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NON-LINEAR ADAPTIVE PHENOMENA WHICH DECREASE THE RISK OF INFECTION AFTER PRE-EXPOSURE TO RADIOFREQUENCY RADIATION

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□ Substantial evidence indicates that adaptive response induced by low doses of ionizing radiation can result in resistance to the damage caused by a subsequently high-dose radiation or cause cross-resistance to other non-radiation stressors. Adaptive response contradicts the linear-non-threshold (LNT) dose-response model for ionizing radiation. We have previously reported that exposure of laboratory animals to radiofrequency radiation can induce a survival adaptive response. Furthermore, we have indicated that pre-exposure of mice to radiofrequency radiation emitted by a GSM mobile phone increased their resistance to a subsequent Escherichia coli infection. In this study, the survival rates in animals receiving both adapting (radiofrequency) and challenge dose (bacteria) and the animals receiving only the challenge dose (bacteria) were 56% and 20%, respectively. In this light, our findings contribute to the assumption that radiofrequency-induced adaptive response can be used as an efficient method for decreasing the risk of infection in immunosuppressed irradiated individuals. The implication of this phenomenon in human's long term stay in the space is also discussed.

Keywords: Non-linearity, Adaptive Response, Radiofrequency (RF), Infection, Escherichia coli, Immune System, Space Research.

INTRODUCTION

Substantial evidence indicates that when cells are pre-irradiated with low doses of ionizing radiation and DNA damaging agents, such as ultraviolet (UV) radiation, alkylating agents, oxidants and heat, they become

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more resistant to high doses of those agents and in some cases to similar agents. This phenomenon is referred to as adaptive response. The discovery of adaptive response dates back to the early experiments of Samson and Cairns (1977) who found that the bacterium, Escherichia Coli (*E. coli*), was less susceptible to high doses of the same and similar agents when exposed to low doses of alkylating agents. Following this challenging finding, it was argued whether ionizing radiation can also induce the same effects. Olivieri *et al.* (1984) first reported that human lymphocytes exposed to tritium-labeled thymidine became resistant to cytogenetic damages caused by high doses of x-rays. Ten years later, United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), in its 1994 report to the United Nations (UN) General Assembly, officially introduced the adaptive response phenomenon induced by low-dose radiation for the first time (UNSCEAR 1994). In this document, stimulation of the immune system by low-dose radiation was reported. It has been widely reported that adaptive response induced by low-dose radiation can induce resistance to the damage caused not only by a subsequently high-dose radiation but also by other non-radiation stressors such as chemical agents. The linear non-threshold (LNT) model, which is widely used by regulatory agencies and in radiation protection, plays an important role in the risk assessment of low-dose radiation (Scott *et al.* 2003). Adaptive response contradicts the LNT dose-response model for ionizing radiation (Day *et al.* 2007).

Although high doses of ionizing radiation are immunosuppressive, the stimulatory effect of low-dose radiation on the immune system has been widely documented (Hattori 1994, Liu *et al.* 1987, Liu *et al.* 2004, Makinodan and James 1990, Zdrojewicz and Strzelczyk 2006). Therefore, stimulation of the immune system may be a key mechanism for the induction of adaptive response. On the other hand, some recent studies showed that radiofrequency radiation causes oxidative injury in different tissues mediated by lipid peroxidation, increased level of nitric oxide (NO), and suppression of antioxidant defense mechanism (Esmekaya *et al.* 2011, Ozgur *et al.* 2010). Feinendegen *et al.* (1996, 1999), in their previous studies, proposed that adaptive response could be induced by reactive oxygen species (ROS). Increased levels of ROS or NO have been usually observed in adapted cells (Tapio and Jacob 2007). The ROS refers to a group of molecules including peroxides and free radicals which are derived from oxygen and are highly reactive toward biomolecules (Maynard *et al.* 2009). ROS reacts with critical biomolecules such as DNA and induces oxidative stress (imbalance of prooxidants versus antioxidants) and damage in these macromolecules, multiple localized lesions such as base damage, single strand breaks (SSBs) and double strand breaks (DSBs), DNA-DNA cross links and DNA-protein cross links (Cejas *et al.* 2004, Goldberg and Lehnert 2002, Marnett *et al.* 2003, Murray *et al.* 2005).

RADIOFREQUENCY-INDUCED ADAPTIVE RESPONSE

It was previously reported that cultured cells pre-exposed to radiofrequency radiation exhibit an adaptive response as increased resistance to mytomycin C (Sannino *et al.* 2009a). Mortazavi *et al.* (2011, 2013a, 2013b) also found that laboratory animals pre-exposed to radiofrequency radiation were more resistant to subsequent lethal effects of high doses of ionizing radiation or infections caused by life-threatening microorganisms. These findings were later confirmed by the limited published studies that investigated the induction of adaptive response after pre-treatment with microwave radiation (Cao *et al.* 2011, Jiang *et al.* 2012, Sannino *et al.* 2011, Zeni *et al.* 2012). Sannino *et al.* (2009) have previously reported that pre-exposure of the peripheral blood lymphocytes collected from human volunteers to non-ionizing RF radiation (900 MHz, at a peak specific absorption rate of 10 W/kg for 20 h) increases their resistance to a challenge dose of mitomycin C (100 ng/ml at 48 h). Later, they confirmed their previous results and showed that the timing of adapting dose exposure of radiofrequency plays an important role in the process of adaptive response induction (Sannino *et al.* 2011). On the other hand, Chinese researchers have recently shown that pre-exposure of mice to non-ionizing 900 MHz RF induced adaptive response, thus reducing the hematopoietic tissue damage from a subsequent challenge dose of ionizing radiation (Cao *et al.* 2011).

As pre-exposure of organisms as diverse as bacteria, animals and plants to heat or a variety of DNA damaging stresses such as UV, alkylating or oxidizing agents can induce adaptive responses which make them resistant to lethal and mutagenic impacts (Samson and Cairns 1977, Samson and Schwartz 1980), one may hypothesize that the heat from RF radiation, rather than the EMF, may be responsible for inducing the observed adaptive response. Therefore, in RF-induced adaptive response studies, the issue of temperature rise should be ruled out.

Our results are in line with those reported recently by Zeni *et al.* (2012), showing that when lymphocytes were pre-exposed to RF at 0.3W/kg SAR and then treated with mitomycin C, the cells showed a significant reduction in the frequency of micronuclei as compared with the cells treated with MMC alone. Recently, Jiang *et al.* (2012) also used a relatively similar method as we did previously (using the gamma radiation as the challenge dose) and indicated that mice pre-exposed to RF for 3, 5, 7 and 14 days showed progressively decreased damage and were significantly different from those exposed to gamma-radiation alone. It has also been reported that pre-exposure of human promyelocytic leukemia HL-60 cells to 900 MHz radiofrequency radiation for 1 hour/day for 3 days has a protective effect on hematopoietic tissue damage induced by doxorubicin, a chemotherapeutic drug (Jin *et al.* 2012). More recently, Jiang *et al.* used the micronuclei (MN) assay as the endpoint, showing

that exposure of mice to both adapting (900MHz RF radiation) and challenge (3Gy gamma-radiation) doses (AD+CD) resulted in a significant decrease in MN indices as compared to those exposed to CD alone (Jiang *et al.* 2013).

One of the limitations of our study and those conducted by many other researchers in this field was lack of data on the amount of RF radiation absorbed by the animals. However, it's worth mentioning that we had previously measured the temperature and found no significant rise. In this light, although none of the few papers published on RF-induced adaptive response so far has measured the amount of RF energy deposited in the body, an attempt should be made to perform these measurements in future experiments.

As mentioned above, Mortazavi *et al.* (2011, 2013b) have recently shown that radiofrequency radiation can induce adaptive response phenomenon. Mortazavi *et al.* (2012) have also recently shown that pre-exposure of BALB/c mice to radiofrequency radiation emitted from a GSM mobile phone increases their resistance to a subsequent bacterial infection. Although there is one report by Plews *et al.* (2010) that indicates the induction of adaptive response induced by pre-exposure to low-dose whole-body radiation treatments prolongs the survival of mice infected with prion by decreasing oxidative stress, to the best of our knowledge our study was the first survey which showed that BALB/c mice infected with *Escherichia coli* after pre-exposure to non-ionizing radiofrequency radiation, exhibit an adaptive response as prolonged survival. In this light, in spite of the basic differences between our study and the above-mentioned research, both confirm the potential of adapting doses of ionizing or non-ionizing radiation for induction of adaptive response as increased resistance to a subsequent infection. The most important difference between our study and that conducted by Plews *et al.* (2010) is the type of the adapting dose; i.e. radiofrequency as a non-ionizing radiation in our study versus gamma radiations emitted from a cobalt-60 source in Plews' (2010) study.

In our recent study, as shown in Table 1, groups of BALB/c mice (exposure groups) were exposed to radiofrequency radiations emitted from a GSM mobile phone for 2, 4, 8 or 12 hours a day for 3 days. Other groups (sham exposed groups) were treated as exposure groups but the mobile phone during the experiment was switched off. It should be noted that although there are universally famous high background radiation areas such as Ramsar in Iran, the background radiation level in our laboratory in Shiraz (the setting where the study performed in) was within the normal range (0.1 μSv/h). On the other hand, all laboratory animals used in this study were obtained from the animal house of Shiraz University of Medical Sciences. Furthermore, the background ionizing radiation level for sham-exposed and RF-exposed animals was the same.

TABLE 1. Grouping of the animals and interventions (adapting and challenge doses) in each group.

Groups	Number of Animals	Treatment	
		Adapting Dose (RF Exposure)	Challenge Dose (Exposure to Bacteria)
Group 1	10	RF 2h/day for 3 days	i.p. Injection of *E. coli*
Group 2	5	RF 2h/day for 3 days	No Bacteria (i.p. Injection of Normal Saline)
Group 3	5	Sham Exposure (No RF)	i.p. Injection of *E. coli*
Group 4	10	RF 4h/day for 3 days	i.p. Injection of *E. coli*
Group 5	5	RF 4h/day for 3 days	No Bacteria (i.p. Injection of Normal Saline)
Group 6	5	Sham Exposure (No RF)	i.p. Injection of *E. coli*
Group 7	10	RF 8h/day for 3 days	i.p. Injection of *E. coli*
Group 8	5	RF 8h/day for 3 days	No Bacteria (i.p. Injection of Normal Saline)
Group 9	5	Sham Exposure (No RF)	i.p. Injection of *E. coli*
Group 10	10	RF 12h/day for 3 days	i.p. Injection of *E. coli*
Group 11	5	RF 12h/day for 3 days	No Bacteria (i.p. Injection of Normal Saline)
Group 12	5	Sham Exposure (No RF)	i.p. Injection of *E. coli*
Group 13 (Repeating Group 10)*	15	RF 12h/day for 3 days	i.p. Injection of *E. coli*
Group 14 (Repeating Group 12)*	15	Sham Exposure (No RF)	i.p. Injection of *E. coli*
Total Number	110		

*As previous 12h/day irradiation protocols showed the highest magnitude of the survival adaptive response, these protocols were repeated to verify whether the results are reproducible.

Reproduced with permission from (Mortazavi et al. 2012).

TABLE 2. Survival rates in different groups of BALB/c mice 15 days after exposure to the *E. coli* bacteria.

	Survival Rate after 15 Days		
Intervention (Exposure to RF for 3 days)	RF → Bacteria	0 → Bacteria	P-Value Log Rank (Mantel-Cox)
2 h/day (20 animals)	20%	0%	0.186
4 h/day (20 animals)	10%	60%	0.046
8 h/day (20 animals)	20%	20%	1.000
12 h/day (20 animals)	50%	20%	0.280
Repeated 12 h/day (30 animals)	60%	20%	0.021
Pooled 12 h/day (45 animals)	56%	20%	0.018

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A Nokia E71 GSM cell phone with a SAR of 1.4 W/kg was used in talk mode as the source of microwave radiation. The mice were immobilized during the microwave exposure by placing their body through plastic restrainers. Restrainers were placed around the antenna in a circular position and the distance between the mobile phone antenna and animal's head was 5 cm. On day 4, the animals were exposed to *Escherichia coli* via an i.p. injection of the bacteria. Survival of the animals after injection was carefully monitored by an expert scientist. As indicated in Table 2, in the 1st phase of our study, 15 days after infecting the animals with E. coli, the survival rates in mice that received both adapting (2h/day RF) and challenge dose (bacteria) and the mice receiving only the challenge dose (bacteria) were 20% and 0%, respectively. For animals exposed 4h/day to RF radiation, the survival rates in the mice pre-exposed to the adapting dose (RF) before exposure to the challenge dose (bacteria) and those exposed only to the challenge dose (bacteria) were 10% and 60%, respectively. For animals exposed 8h/day to RF radiation, the survival rates in the mice pre-exposed to the adapting dose (RF) before exposure to the challenge dose (bacteria) and those exposed only to the challenge dose (bacteria) were 20% and 20%, respectively. All of the differences mentioned above were not statistically significant.

As some of the figures in Table 2 seem to be puzzling, it should be noted that the P-value of 0.046 that was ascribed to the 60% survival experienced by sham-exposed mice is a borderline p-value. In contrast with very small p-values which can be easily interpreted, borderline p-values are observed when the effect is not large and hence cannot be interpreted easily. On the other hand, the non-significant p-value of 0.280 for the 50% survival experienced by the12-hour RF pre-exposed mice can be due to the small sample size because both of the following experiments, i.e. repeated 12 h/day (30 animals) and pooled 12 h/day (45 animals), showed statistically significant differences.

For mice exposed 12h/day to RF radiation, the survival rates in animals pre-exposed to the adapting dose (RF) before receiving the challenge dose (bacteria) and those receiving only the challenge dose (bacteria) were 50% and 20%, respectively. As 12h/day exposure showed the maximum level of survival adaptive response, we repeated this experiment to ascertain whether our findings are reproducible. When this experiment was repeated, the survival rates in animals pre-exposed to the adapting dose (RF) before receiving the challenge dose (bacteria) and those receiving only the challenge dose (bacteria) were 60% and 20%, respectively (p=0.021). When we pooled the results of these two phases (12h/day exposures), the survival rates in the 25 mice that pre-exposed to RF before receiving the challenge dose (bacteria) and the 20 mice receiving only the challenge dose (bacteria) were 56% and 20%, respectively. Statistical analysis showed that the difference again was significant (p=0.018). Kaplan-Meier survival plots of the animals pre-exposed/sham-exposed to microwave, low dose rate gamma or both of these adapting doses before exposure to a lethal dose (LD) of gamma radiation are shown in Figure 1. In contrast with the innate immunity that is an antigen-nonspecific defense mechanism and starts immediately or within several hours after exposure to microbes, adaptive (acquired) immunity which refers to antigen-specific defense mechanisms usually takes several days to show complete protective effects. As shown in Figure 1, the maxi-

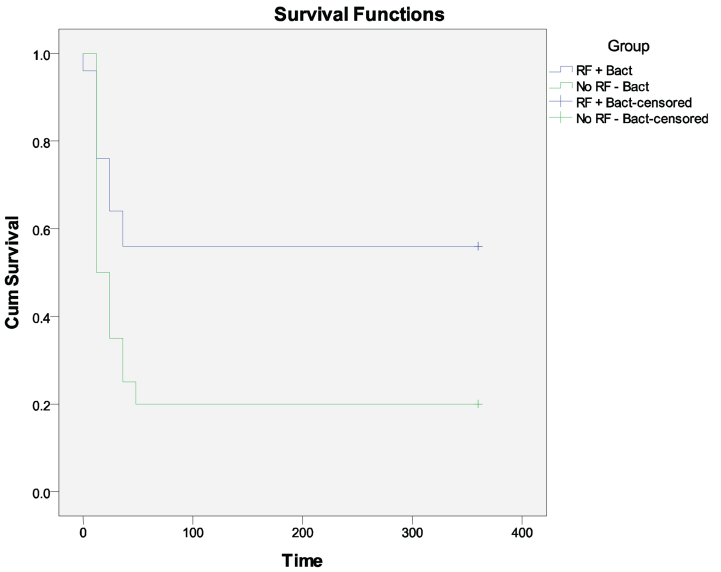

FIGURE 1. Kaplan-Meier survival curves of the BALB/c mice pre-exposed/sham-exposed to microwave (MW), before exposure to bacteria. The results of two repeated phases of 12h/day exposure are pooled. The survival rate in 25 animals that received both adapting (RF) and challenge dose (bacteria) was significantly higher than those of the 20 animals receiving only the challenge dose of bacteria (p=0.018). Horizontal axis shows time in hours. Reproduced with permission from Mortazavi et al. 2012.

mum difference in survival rates of the RF-exposed and sham-exposed groups can be seen several days after exposure to E. coli bacteria. In this light, it can be hypothesized that pre-exposure to RF radiation possibly stimulates the adaptive immune system.

Based on the four exposure scenarios used in our experiment, the 12-hour exposure condition was the most effective one. It is important to point out, however, that this effective exposure scenario most likely does not equate to the maximum or optimal exposure condition. So many other experiments involving dose rates, durations, frequencies, intervals and modes of exposures (radiation frequency, pulsed, continuous, etc) are required to find an optimized protocol for induction of adaptive response.

In spite of the above-mentioned limitation, it can be concluded that the survival rate in animals receiving both adapting (RF) and challenge dose (bacteria) was significantly higher than that of the animals receiving only the challenge dose. These findings are generally in line with the widely accepted concept indicating that an earlier exposure of the cells or tissues to an adapting dose can increase their resistance to toxicity caused by a challenge dose- a phenomenon that is usually called adaptive response.

As indicated by some researchers (Bose Girigoswami and Ghosh 2005, Dimova *et al.* 2008, Yan *et al.* 2006), we also believe that induction of adaptive response by pre-exposure to ionizing or non-ionizing radiation needs a minimum level of damage that triggers this phenomenon and increases the resistance of living organisms (in vivo) or cells (in vitro) to higher levels of the same or different sources of stress. In our experiments, only the animals exposed to mobile radiations for 12h/day showed a significantly higher survival compared to those only exposed to bacteria (no pre-exposure to radiofrequency radiation). In this regard, our findings are in line with the results of a recent study conducted by Jiang *et al.* (2012), indicating that the pre-exposure for more than 4 hours per day is necessary to induce the adaptive response. Altogether, these findings can be explained according to this fact that the lower dose threshold for adaptation depends on the presence of a minimum number of lesions per unit time. Mitchel (2010) has previously reported the existence of a certain window for adapting doses of ionizing radiation, "the adaptive response in mammalian cells and mammals operates within a certain window that can be defined by upper and lower dose thresholds, typically between about 1 and 100 mGy for a single low dose rate exposure". Mortazavi (2013a) has recently reported that there were similar patterns for induction of adaptive response by ionizing and non-ionizing radiation and confirmed the existence of such a window for adapting doses of non-ionizing radiation.

Another point worth considering is the time window for activation of the immune system. As it was fully discussed before, in our experiment the mice pre-exposed/sham-exposed to radiofrequency radiations emitted from a GSM mobile phone for 2, 4, 8 or 12 hours a day for 3 days were exposed to Escherichia coli via an i.p. injection of the bacteria on day 4. In contrast with the innate immunity that is an antigen-non-specific defense mechanism and starts immediately or within several hours after exposure to microbes, adaptive (acquired) immunity which refers to antigen-specific defense mechanisms usually takes several days to become fully protective. As shown in Figure 1, the maximum difference in survival rates of the RF-exposed and sham-exposed groups can be seen several days after exposure to E. coli bacteria. In this light, it can be hypothesized that pre-exposure to RF radiation possibly stimulates the adaptive immune system. However, the optimal adaptive response might not have been experienced in our study.

IMPLICATIONS OF RF-INDUCED ADAPTIVE RESPONSE IN SPACE RESEARCH

In a report entitled "Adaptive response studies may help choose astronauts for long-term space travel", which was published in "Advances in Space Research", Mortazavi *et al.* (2003) previously hypothesized that screening of the candidates of deep space missions by Ground-based *in vitro* adaptive response tests before any mission can be used to identify the individuals who respond well to low levels of ionizing radiation and reveal high magnitudes of radioadaptive response. They concluded that chronic exposure to high levels of space radiation during any long-term space mission in these individuals will increase their radiation resistance and protect them against any unpredictable exposure to high levels of radiation caused by possible solar activities (Mortazavi *et al.* 2003, Mortazavi *et al.* 2005). Different methods that can be used for reducing the risk of radiation during deep space missions are shown in Figure 2.

On the other hand, it has been shown that the immune system is highly susceptible to different stressors existing during space flight (Gridley *et al.* 2009). Numerous studies indicated dysregulation of the immune system during and immediately following space missions (Crucian *et al.* 2011, Crucian *et al.* 2008). Despite the well-known reversible immunological alterations in short-term spaceflights, the bioeffects of long-duration spaceflight on the neuro-immune responses have not been completely known so far (Stowe *et al.* 2011). Solar and galactic radiation are associated with increased risk of infection during long term stay of human outside the Earth's magnetic field (Zhou *et al.* 2012). Finally as discussed above in detail, we recently showed that pre-exposure of mice to radiofrequency radiation emitted by a GSM mobile phone increased their resistance to a subsequent Escherichia coli infection. Altogether, we can come

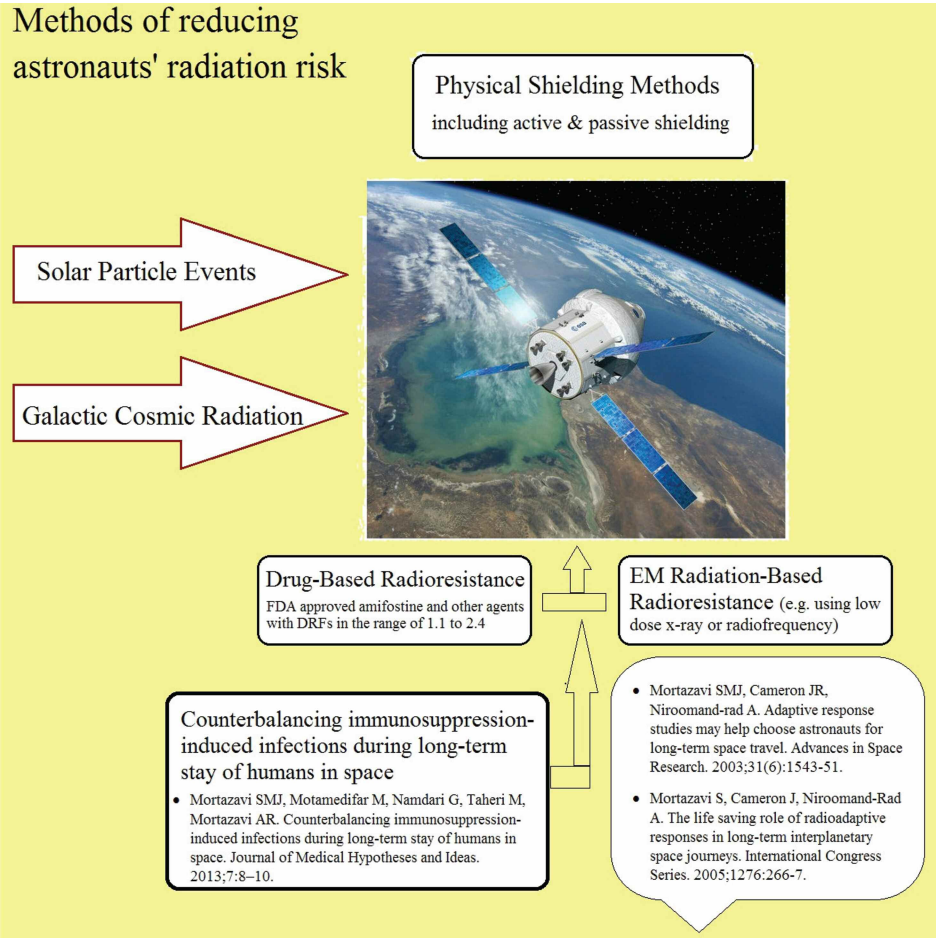

FIGURE 2. Different methods for reducing the risk of radiation during deep space missions.

to this conclusion that exposure of astronauts to low levels of radiofrequency radiations emitted by an appropriate source or chronic space radiation can increase their resistance against infections caused by life-threatening microorganisms (Mortazavi *et al.* 2012, Mortazavi 2013b, Mortazavi *et al.* 2013a).

CONCLUSION

The results obtained in our previous studies indicate that exposure of laboratory animals to radiofrequency (RF) radiation emitted by a common cell phone can increase the survival rate of these animals at a specific time after exposure to a pathogenic microorganism (inducing a survival adaptive response). These findings lead to the assumption that this phenomenon can be used as a method for decreasing the risk of infection

in immunosuppressed individuals. This phenomenon may also have implications in reducing the risk of infection during deep space missions.

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