, defined as radiation-induced beneficial effects to the organism, were mediated by systemic and long-distance abscopal reactions, hormesis and adaptive responses, leading to favorable consequences in the organism.<sup>31-35</sup> Nevertheless, in some cases, these effects can also be bionegative.<sup>36</sup>

Hormesis serves as an example of beneficial low-dose IR effects,<sup>37-39</sup> specifically in terms of enhancing mitochondrial functions.<sup>40</sup> In fact, low dose IR can effectively prompt cell proliferation and survival, while elevating antioxidant and immune responses. This intricate mechanism acts to strengthen cellular defense systems, thereby enabling cells to endure subsequent stress. Hormesis may be induced via a direct stimulation or by over compensation to a disruption of homeostasis.<sup>41</sup>

Protective adaptive radiation processes are evolutionarily conserved.<sup>42</sup> The adaptive radiation response has been aptly characterized by the observations<sup>43</sup> that when human lymphocytes are first exposed to a low "priming" radiation dose from low concentrations of tritiated thymidine, followed by a subsequent, higher challenging dose of 1.5 Gy of X-rays, they exhibit fewer chromosomal aberrations than when

E-mail address: [tongjian@suda.edu.cn](mailto:tongjian@suda.edu.cn).

<https://doi.org/10.1016/j.radmp.2024.06.004>

Received 10 May 2024; Received in revised form 12 June 2024; Accepted 19 June 2024

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exposed only to the high challenging radiation dose, so that to confer protection.<sup>44,45</sup> On the other hand, epidemiological studies conducted on human populations have revealed adaptive responses in residents living in high background-radiation area of Yangjiang in China. The lower cancer mortality rates observed in this area are likely attributed to enhanced DNA repair and antioxidant capacities.<sup>46</sup>

Cells that are exposed to ionizing radiation possess the ability to release communication signals, subsequently eliciting biological alterations in distant cells that have not been irradiated.<sup>47-49</sup> This remarkable phenomenon, where intercellular communication and biological transformation are triggered by irradiation, is known as the radiation-induced bystander effects (RIBE). Extensive research has indicated that RIBE prompt a range of responses in bystander cells that closely mimic the responses in cells which have been directly irradiated. Biological effects such as sister chromatid exchanges, micronuclei formation, apoptosis, genomic instability, and mitochondrial dysfunction have all been observed in bystander cells following the reception of signals released by directly irradiated cells.<sup>50-52</sup>

Over the past decades, there has been comprehensive exploration on the signals and subsequent cellular events induced by bystander cells.<sup>53-55</sup> Historically, the bystander effects primarily refer to the intercellular communication facilitated by chemical and biochemical messengers, including calcium, reactive oxygen species (ROS), nitric oxide (NO), mitochondrial DNA (mtDNA), adenosine triphosphate (ATP), microRNAs, interferon and cytokines. This signaling transduction occurs via intercellular gap junctions, extracellular vesicles such as exosomes, and mitochondria, efficiently transforming signals from targeted cells to bystander cells.<sup>56</sup>

More recently, experimental evidence of non-chemical and non-contact cell-to-cell communication across diverse biological systems has been inspiringly provided.<sup>57-60</sup> The phenomenon known as "physically mediated communication" has been reported,<sup>61</sup> involving identified physical signals such as ultraviolet, visible and infrared light, electromagnetic fields of extremely high and low frequencies, as well as sound waves.<sup>58,62,63</sup>

Among these physical signals, biophotons have drawn substantial attention, especially those of ultraweak photons emitted by both living and dead organic materials in living organisms. Subsequently, the photon emission from the organisms is usually referred to as ultraweak photon emission (UPE), ultraweak bioluminescence, and biophoton emission.<sup>64-66</sup> At present, these terms are often used interchangeably in the field of biophoton research. Remarkably, even in the absence of external stimuli, biophoton emission at very low fluxes has been observed from the organisms, leading to the phenomenon of "spontaneous photon emission".<sup>67</sup> On the other hand, biophoton emission can be elicited in response to an environmental stimulus such as IR.<sup>68,69</sup> Biophoton emission thus induced in cells as a result of the initial high and low LET irradiation has been defined as "induced or secondary biophoton emission".<sup>69,70</sup>

The biophoton emissions are hypothesized to serve as cellular cross-talk signals, facilitating both inter- and intra-cellular communication within cellular populations, tissues, or organisms.<sup>67,71,72</sup> Consequently, they have been considered as potential information carriers,<sup>73-75</sup> capable of triggering the release of bystander-eliciting soluble factors. The significance of secondary biophoton emission in the triggering of biological processes has been postulated, indicating that the emission and absorption of photons at the UV wavelength could account for some radiation-induced bystander effects that were previously ascribed to chemical mediation.<sup>70</sup>

This paper reviews the history and development in biophoton studies, especially on the roles of biophoton signaling for cell-to-cell communication and RIBE. The engagement of mitochondria and exosomes in these biological effects of radiation is particularly elucidated to highlight the significance of these two organelles in biophoton mediated RIBE. The progress in this dynamic and demanding field of research holds substantial potential in future radiation biology and radiation medicine.

## 2. History and development of biophoton research

### 2.1. From mitogenetic radiation to biophoton emission

In 1912, the former Soviet biologist Gurwitsch revolutionized the understanding of embryonic development with his pioneering paper. In the paper, he introduced the innovative theory of "morphogenetic field" acting as a regulatory mechanism in direction of the behavior of individual cells in a developing embryo. The field orchestrates the cell movement, controls cell division and differentiation, and evolves alongside the embryo's growth.<sup>76</sup>

In 1923, Gurwitsch conducted his renowned "onion experiment" to test his hypothesis that photons trigger cell division. In this experiment, he positioned the tip of an onion root, designated as the inducer, towards the wall of another onion root, designated as the detector. He soon after observed a remarkable increase in mitotic activity on the detector side facing the inducer root's tip, compared to the opposite side. Interestingly, when a glass plate was inserted between the inducer and detector, no stimulatory effect on mitotic activity was observed. However, a quartz plate placed over the inducer root's tip did not interfere with its stimulatory action. Furthermore, when the inducer's tip was aimed at a metal mirror in such a way that its reflection fell onto the detector's wall, stimulatory effect was once again observed.<sup>77</sup>

As the observed results could not be rationalized through either chemical or mechanical interactions among roots, a compelling hypothesis emerged: a living organism has the capacity to emit photons that trigger cell divisions. These photons reside within the ultraviolet segment of the electromagnetic spectrum, as evidenced by the fact that quartz, but not glass, allows them to pass through unhindered. Consequently, the photonic emission emanating from the tip of a root, which motivate mitoses in another root, was defined as "mitogenetic radiation" (MGR).<sup>78-80</sup>

The research on mitogenetic effects reached its peak during the 1930s, marked by the publication of hundreds of papers and a dozen comprehensive reviews on MGR.<sup>81-83</sup> However, the outbreak of World War II devastated all European research centers that were exploring MGR, leading to a hiatus in independent investigations on this fascinating phenomenon.<sup>78</sup>

The studies on ultraweak light emission from living organisms resumed in the early 1960s at the Moscow State University. Tarusov and his colleagues postulated that this ultraweak biological emission was a direct consequence of free radical reactions, particularly lipid peroxidation reactions and the recombination of active oxygen species. According to their theory, biological photon emission was merely a byproduct of these reactions and did not serve any significant functional role.<sup>84</sup> This perspective dominated researches in biochemistry and physiology for quite a few years.

In the 1970s, the German physicist Friz-Albert Popp embarked on this line of research and made a groundbreaking discovery: the ultraweak light emission of biological systems, whether of plant or animal origin, exhibited remarkable coherence across the entire detection range, spanning from ultraviolet to the red portion of the electromagnetic spectrum.<sup>85</sup> He demonstrated that not just individual organisms but also their communities, such as daphnia in a small aquarium, seeds placed in a single vessel, yeast cultures, or animal cell suspensions, all behaved as coherent emitters. By attracting quantum-physical theory as well as modern theories of cavity quantum electrodynamics and of coherent electromagnetic field, and taking into consideration the specific properties of biological electromagnetic radiation, Popp suggested for the light emission from biological systems a new term - "biophoton emission".<sup>86</sup>

### 2.2. Properties and potential mechanisms of biophoton emission

The spectrum of biophoton emission emanating from living systems has been demonstrated to span at a range from 200 to 800 nm,<sup>87</sup> which

consists of ultraviolet (UV), visible and infrared spectra. The visible and infrared spectrum ranges from 400 to 750 nm and 750–1,000 nm respectively, while the UV spectrum is subdivided into three electromagnetic wave ranges of UVA (320–400 nm), UVB (290–320 nm) and UVC (<290 nm). The energy and the frequency of a given photon shares an inverse relationship with its wavelength. For instance, the energy of a 100 nm UV photon is 12.4 eV and its corresponding frequency is 3 PHz, whereas a 1000 nm infrared photon only has the energy of 1.24 eV and a frequency of 100 THz. Based on this characteristic, it is evident that shorter wavelength photons, such as those at the UV range, possess greater energy than visible and infrared photons, which have longer wavelengths.

The salient features of biophoton emission can be described as follows: (1) It can be generally observed in all organisms, both at the microscopic and macroscopic scales, with or without external stimuli. (2) The emission intensity is extremely low, reaching magnitudes of approximately of  $\sim 10^{-13}$  W/cm<sup>2</sup> or even less. (3) The emission occurs across a vast spectral range, encompassing ultraviolet to near-infrared wavelength regions. (4) While the emission mechanisms remain under research, they are hypothesized to stem from the endogenous generation of excited states resulting from metabolic reactions within the organisms. (5) Two-dimensional biophoton imaging studies reveal that the emission intensity is localized.<sup>88,89</sup>

Despite the abundant experimental results, the mysteries surrounding biophotons persist unresolved. Inquiries continue regarding their essence, the mechanisms underlying their generation, and their intricate role in life processes. Accordingly, two hypotheses are proposed to explain these phenomena.<sup>90,91</sup> The first hypothesis views the emission of biophotons as the “random radiative decay” of molecules excited by metabolic activities. Alternatively, the second hypothesis attributes the emission to a coherent electromagnetic field generated both within and between cells, presumably arising from biochemical reactions involving oxygen atoms.

The primary candidate for intracellular biophoton production lies in the generation of excited species and their subsequent transition to a stable state. Lipid peroxidation and oxidative metabolism within mitochondria are proved capable of triggering the production of electronically excited states within biological systems.<sup>92</sup> Both singlet oxygen (<sup>1</sup>O<sub>2</sub>) and carbonyl compounds in the triplet state have been identified as sources of biophoton emission.<sup>93</sup>

In the field of biophoton research, there are two types of photon emission. Spontaneous photon emission occurs in a natural way, in general without the addition of external chemicals or physical stimuli, in almost all types of cells, whereby it is generally stronger in more highly developed organisms. On the other hand, induced photon emission serves as a pivotal methodology for observing the coherence state of light triggered by stressors such as chemicals, virus and radiations.<sup>94–97</sup> This methodology involves exposing an organic sample to a flash of light, which subsequently prompts the sample to emit a distinctive photon signal known as “delayed luminescence”. By carefully analyzing this signal, it becomes evident that the decay characteristics of biophoton luminescence exhibits a non-exponential pattern, which provides compelling evidence for the inherent coherence present in the emission.<sup>98,99</sup>

In the quantum realm, coherence signifies that subatomic particles exist in a state of harmonious alignment. Technically, it denotes a state where subatomic waves or particles are synchronized, sharing the same phase. In the context of biophotons, the concept of coherence was introduced alongside the idea of synergy, emphasizing a cooperative dynamic among particles.<sup>100</sup> Coherence implies that the photon particles or waves emitted by cells integrate into an interconnected system, operating as a synchronized electromagnetic field. The degree of order exhibited by such light is indicative of its laser-like attributes, testament to the intricate interplay among its constituent components.

The biophotonic theory postulates that light is sequestered within the DNA of cells.<sup>86</sup> This assertion was corroborated by observations made

when ultraweak photo emission ceased to manifest upon the removal of cell nuclei. According to this theory, DNA functions akin to an “exciplex/excimer laser system”, and serves as a repository for photons, subsequently releasing them as coherent light. Technically speaking, the coherent states of light originate in the DNA as a result of complex interactions between electromagnetic waves and the mechanical oscillations of the bases within the DNA molecular structure.<sup>101</sup>

Just as the onion experiment demonstrated that ultraviolet photons can serve as a trigger for cell division by as much as 30 % increase of the division rate,<sup>102</sup> there is ample evidence suggesting that biophotons belonging to wider ranges of electromagnetic spectrum must also be tightly linked to biological and physiological functions, serving as the medium for biological information transfer.<sup>103</sup>

### 2.3. Biophoton emission from biological systems

#### 2.3.1. Biophoton emission from microbes and plants

The emission of biophotons from yeast and bacterial cultures has been documented throughout various growth stages of the organisms.<sup>104–106</sup> Notably, both cultures exhibited UV components within their emission spectra during the exponential growth phase. Marked increase in the intensity and distinct changes in the spectra of biophoton emission were observed in yeast, accompanied by significantly altered metabolism.<sup>107</sup> Experiments with bacterial cultures (*Escherichia coli* and *Serratia marcescens*) suggested that the biophotons were released in response to stress and with species specific feature.<sup>108</sup>

In a study on the relation between gene activity and UPE from *Escherichia coli* (*E.coli*), it was found that higher gene activity produced more UPE by comparing the *E. coli* with the *LacI* gene bacteria.<sup>109</sup> In the yeast of *Saccharomyces cerevisiae*, the luminescence emitted by the respiratory-deficient mutant also showed a higher emission intensity than the wildtype yeast during the exponential phase of growth, which was explained by higher O<sub>2</sub><sup>-</sup> concentrations in lipid peroxidation reactions in the respiratory-deficient mutant.<sup>110</sup>

The phenomenon of bioluminescence in green plants was discovered in the early 1950s,<sup>111</sup> and was initially assigned to chlorophyll reactions. Since then, it has been extensively studied in plant tissues and cells, and in isolated chloroplasts.<sup>112–117</sup> Furthermore, consistent reports have emerged on the detection of biophoton emission from germinating seedlings and leaves. As plant seedlings grow, they emit very small number of tens to hundreds of photons per second. UPE recordings have been performed on single germinating seedlings of mung beans, corn and wheat, with differences between seedlings time and plant species.<sup>118</sup> The relation between the seedling's development in total length of roots plus leaflet and the UPE counts showed a general pattern of linear UPE with seedling growth, indicating that the total photon counts may serve as a function of plant seedling growth in time.<sup>119</sup> Employing a two-dimensional photon counting tube, the first biophoton image of a germinating soybean seedling was captured, which was attributed to an elevation in metabolism during the critical phase of cell division.<sup>120</sup>

Various stimuli have been shown to alter UPE in plants.<sup>121–123</sup> For example, mechanical wounding to discrete regions of the *Arabidopsis* plant induced high levels of UPE, which lasted for several hours and was strictly limited to the injured areas.<sup>124</sup> Higher emission intensities were also observed around the injured area of *Spathiphyllum* and *adzuki* seedling, suggesting that the emission serves as a reflection of the plant's defense mechanisms against injury or infection.<sup>125–128</sup> Besides, UPE was used to track red bean plant function following exposure to the stressors of elevated salt concentration and drought.<sup>129,130</sup>

In a comprehensive study including 2,000 germinating red bean seedlings, a linear increase in biophoton emission intensity was observed in tandem with the acceleration of root growth. It was then discovered that the germination rate of the seedlings could be accurately predicted by measuring the intensity of biophoton emission, providing a novel and reliable method for assessing germination progress.<sup>131,132</sup>

An imaged biophoton emission was reported from germinating

cucumber seedlings, revealing that the region emitting light was situated remotely from the area responsible for generating the light, which implied a high light guiding efficiency that would enable a considerable amount of generated light to travel over distances as long as 20 mm.<sup>133</sup> In a separate investigation, the spatial and temporal distribution of biophoton emission from germinating soybean seedlings was analyzed under various conditions of physical, chemical, or mechanical stress. Accordingly, intense light emitting regions were observed at distant locations as well, disconnected from the site of the applied stress.<sup>134</sup>

Biophoton emission measurements have been proved to be invaluable in tracking diverse physiological processes within the plant system, such as membrane transport, cell growth and differentiation. An intriguing aspect of this research lies in the temperature dependency of biophoton emission observed in whole leaves of various plants, which indicates that these measurements may serve as a practical tool to distinguish between chilling-sensitive and chilling-resistant plants.<sup>135</sup> Furthermore, processes like plant pathology, as well as wound and insect-contamination can be effectively studied by closely monitoring the patterns of biophoton emission.<sup>136–139</sup>

### 2.3.2. Biophoton emission from mammalian cells and tissues

Biophoton emission has been reported to occur in a wide range of cells, organelles, and organisms, including humans, under diverse physiological conditions.<sup>140</sup> In an earlier investigation, the biophoton emission from mammalian nuclei was linked to the peroxidation of the nuclear membrane.<sup>96</sup> The temperature dependence of biophoton emission from nuclei was measured, specifically focusing on the phase transitions undergone by the membranes, which is crucial for understanding the process of information transfer to and from the nucleus.<sup>141</sup> In another study to assess UPE from cultured human cells, a distinct UV dose-dependent emission pattern was observed in DNA-excision-repair-deficient xeroderma pigmentosum (XP) cells, which differed significantly from that exhibited by normal cells.<sup>142</sup>

The investigation on biophoton emission induced by hydrogen peroxide in mouse liver slices and hepatocyte nuclei was reported and the results showed that the perfusion of different concentrations of H<sub>2</sub>O<sub>2</sub> significantly increased biophoton emissions in a concentration-dependent manner, with the maximum effect appeared at the concentration of 400 µM for the liver tissue and the significant enhancement at 500 µM for the hepatocyte nuclei.<sup>143</sup>

Using a single photon counting device with a cooled photomultiplier tube, biophoton emission induced by light was examined from mammalian cells of different tissues and species including cat, Chinese hamster, cow, dog, human, monkey, mouse and rat. The results revealed different number of biophotons for the various cell types, ranging from 4 to 100 photons per 10<sup>4</sup> cells, with the highest values from cells of fibroblastic origin.<sup>144</sup> When a super-high sensitivity photon counting system was applied, rat blood and organ homogenates were found to emit UPE which was enhanced by the progression of in vivo lipid peroxidation.<sup>145</sup>

Spontaneous biophoton emission from various human cancer tissues were measured and the intensities of the emission were found to be apparently higher than those of adjacent normal tissues.<sup>146,147</sup> The measurement was also taken on UPE from nude mice with transplanted tumors and the profiles of the emission were compared with those obtained from the control mice.<sup>148</sup>

By applying an improved detection procedure, the spontaneous biophoton emission was found to be efficiently increased by UVA at the wavelength of 330–380 nm, leading to the light bursts up to 10<sup>7</sup> photons/s instead of several hundred as with classical designs in differentiated human skin fibroblasts. Conversely, decreasing induction ratings from melanoma cells to cancer-prone and normal cells were revealed, and elevated levels of biophoton emission following UVA stimulation were found within the cells.<sup>149</sup>

A recent study has indicated UPE as a promising novel marker for altered cell functions and disease states.<sup>150</sup> The findings demonstrated a

notable decrease in UPE among oligospermia mice treated with busulfan. This reduction was accompanied by significant alteration in the spatial organization of testicular cells, as well as an extraordinary decline in testis volume, the length of seminiferous tubules, and the overall number of testicular cells. Additionally, the Johnsen score indicated severe degenerative changes within the seminiferous tubules, providing further evidence of oligospermia. Based on these observations, it was deduced that the decreased UPE from testis tissue in oligospermia mice may serve as an indicator of altered cell arrangement, reduced intercellular interaction, and potentially the onset of disease.<sup>151</sup>

### 2.3.3. Biophoton emission from animals and humans

Similar to plants, biophoton emission from animals have been detected and documented in mouse skin and brain,<sup>152–154</sup> rat liver nuclei,<sup>155</sup> rat eyes<sup>156</sup> and brain,<sup>157–159</sup> and experimental mouse models.<sup>160–162</sup> In a study on rheumatoid arthritis (RA) mouse model, higher UPE intensities were detected from the front and back paws of mice after initiating arthritis by co-administration of type II collagen and lipopolysaccharide, along with increased levels of inflammatory and ROS-mediated plasma metabolites in the animals.<sup>163</sup> The results indicate a correlation of UPE alteration with metabolomics.<sup>164</sup>

Using a human breast cancer-bearing nude mice model, the spectral characteristics of UPE from the body surface were analyzed. The results showed that the spectral distribution of UPE from the lesion side of the body surface of tumor mice was significantly different from that of healthy controls, regardless of whether visible morphological changes at the lesion site and which stages of the breast cancer development were involved.<sup>165</sup>

UPE measurement may provide a valuable tool for monitoring injury and wound healing in animals.<sup>166,167</sup> Through 2D imaging studies, it was demonstrated that, following an injury to the back of a mouse, the shape of the wound remained consistent over time. However, the emission intensity exhibited a distinct pattern, gradually increasing and peaking between the 3–5 days post-injury. From 6 d onward, the emission intensity began to decline, ultimately returning to normal levels at 8 d, coinciding with the complete healing of the wound and the shedding of the scab.<sup>168</sup>

In humans, UPE is usually measured using a photomultiplier tube (PMT) or a charge-coupled device (CCD). Emitted photons can be measured directly through the skin in a light-tight, dark environment.<sup>169–171</sup> The intensity of UPE emitted from the human body can be influenced by some physiological factors such as age,<sup>172,173</sup> gender,<sup>174</sup> biological rhythms,<sup>170,175,176</sup> and conscious activities.<sup>177–179</sup> The use of UPE has been proposed as both a research and a putative diagnostic tool for health-related issues in humans.<sup>180–182</sup>

The 2D images of biophoton emission captured from the human body revealed a distinct pattern with the UPE spectrum ranged from 450 to 750 nm and peaking in the 600–650 nm region.<sup>183</sup> The images uncovered that the intensity of biophoton emission from the hands of patients suffering from hypothyroidism was consistently lower than that of normal persons. Similarly, reduced emission intensity was observed in patients who had undergone thyroid gland removal.<sup>166,167</sup>

The measurements of biophoton emission from human hands and forehead were performed daily for a period of over 9 months. The result displayed clearly identified biological rhythms of the emissions from the hands and forehead, with periods of 7, 14, 21, 27, 80 and 270 d. While the photon intensities of the hands were in the same phase of the rhythm, the emissions from the forehead were phase-shifted relative to those of the hands,<sup>184</sup> which disclosed a quantum coherence nature.<sup>185</sup>

The biophoton emissions from human blood plasma, urine and breath were also detected and a higher intensity of UPE from the blood of smokers was observed when compared to the blood of nonsmokers.<sup>186</sup> Similar observation was noted in hemodialysis patients who were more vulnerable to oxidative stress than normal persons.<sup>187</sup> Biophoton emission of human breath under exercise was reported to increase gradually and corresponded to 'minute ventilation', i.e. the volume of expired air

per minute. The emission intensity remained high even after the exercise had stopped.<sup>188</sup>

Alterations of biophoton emission from human body have been demonstrated to be linked to pathogenic processes and human diseases, such as metabolic dysfunction,<sup>189</sup> heat shock,<sup>190</sup> cold,<sup>174</sup> acute myeloid leukemia (AML),<sup>191</sup> cardiovascular disease,<sup>192</sup> allergic and inflammatory skin diseases,<sup>193</sup> transcendental meditation and anesthetic state,<sup>177,194</sup> hemiparesis,<sup>195</sup> type 2 diabetes,<sup>196</sup> and cancer.<sup>197–200</sup>

These measurements and findings suggest that biophoton emission may offer valuable insights into the physiological state of the body as well as the feasibility of its use as a novel technique in diagnosis of pathological changes and human diseases.

### 3. Cell-to-cell communication mediated by biophoton signaling

#### 3.1. Physical signaling for cell-to-cell communication

Cell-to-cell communication, also known as cell-to-cell interaction, is an essential feature of multicellular organisms. The dynamic communicating network formed through communication and cooperation between cells plays crucial roles in numerous biological processes.<sup>201</sup> So far, diverse mechanisms underlying this communication have appeared, including communication via direct cell-to-cell contact (e.g., Delta-/Notch signaling), the release of soluble factors (e.g., hormones, cytokines) that activate target cells locally or distantly through surface receptors, and the direct transfer of signals through gap junction channels that span the plasma membranes of adjacent cells.<sup>202</sup>

During the last decade in particular, much progress has been made in the understanding of intercellular communication and signaling pathways that are independent on the exchange of chemical substances. As outlined in a conclusive review, there are at least three types of physical signals that may mediate cell-to-cell communications, i.e., sound, electric current and electromagnetic radiation.<sup>203</sup>

There is evidence from plants, animals and microbes suggesting that sound could be a stimulus for cellular stress responses in different contexts, and for initiating population level responses.<sup>204</sup> Altered cell membrane and cell wall potentials have been shown to produce acoustic waves from kHz to THz range,<sup>205</sup> which trigger mechanical vibrations within cells. These vibrations can then propagate through cytoplasm and create a vibrational cascade in surrounding cells. In addition, a process known as coherent excitation, where multiple cells work collectively, may also produce sound signals in frequencies between 150 and 200 kHz.<sup>206</sup>

Endogenous voltage gradients have been reported as electric mediators of cell-to-cell communication.<sup>207</sup> This bioelectrical signaling is embodied by changes in the resting voltage potential ( $V_{mem}$ ) of the plasma membrane driven by ion channels, pumps and gap junctions, which serves as a highly conserved information-bearing pathway that regulates cell proliferation, migration and differentiation. The changes of  $V_{mem}$  in adjacent cells can propagate over long distances via conventional gap-junctional paths<sup>208</sup> or the more exotic nanotubes to transform electrical signals between cells as a kind of nanowire.<sup>209</sup> All cells, not just excitable neurons and muscle, generate and receive bioelectrical signals encoded in transmembrane potential and ion fluxes, and these biophysical events are crucial components of the bioelectric cell-to-cell communication.<sup>210</sup>

Electromagnetic signals have been extensively investigated on their bioeffects in different biological systems with their roles in mediating biological functions such as intracellular processes and cell-to-cell interactions.<sup>60,211,212</sup> In a study on the effect of low frequency electromagnetic signals on cell proliferation and morphology, two cell populations of immortal fibroblasts (NIH3T3) and primary endothelial cells (HMVECad) were cultured in separate polystyrene Petri dishes which are completely transparent to visible light in the 400–800 nm band, but absorbs strongly in the ultraviolet range of 200–390 nm. The result showed that the cell number and morphology of the HMVECad

cells could be modified, when they were separated from the NIH3T3 cells with only the wall of a polystyrene Petri dish between them, but not so if they were separated by a black filter.<sup>213</sup> It was concluded that the signals responsible for cell-to-cell communication were carried by the electromagnetic radiation since the NIH3T3 cells were reported to emit infrared radiation.<sup>214</sup>

Mitochondria have been identified as sources of both electrical currents and electromagnetic fields.<sup>215</sup> In addition to low-frequency non-radiation quasi-static fields (electromagnetic fields), mitochondria are also radiating high-frequency electromagnetic fields in the optical spectral region measured as spontaneous chemiluminescence. Based on the recent findings of nanotubular structures termed as “tunneling nanotubes”, it has been hypothesized that mitochondria might serve as physical mediators in the conciliation of cell-to-cell communication.<sup>216–218</sup>

#### 3.2. Biophoton signaling for cell-to-cell communication

Cellular communication and interactions constitute the fundamental building blocks of the organization, development, and sustenance of multicellular organisms. The functions of cells within a highly complex system depend on sophisticated signaling mechanisms that facilitate precise intercellular communication.<sup>102,219</sup> Recently, research exploring biophoton emission as a potential biomarker of cellular interactions and pathological states has emerged, indicating that cells engage in a subtle dialogue with each other through the exchange of biophoton signals. This revelation offers a novel and fascinating perspective on the complicated nature of intercellular communication.<sup>220</sup>

Cells are capable of interacting reciprocally without relying solely on molecular signals, implying that not all cellular processes hinge exclusively on molecule-receptor recognition. In addition to being a world of molecules, cells are also a world of electromagnetic fields that play major roles in morphogenesis of multicellular organisms.<sup>221</sup> Biophotons, as the most probably non-molecular signals, may provide with cells to use more than one frequency of electromagnetic waves to correspond for information transfer and mutual interaction.

There are plenty of reports to indicate that biological systems communicate with each other via the exchange of biophoton signals.<sup>59,103,222–225</sup> Cellular communication, facilitated by electromagnetic radiation, arises from the photon emission by one cell population and its subsequent reception by another. Biophotons, distinctively characterized by photons within the UV and visible wavelength ranges, are emitted from biological materials through processes alternative to conventional chemiluminescence.<sup>226</sup> Although the precise mechanisms underlying biophoton emission remain elusive, the excitation of various intracellular molecules stands as a plausible candidate.<sup>227</sup> So far the initiation of biophoton emission has been observed in biological systems following the induction of stress by ionizing radiation,<sup>70,228,229</sup> viral infection,<sup>230</sup> and mechanical disruption.<sup>231</sup>

The action of biophotons as a means of intercellular communication was identified in 1980 by treating a fibroblast culture with the Cocksackie A13 virus. It was demonstrated that the induction of significant adverse effects was optically-coupled, but not chemically associated, in a fibroblast cell population.<sup>230</sup> This effect has since been corroborated by multiple supporting studies citing evidence for intercellular communication via a signal that is electromagnetic in nature,<sup>103,225,232</sup> and has further established the role of biophotons in cellular communication.

There is evidence to indicate that biophotons function as coherent information-encoding signals, similar to binary-encoded data, to exchange information between biological systems.<sup>86</sup> The coherent and squeezed coherent states hold a noteworthy advantage in cellular communication. In a study with baby hamster kidney (BHK) cells grown on one side of glass slides with different filter coats, fresh cells were inoculated on the opposing face of the slides to observe the growth of these newly inoculated cells. The results suggested that the newly inoculated cells were able to detect the orientation of cells residing on the

other face. However, this correlation vanished when a thin metal filter coat was applied between the two faces. Conversely, the presence of a thin silicone coating on the glass had no impact on this effect, hinting that the wavelength of this radiation likely falls within the red to infrared spectrum. This intriguing phenomenon points to a rudimentary form of cellular "vision".<sup>223</sup>

In a separate investigation involving isolated pig neutrophils, two distinct populations of these cells were positioned in isolated chambers, designated as Chamber A and Chamber B, within a dual chamber system. A shutter was interposed between the chambers, allowing the samples to visually interact with each other via light when the shutter was open, but not when it was closed. The biophoton emissions emanating from each sample were independently registered by a photomultiplier. It was discovered that neutrophils, once stimulated to undergo a respiratory burst, had the ability to activate a second population of neutrophils that were chemically isolated but optically connected. The response of the latter population manifested as a transient elevation in their baseline chemiluminescence levels, along with an intensified production of superoxide radicals which were detected through both the reduction of ferricytochrome c and spin trapping techniques. The findings provide compelling evidence for the existence of a biologically significant long-range optical coupling between living cells.<sup>232,233</sup>

Consistent phenomenon was observed in two *dinoflagellate* cultures in the context of light contact flickering, which exhibited synchronization. When the double chamber system was equipped with a coincident device, it became feasible to measure the photonic properties emanating from the samples. However, upon closing the shutter, the bioluminescence flickering ceased to synchronize. This observation can be interpreted as follows: when the two samples are visually interconnected, the coherence of the emitted light gives rise to destructive interference. This interference triggers a simultaneous response from both samples, ultimately leading to an increase in photon emission.<sup>234</sup>

To explore the potential of biophotons for intercellular communication, an experiment with the ciliate *Paramecium caudatum* was designed to test for non-molecule-based triggering of two fundamental cell functions of cell division and energy uptake. Mutual exposure of the cell populations occurred under conditions of darkness and separation with cuvettes (vials), allowing photon but not molecule transfer. The cell populations were separated either with glass enabling photon transmission from 340 nm to longer waves, or quartz being transmittable from 150 nm of UV-light to longer waves. As there were significant differences when separating the populations with glass or quartz, it is suggested that the cell populations use two (or more) frequencies of the light waves for cellular information transfer, which then influences energy uptake and cell division. The experiment strongly supports a cellular communication system that is different from a molecule-receptor-based system.<sup>103</sup>

There is also evidence to show that biophoton may play a regulatory role in neuronal communication and information processing. Application of glutamate to coronal brain slices produced a gradual and significant increase of biophoton activities, with a maximal effect appeared at approximately 90 min and lasted for over 200 min. The glutamate-induced biophoton activities reflect biophoton transmission along the axons and in neural circuits, suggesting a potential novel mechanism for the processing of neural information,<sup>235,236</sup> which may be analogous to a "holographic computer".<sup>237</sup>

Mitochondria, a powerful generator of biophotons, possess the capability to absorb and direct biophoton-triggered excitation across distances via resonance energy transfer.<sup>238</sup> Situated within dynamic and interconnected networks, mitochondria have been hypothesized to function as potential "optical waveguides" that facilitate communication over long distances between mitochondria located afar.<sup>239,240</sup> Consequently, microtubule or mitochondrial networks could operate as "organic fiber optic networks" to enable effective communication throughout the cells.<sup>241</sup> Similar to the proposed quantum model of photosynthesis,<sup>242</sup> the mitochondria-mediated biophoton relay appears to be a highly probable, rapid, and resilient intracellular communication

mechanism crucial for maintaining cellular homeostasis.

#### 4. Radiation-induced bystander effects mediated by biophoton signaling

##### 4.1. Biophoton signaling for RIBE

The phenomenon known as RIBE was initially documented in 1992 in a study to irradiate Chinese hamster ovary (CHO) cells with 0.31 mGy  $\alpha$ -particles. Although less than 1 % of the nuclei were traversed by  $\alpha$ -particles, approximately 30 % of the cells showed an increased frequency of sister chromatid exchange, whereas, under normal circumstances, a radiation dose of approximately 2.0 Gy would be required to achieve a comparable radiobiological effect.<sup>243</sup> Soon after, an unequivocal study using a charged particle microbeam provided clear evidence that irradiated cells could induce a bystander mutagenic response in neighboring cells not directly traversed by  $\alpha$ -particles and that cell-cell communication process played a critical role in mediating the bystander phenomenon. Subsequent investigations further corroborated this effect across a range of biological endpoints, including chromosomal aberration, cell lethality, DNA mutation, and oncogenic transformation.<sup>244-247</sup>

In the field of RIBE research, two primary forms of bystander experiments are predominantly applied within the radiation biology community. The first form of the bystander effect is evident through medium transfer experiments in which cells are irradiated and the medium containing their secreted factors is subsequently removed and introduced (or "transferred") to a distinct population of non-irradiated reporter cells. Despite these reporter cells not being directly exposed to irradiation, notable changes are observed within their cell lines. The second experimental form of the bystander effect involves the utilization of microbeams to irradiate specific cells on a plate, while studying the effects on nearby non-irradiated cells. Although both sets of experiments are categorized as "bystander" experiments, they differ significantly in terms of their characteristics and experimental designs.<sup>248-250</sup>

The investigation into the correlation between the dosage employed for cell irradiation and the resulting bystander effects has revealed an appealing "all or none" switching mechanism.<sup>251,252</sup> Upon activated, this mechanism remains unaffected by the irradiation dose and elicits a consistent response effect. This effect is not only long-lasting but also transmissible to subsequent generations of cells as they reproduce.<sup>253,254</sup>

RIBE is once regarded as a negative reaction of non-irradiated cells, which accept molecules from irradiated cell-conditioned media (ICCM) or from molecular signatures that are released by irradiated cells via gap junctional intercellular communication (GJIC).<sup>255</sup> Several biological endpoints of RIBE have been reported, including genetic mutations,<sup>256</sup> micronuclei formation,<sup>257</sup> chromosomal aberrations,<sup>258</sup> DNA damage,<sup>259</sup> inflammation,<sup>260</sup> apoptosis<sup>261</sup> and cellular necrosis,<sup>262</sup> all of which are damaging to cell survival. Soluble signaling factors also play crucial roles in RIBE. To date, established and representative soluble signaling factors include ROS and NO, as well as secondary messengers such as calcium fluxes and cytokines,<sup>263,264</sup> which are important mediators for RIBE.

Apart from exploring the bystander effects at the cellular level, there is comparable research on animal models as well. For instance, apparent decreases in leukocyte count were noticed in non-irradiated rats and mice cohabiting in the same cage as in irradiated animals.<sup>265</sup> The effect of immunosuppression was displayed in the non-irradiated cagemates of the irradiated mice.<sup>266</sup> By using a fish model, physical separation of two fish by a partition still resulted in the increased calcium flux in the non-irradiated bystander fish.<sup>267</sup> Given that the animals did not engage in physical contact with each other, it was hypothesized that these observed effects might have been due to the exchange of volatile molecules through an airborne route among the cagemates.<sup>268</sup>

The suspicion of the existence of a physical signal implicated in RIBE arose when the altered bystander response was discovered as a result of the introduction of melanin, a compound known to absorb specific

frequencies of light, in both direct exposure and medium transfer experiments designed to investigate RIBE.<sup>269</sup> The subsequent studies conducted by two separate groups further supported this idea, in which cells were exposed to either direct or scattered irradiation emitted by radiotherapy units (<sup>60</sup>Co and LINAC). Notably, equally distinguishable bystander responses were observed in both scenarios, providing additional evidence for the potential role of a physical signal in RIBE.<sup>270–272</sup>

It has been demonstrated that UV photons induced by irradiation can function as bystander signals, triggering radiation-like responses in non-targeted cells.<sup>273</sup> The experiments that led to the discovery involved arranging a layer of tritium-incubated cells beneath another layer of untreated cells, separated by a barrier. This setup ensured that the upper cells were solely exposed to the radiation-induced UV photons from the layer below, rather than the initial  $\beta$ -radiation emitted by the tritium. Subsequently, a bystander effect was observed in the upper layer of cells that were not directly exposed to  $\beta$ -radiation, indicating the occurrence of UV-induced cell communication. However, when a UV filter was inserted between the two layers, the bystander effect, specifically the induced intercellular communication, was absent.<sup>48,274,275</sup>

As another example, cells exposed to  $\beta$ -radiation from two distinct sources, tritium and yttrium-90, were observed to emit a potent ultraviolet A (UVA) biophoton, which was designated as radiation-induced secondary biophoton. As a result, the increasing quantities of UVA biophoton emission triggered by  $\beta$ -radiation were found to be directly correlated with the escalating mortality rates in neighboring cells, thus suggesting their function as physical signals that contribute to RIBE.<sup>70,276</sup>

There is also evidence to show that exposure of cells to  $\alpha$ - and  $\gamma$ -radiation can result in the emission of biophotons from biological cells.<sup>68,277</sup> In an experiment conducted with cesium-137 (<sup>137</sup>Cs) serving as the external  $\gamma$ -radiation source, a consistently elevated number of biophotons were observed to emit from the human colorectal carcinoma cell line HCT116 p53+/+ following  $\gamma$ -radiation exposure.<sup>68,278</sup> In addition, charged particles like microbeams are capable of producing UV photons induced by  $\alpha$ -radiation through interaction with cells, thus activating various molecular pathways that ultimately lead to bystander effects.<sup>228</sup>

The transmission of bystander signals between irradiated and non-irradiated cells occurs through diverse mechanisms. These include facilitating molecular exchange via gap junctions between adjacent cells,<sup>47,279,280</sup> communicating between distant cells through the transfer of soluble factors,<sup>249</sup> interchanging volatile components across physically separated cell populations,<sup>281</sup> and transmitting electromagnetic signals from irradiated cells to remote recipient cells.<sup>78,276</sup> In the study of bystander effects by signaling through the exchange of soluble factors, various biochemical molecules have been implicated, such as reactive oxygen species,<sup>263</sup> siRNA hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ),<sup>282</sup> cytokines and exosomes,<sup>264,283</sup> in generating bystander responses. The propagation of these bystander signals necessitates either direct contact of cells with the exchange of biological fluids like blood serum or cell culture media between irradiated and non-irradiated cells, or an open system that promotes the exchange of volatile components between two separate organisms or cell populations. Alternatively, the role of electromagnetic radiation in the ultraviolet wavelength range has been recognized.<sup>78</sup> This novel bystander mechanism, known as the UV-mediated bystander effect, allows for signal communication via light fields without the need for direct contact between irradiated and bystander cells.<sup>276</sup>

The dependence of the p53 mediated bystander effects has been associated to signal generation and bystander response to irradiation.<sup>262,284</sup> In a study to investigate the potential effects of different p53 status on the response of bystander cells to biophoton signal triggered by  $\beta$ -radiation, five cell lines of various p53 status with wild type or knockout TP53 were used for the experiment and irradiated with  $\beta$ -particles from tritium.<sup>285</sup> The results indicated that the UV-mediated bystander response is affected by the p53 status of the cell line. Wild-type p53 cells demonstrated significant responses to UV signals

whereas the p53-null cell line lacked any response. The reduced response (cell death) exhibited by p53-mutated cells compared to p53 wild-type cells suggests a possible role of p53 mutations in radiation-induced and UV-mediated bystander effect.<sup>286</sup>

In recent years, a novel model of biological quantum entanglement has been put forward to interpret the RIBE phenomenon. Quantum effects, well established in modern physics, are increasingly explored in biological sciences to expedite processes such as photosynthesis, respiration, neurobiology, and biological signaling. Their relevance is particularly profound in mechanisms involving excitation, energy transduction, and decay of the excited state, similar to those observed in bystander-based communication.<sup>287,288</sup>

To visualize a quantum-based bystander mechanism operating at the organismal level, an experiment was conducted where fish of rainbow trout from two geographically distinct locations were allowed to interact for a duration of 2 h. Subsequently, fish from one of the locations (designated as group A) were irradiated, either before or after their encounters. The findings unequivocally confirmed the production of RIBE signals in both the skin and gills of the fish, regardless of whether they met before or after the irradiation of group A. Proteomic analysis further revealed that direct irradiation triggered tumorigenic proteomic responses in the rainbow trout. However, interestingly, the communication from these irradiated fish, both prior to and following their exposure to a 0.5 Gy X-radiation, elicited predominantly beneficial proteomic responses in completely unirradiated trout. These results suggest the existence of a form of anticipatory response to a potential stressor, leading to a preconditioning effect or a temporally displaced awareness in the fish once they become entangled in this quantum phenomenon.<sup>289</sup>

RIBE is not always regarded as a negative reaction of cells. Although there is a close association between low-dose radiation and a relatively higher incidence of cancer, as well as the occurrence of "secondary" cancers in unirradiated tissues among radiation therapy survivors, RIBE is not entirely a negative phenomenon. As a protective biological effect, RIBE may serve to eliminate mutated and aberrantly functioning cells from the population.<sup>290</sup> This perspective concurs with the redundancy expressed in RIBE signaling, indicating that bystander effects can be actually beneficial to the overall cell population, tissue, or organism. Furthermore, the importance of intercellular communication mediated by biophoton signaling appears to function as a biological redundancy, ensuring that bystander effects are effectively communicated, even in instances where the exchange of biological fluids or direct cell-to-cell communication is not feasible.

#### 4.2. Role of mitochondria in biophoton signaling for RIBE

Non-targeted effects such as RIBE are typically considered as consequences of ionizing radiation exposure at low doses and low dose rates.<sup>14,243,291–294</sup> It seems evident that RIBE involve multiple cellular signaling mechanisms, particularly those mediated by mitochondria,<sup>295–297</sup> which are at the origin of innate and adaptive immune defenses,<sup>298,299</sup> and are closely related to IR-induced immune responses.<sup>300</sup>

Mitochondria, the unique organelles once regarded solely as the energy source of the cell, are now recognized to perform multiple essential functions as an integration of three independent roles: as ATP creators (power houses), as ROS producers (causing damage), and as sources of biophoton emission (signal transmitters).<sup>301</sup> Recent evidence has suggested that mitochondria, beyond their canonical roles in bioenergetics and biosynthesis, can act as signaling organelles<sup>302</sup> and as "cellular stress sensors" in various biological functions under physiological and stress conditions.<sup>303,304</sup> The role of mitochondrial reactions in metabolic regulation, intercellular communication, and RIBE following IR has been thoroughly examined, as it holds importance in assessing radiation risks to human health. Mitochondria perform as a signaling platform by releasing mitochondrial components into the cytoplasm, thereby modulating cellular communication as well as RIBE.<sup>305,306</sup> In contrast, cells

without functional mitochondrial (rho zero) and are deficient in oxidative metabolism fail to yield a bystander response.<sup>323</sup>

As one of the major biological sources of radiation-induced radical species,<sup>307,308</sup> mitochondria functions in mediation of bystander signals by regulating redox reactions which are essential for cellular metabolism. The mitochondrial ROS produced in response to IR can affect metabolic enzymes and molecules within the directly-irradiated cell itself, and has also proved to be an effective mediator of biological changes in bystander cells.<sup>309</sup>

A variety of fascinating mechanisms may underlie bystander effects observed in cells and tissues following IR, particularly those involving mitochondria. Bystander signaling occurs between irradiated and unirradiated cells facilitated by the release of soluble molecules, extracellular vesicles (EVs), or exosomes containing mitochondrial DNA (mtDNA), nuclear DNA (nDNA), microRNAs (miRNAs), specific proteins, and other biological molecules. Recently, research has highlighted the role of IR-induced UVA biophoton emission in modulating mitochondrial oxidative phosphorylation (OXPHOS),<sup>310</sup> further enriching our understanding of these complex biological responses.

Mitochondria have been identified as an integral participant in RIBE, either as an extra-nuclear target of direct irradiation<sup>308</sup> or as a recipient of bystander signals.<sup>311,312</sup> It was hypothesized that the energy influx transmitted by biophotons into the mitochondrial electron transport chain (ETC) could either activate or inhibit the redox reactions involved in electron shuttling. Both the enhancement and suppression of electron transport chain activities could exert profound impacts on cellular responses including RIBE.

Disturbances in oxidative energy metabolism and redox biochemistry trigger apoptotic cascades in mitochondria of non-irradiated neighboring cells.<sup>313,314</sup> During this process, the emission of biophotons acts as a bystander signal mediating a reduction in the activity of Complex I (NADH dehydrogenase), the key complex responsible for proton pumping. In a study with the human epithelial line (HCT116 p53 +/-) developed from a colorectal tumor, the biophotons emitted as a result of  $\beta$ -radiation were shown effective in reducing the activity of Complex I, which consequently affected the activity of ATP synthase and impaired the production of ATP.<sup>315</sup>

On the other hand, mitochondrion has been considered as a key or significant contributor to biophoton emission. The intensity of biophoton emission from mitochondria is reported to be extraordinarily low, falls within the range of 1–1000 photons  $\text{cm}^{-2}\text{s}^{-1}$  and spans wavelengths approximately from 200 to 800 nm.<sup>301</sup> Within a cell, biophoton emission may facilitate energy transfer from the site of origin to adjacent aromatic structures such as microtubules, which then propagate signals all over the entire cells.<sup>316</sup>

Like nuclei, mitochondria contain their own genetic material which are regarded as targets of IR.<sup>317–319</sup> It is widely accepted that IR induces bystander effects in cells that are indirectly exposed to a irradiation track, and mitochondrial-derived ROS, such as hydroxyl radicals ( $\text{OH}^\cdot$ ) and  $\text{O}_2^\cdot$ , function as bystander signals in RIBE.<sup>309,320,321</sup> In the process of RIBE, irradiated cells' mtDNA migrates to non-irradiated cells, effectively "disseminating" the oxidative stress signal throughout a cell population.<sup>322</sup>

Mitochondrial DNA is also crucial for cells to produce bystander signals as demonstrated by an early observation. Fibroblast cells depleted of mitochondrial DNA were unable to produce these signals, whereas fibroblasts with fully functional mitochondria exhibited notable signal production.<sup>323</sup> In recent years, it has become increasingly apparent that mitochondria occupy a critical position in intra- and intercellular communication, particularly in the context of non-targeted effects and bystander responses. The experiments performed by different research groups strongly suggest that mitochondria are indispensable in transduction of the ionizing radiation energy to induce bystander effects.<sup>311,312,324–327</sup> There are many other factors that may influence RIBE, and the engagement of mitochondria in bystander response is striking.<sup>328</sup>

In the effort to identify the role of mitochondrial function in bystander effects, mitochondrial membrane potential is commonly used as an endpoint. Mitochondrial membrane depolarization has been found to be induced in bystander cells by medium transferred from  $\gamma$ -radiated human keratinocyte cells,<sup>52,312</sup> UVA-radiated melanoma cells,<sup>275</sup> and  $\gamma$ -radiated colorectal tissue explants.<sup>329</sup> In this context, Intercellular biophoton signaling has a profound impact on mitochondria, as evidenced by its effectiveness in inducing mitochondrial membrane depolarization.<sup>278</sup> This effect suggests that the mechanism behind biophoton signals driving bystander responses is closely interlinked to mitochondrial function.

In addition, there is evidence showing that, even after exposure to a low dose (22 mGy) of  $\gamma$ -radiation, biophoton emission was still detectable in HCT116 p53 wt cells that were irradiated.<sup>68</sup> In this scenario, it is believed that the deposition of energy by IR within cells triggers excitation decay processes, resulting in the emission of biophotons. These biophotons are capable of altering mitochondrial functions such as energy production. Consequently, this biophoton emission may initiate bystander responses in neighboring cells, including adaptive responses, genomic instability, and even cell death.<sup>330</sup>

Hence, it is manifestly apparent that mitochondrion-engaged biophoton signaling plays a significant role in a wide range of biological responses, such as energy metabolism, oxidative stress and bystander response, which has verified the importance of mitochondria in biophoton mediated RIBE.

#### 4.3. Role of exosomes in biophoton signaling for RIBE

Exosomes are extracellular vesicles, originating from the pinched-off sections of the endosomal membrane. These membrane-bound vesicles, ranging from 50 to 150 nm in size, encapsulate cytoplasmic contents such as RNAs and proteins during their formation.<sup>331</sup> Subsequently, they are released into the extracellular space, ready to interact with their surrounding molecules. The contents of these exosomes exert important effects on neighboring cells. As they migrate through the extracellular space towards distant cells, they are internalized through endocytosis, allowing their cargo to be delivered into the recipient cells. This efficient transportation of essential biological molecules from one cell to another underscores the vital roles that exosomes play in soluble-factor-mediated intercellular signaling.<sup>332,333</sup>

Extensive research has demonstrated the distinctive ability of exosomes as a signaling agent. They have been shown to induce carcinogenic behavior and promote tumor cell growth and migration in cells that receive exosomes derived from gastric tumor cells.<sup>334</sup> Furthermore, exosomes have been implicated in causing DNA damage in bystander cells, particularly when these cells receive exosome-encapsulated RNA from X-radiated breast cancer cells.<sup>283</sup>

Up-to-date study has highlighted the crucial role of exosomal RNAs in RIBE following irradiation.<sup>335</sup> miRNAs, discovered within exosomes, act as cellular communication signals,<sup>336</sup> implying their potential as mediators of bystander effects.<sup>337</sup> Among multiple recent reports, an in vivo investigation revealed that post-radiation exposure, the levels of miR-33, miR-152, miR-199a, and miR-744 in serum were upregulated.<sup>338</sup> Utilizing the EpiAirway model, another study demonstrated deregulated expression of specific miRNAs in three-dimensional bystander tissues.<sup>339</sup> Notably, the miRNA expression profiles in these tissues differed significantly from those of cells or tissues that had been directly irradiated.<sup>340,341</sup> As an example, miR-21 has been implicated in RIBE, exhibiting upregulation in both directly irradiated cells and bystander cells. consequently, bystander-like effects can be elicited by introducing miR-21 mimetic into non-irradiated human fetal lung MRC-5 fibroblasts.<sup>342,343</sup> Furthermore, upregulation of miR-769-5p has been shown to induce bystander effect, while its downregulation suppresses the effect, suggesting that exosome-mediated miRNAs transfer may serve as an intercellular messengers<sup>344</sup> and putative transmitters of RIBE.<sup>345–347</sup>

Earlier exosome investigations revealed elevated levels of Fas ligand,



also known as the 'death ligand', on extracellular vesicles in response to IR.<sup>348</sup> Since then, a variety of exosome cargo, including mitochondrial DNA, non-coding RNAs, immune modulators, lipids, and protein mediators, have been implicated in RIBE.<sup>34</sup> The basic nature of exosome-mediated RIBE was convincingly demonstrated in experiments where non-irradiated cells treated with exosomes derived from progeny of bystander cells exhibited RIBE as well.<sup>332</sup>

Although the participation of exosomes in the RIBE has been documented in early studies,<sup>283,332,349-351</sup> the exploration of exosomes in the context of secondary UV biophotons remains to be a challenging area in RIBE research. There is persuasive evidence indicating that ultraviolet radiation has the capacity to regulate the functions of exosomes released by human keratinocyte cells. Exosomes extracted from keratinocytes exposed to UVB radiation were capable of stimulating a higher production of melanin in melanocyte cells.<sup>352</sup> The comprehension of regulatory impact by UV on exosome function holds significant promise, as it has the potential to establish a connection between the UV-induced bystander effect and the previously documented soluble factor-mediated bystander effect, thus bridging the two superficially unrelated mechanisms.

The rationale for exploring the relation between biophoton and exosome stems from the hypothesis that UV biophoton may trigger the release of a diverse array of soluble factors that are typically implicated in RIBE. Among the numerous soluble factor candidates suitable for investigation, exosome was chosen as the primary focus due to the well-established protocols for its clean isolation from cell cultures. Additionally, the vesicular nature of exosome offers ample opportunities for comprehensive researches, making it an ideal candidate for studying the complicated interactions between UV biophoton and RIBE.<sup>353</sup>

As mentioned before, UV photons have been shown to trigger responses in bystander cells.<sup>354</sup> UV biophoton emission of 340 nm and 610 nm wavelengths by  $\gamma$ -radiation was identified to elicit a bystander response to irradiation with  $\beta$ -particles.<sup>70,276</sup> The wavelength of 340 nm makes up the predominant energy of UV spectrum, while the secondary photons emitted at visible spectrum of 610 nm have the potential to induce direct or indirect effect through the release of exosomes from bystander cells, which in turn stimulate responses in neighboring bystander cells.<sup>278</sup>

The probe into the connection between cellular exposure to UV biophoton and the subsequent release of exosome as a response to such exposure offers a fascinating perspective. It suggests that soluble factors, including exosome, can serve as the signals emanating from directly irradiated cells which prompt the bystander effect. Alternatively, two plausible explanations emerge to clarify these effects. Firstly, there might be two mutually exclusive mechanisms that can independently induce the bystander effect. Secondly, the UV signal might have the capacity to promote the release of soluble factors from non-irradiated bystander cells. To unravel the apparent paradox posed by these seemingly incompatible mechanisms, i.e., a physical UV signal versus a soluble factor-mediated bystander signal, experiments have been attentively conducted. These experiments are based on the hypothesis that exposure of cells to UV biophotons prompts the release of soluble factors, which in turn have the ability to elicit bystander responses.<sup>278</sup>

To validate the hypothesis, a tried-and-tested experimental system<sup>276</sup> was employed, utilizing the HCT116 p53 +/+ cell line for in vitro study. The cells were directly exposed to 0.5 Gy of tritium  $\beta$ -particles, triggering the emission of ultraviolet biophotons. While bystander cells were spared direct irradiation, they were exposed to the emitted UV biophotons. Subsequently, the medium from the UV-exposed bystander cells was collected, and the exosomes extracted from it were incubated with reporter cell populations. These reporter cells were then assayed for clonogenic survival and mitochondrial membrane potential, both with and without prior treatment of the exosomes with RNase.

The results revealed a marked decrease in clonogenic cell survival among reporter cells incubated with exosomes derived from cells exposed to secondarily-emitted UV. These exosomes also significantly induced mitochondrial membrane depolarization in the reporter cells.

On the other hand, exosomes extracted from non-UV-exposed cells did not exhibit any bystander effects in the reporter cells. Notably, treating the exosomes with RNase before incubating them with the reporter cells effectively abolished the bystander effects, suggesting a crucial role for exosome-contained RNA in mediating the bystander response triggered by UV biophotons and their resulting exosomes.<sup>278</sup>

In an attentive investigation exploring the role of exosomes released by normal human keratinocytes (NHK) following UVB treatment in pigmentation regulation, it was discovered that the melanocytes incubated in an exosome-depleted medium derived from UVB-exposed NHK showed a marked increase in the content of melanin, a known antioxidant and radioprotector. This increase was significantly higher than that observed in the melanocytes incubated with exosomes isolated from non-UVB-treated cells, amounting to a difference of  $(43 \pm 22)\%$  and  $(2 \pm 11)\%$ , respectively.<sup>352</sup> Similar to the effects observed with UVB-stimulated exosomes, the incubation of exosomes released from high-phototype NHK led to an enhancement in the melanin content of low-phototype melanocytes.<sup>355</sup>

Collectively, these experimental data strongly support the existence of a bystander mechanism whereby the UV biophotons generated by directly-irradiated cells as an intermediate signal, interact with bystander cells to stimulate the release of response-eliciting exosomes. These exosomes capable of inducing bystander effects are released from cells in response to exposure to UV signals emitted from directly-irradiated cells rather than being released as a direct result of the primary  $\beta$ -radiation itself. This insight offers a novel perspective in understanding the intricate interplay between ultraviolet radiation and cellular communication. The complexity and significance of exosome in RIBE and disease progression will possibly continue to captivate researchers, transforming it into a promising domain of study in radiobiology.

## 5. Perspectives

Radiation protection is not only focused on understanding and mitigating the adverse effects of IR; it also acknowledges the potential beneficial effects such as adaptive responses and immune stimulation that may arise from low-dose radiation exposure. Given the significant role and complicated nature of the biological and health effects induced by LDIR, it is necessary for us to adopt a more comprehensive perspective in RIBE research.<sup>356</sup>

Among the recently uncovered mechanisms underlying the molecular and biological networks involved in RIBE, biophotons have emerged as promising intercellular messengers of radiation-induced stress. They have been demonstrated to prompt bystander cells to release exosomes and modulate mitochondrial oxidative phosphorylation, thereby facilitating signal communication between irradiated and bystander cells. This elaborate interplay emphasizes the need for broadened approaches in radiation biology, such as systems biology and artificial intelligence, to fully comprehend and harness the potential benefits and risks associated with low-dose radiation exposure.

Despite the indisputable confirmation of the pivotal role of biophotons in mediating cell-to-cell communication and RIBE, there remain some inquiries that necessitate future mechanistic investigation. For instance, further identification on the spectral profiles of biophoton emission across diverse functional scenarios stays a pending task. Furthermore, a detailed elucidation of the precise physical and biological processes in which bystander cells absorb and transmit biophoton signals is imperative. These forthcoming endeavors will substantially enhance our understanding of intercellular communication under homeostatic and stress conditions.

While the mechanisms involved in the generation and signal transduction of biophotons induced by IR are fascinating, they may have major relevance in a practical sense for precision medicine.<sup>357</sup> For example, RIBE as an important aspect of radiobiology may contribute to reduce health risks in radiotherapy. During intensity-modulated radiation therapy (IMRT), regions next to high-dose targeted areas may be

exposed to low doses. This increases the development of bystander effects because RIBE is manifested typically at low doses. Radiation-dependent cancer therapies can exploit the properties of the different regulators to increase therapeutic efficacy, which is modulated differentially between radiation-induced cancerous and normal bystander cells.<sup>358,359</sup> Such an ideal modulator should have distinctive actions both to sensitize the tumor bystander cells and to confer protection to the healthy bystander cells.

In contrast to the direct effects of radiation, RIBE exhibits a non-linear dose-response with effects observed at very low doses and may be linked to secondary cancers in patients who have undergone radiation treatment. These systemic long-term effects of irradiation, occurring at sites distant from the irradiated volume within the same organism, are referred to as abscopal effects,<sup>360–362</sup> and have led to the identification of inhibitors of RIBE to minimize radiation risks for cancer patients.<sup>363,364</sup> Given the role of biophotons involved in RIBE as effective intercellular messengers, there could be potential implications for biophotons in the practice of radiation medicine and protection.

Over the past century, noteworthy advancements have been achieved in biophoton research, offering new thorough insights into previously obscured cellular networks that underlie the extraordinary finesse of biological systems.<sup>226</sup> With these revelations, we hold the promise that this research avenue will enable us to more rationally and precisely elucidate the beneficial and adverse effects of ionizing radiation on both humanity and the environment.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jian Tong reports was provided by Soochow University. Jian Tong reports a relationship with Soochow University that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

The author is profoundly grateful to Professor Tom K. Hei of the Center for Radiological Research at Columbia University, USA, for his critical review and constructive advice for this article.

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