Effects of Radiofrequency Exposure and Co-Exposure on Human Lymphocytes: The Influence of Signal Modulation and Bandwidth

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***Abstract*—The occurrence of modulation-specific effects after co-exposures to radio-frequency (RF) and other agents has been discussed in the literature. In this paper, the influence of modulation and bandwidth in eliciting the DNA damage of RF alone and in combination with mitomycin-C (MMC) is analyzed in human lymphocytes. Blood cultures from healthy donors were exposed to 1950 MHz, and continuous wave (CW), wideband direct-sequence code division multiple access (WCDMA, 4.5 MHz bandwidth), and additive white Gaussian noise (AWGN, 9 MHz bandwidth) signals were considered. For each signal, specific absorption rate (SAR) values of 0.15, 0.3, 0.6, 1.25 W/kg were tested. RF exposure alone never induced DNA damage in the micronucleus assay. When RF exposure was followed by MMC treatment, the effect depended on modulation and bandwidth. CW exposure never altered the MMC-induced DNA damage, while such damage was reduced when either signals WCDMA at 0.3 W/kg SAR or AWGN at 0.15 and 0.3 W/kg were applied. These results indicate the influence of modulation for the occurrence of the protective effect, with a relation between the bandwidth and the power absorbed by samples. If confirmed *in vivo*, clinical applications using modulated RF signals could be devised to protect cells from side effects of therapeutic treatments.**

***Index Terms*—Biological effects of radiation, biomedical applications of radiation, DNA, modulation, protection, radio-frequency (RF) signals.**

I. Introduction

A CONTRADICTION exists in peer-reviewed papers dealing with non-thermal biological effects and interaction mechanisms of radio-frequency (RF) electromagnetic fields with bio-systems. A number of papers points to absence of observable effects, while in other studies, certain biological modifications are reported [1], [2].

Results depend on a variety of factors, including 1) RF exposure conditions (frequency, continuous or pulsed wave, modulation pattern, exposure duration and schedule, specific absorption rate); 2) biological material (cell and animal model, physiological status of the exposed model system); and 3) sensitivity, reliability, timing of the biological assay.

Among the electromagnetic parameters, the influence of modulation pattern deserves particular attention. Review papers have indicated that experimental evidence for modulation-specific effects of RF is weak, and the sporadic positive findings have not been independently replicated [3]–[6]. However, it is of interest that many of such positive studies involved combined exposures to RF fields and other chemical or physical agents [3], [7]. In addition, there are examples in the literature where RF exposure has no effect by itself, but results in potentiating or reducing the effects of other agents (combined effects). Generally, the occurrence of combined effects is strictly related to the cell type and to the dose and time schedule of the chemical or physical treatment.

From an electromagnetic point of view, combined effects have been observed in specific 'windows': at one frequency but not at another, at one specific absorption rate (SAR) value but not at another, at one modulation pattern but not at another, at different exposure durations, and so forth [8], [9].

A particular case of combined effect, strictly dependent on electromagnetic conditions, has been observed, for the first time, by our research group in cell cultures, and then confirmed by other authors. RF pre-exposures protected mammalian cells from the damage elicited by chemical or physical treatments [10], as in the phenomenon of Adaptive Response (AR), well known in radio-biology [11].

In earlier experiments on human lymphocytes, 20 h pre-exposure to 900 MHz, 1.25 W/kg SAR, reduced the effect of mitomycin-C (MMC, a chemotherapeutic drug) when the Global System for Mobile Communication (GSM) signal was employed [12], and only in lymphocytes exposed during the S phase of the cell cycle [13]. When the 1950 MHz, Wideband Direct-Sequence Code Division Multiple Access (WCDMA) signal was applied, 0.3 W/kg SAR, but not 1.25 W/kg, was effective in inducing protection *vs.* MMC [14] and X-rays [15] treatments.

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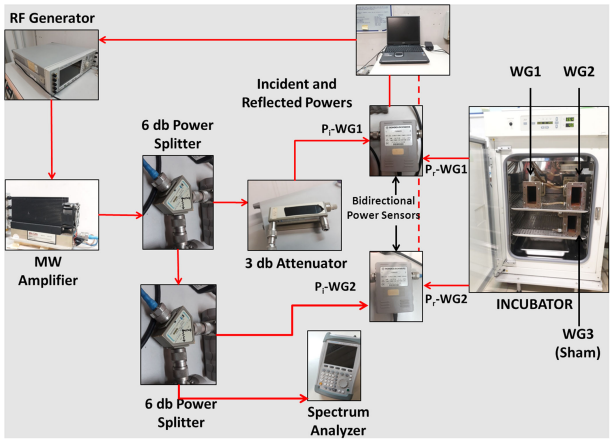


Fig. 1. Schematics of the exposure set-up.

In the same exposure conditions, the protective effect was induced also in Chinese Hamster lung fibroblast cell line (V79), but the effective SAR was 1.25 W/kg and not 0.3 W/kg, suggesting that the cell model might be a factor in eliciting the effect [16].

In this paper, we give insight into the influence of modulation and bandwidth of RF signal, in eliciting the biological response of human lymphocytes to RF *per se* or given in combination with MMC. Namely, three different signals at 1950 MHz were considered: 1) a Continuous Wave (CW) signal, which has an ideally zero bandwidth; 2) a WCDMA modulated signal with a 4.5 MHz bandwidth; 3) an Additive White Gaussian Noise (AWGN) modulated signal with a 9 MHz bandwidth. The role of power absorbed by the samples was also considered by testing, for each signal, four SAR values (0.15, 0.3, 0.6 and 1.25 W/kg). DNA damage was evaluated in terms of micronuclei (MN) formation.

II. Materials and Methods

A. Exposure System and Dosimetry

The experimental set-up for RF signal generation and conditioning, and for cell cultures exposure has been designed and developed by employing numerical and experimental electromagnetic dosimetry techniques, described in details in our previous papers [16], [17].

As shown in Fig. 1, the set-up is composed by a PC, a RF generator (Agilent, E4432B ESG-D series), providing the 1950 MHz signal (CW, WCDMA or AWGN), a microwave amplifier (MA-LTD, AM38A-0925-40-43), two, 6dB power splitters (HP, 11667A), a 3dB attenuator (HP, 8494 A), two bidirectional power sensors (Rohde & Schwarz, NRT-Z43), a spectrum analyzer (Rohde & Schwarz, FSH-3), and three RF applicators. The amplified signal is split (−6 dB) into two fractions: one of them is split (−6 dB) again, while the other is sent to the attenuator, obtaining a 1:2 power ratio between the former and the latter. The signal coming from the attenuator and one of the signals coming from the second splitter are conveyed to the power sensors, and thus to the RF applicators. The other signal coming from the second splitter is acquired by the spectrum analyzer to monitor the spectral power density. The RF applicators, two for exposures and one for sham-exposure (no RF transmission), consist of rectangular, short-circuited waveguides (WG, WR430, 350 mm long), with a coaxial adapter (Maury Microwave R213A2, VSWR: 1.05) at the feeding end. In each WG, four Petri dishes hosting lymphocyte cultures are exposed by means of a vertical, four-layer Plexiglas stand. As detailed in our previous papers**,** such configuration guarantees exposure of two couples of samples to two different SAR values with high efficiency (>70%) [18], [19]. In addition, a coefficient of variation (the ratio between the standard deviation of SAR and the average SAR in the sample volume) less than 0.3 was achieved, that is considered an acceptable non-uniformity degree of induced field distribution into the sample volume, and one of the minimal requirements to be satisfied in exposure system design [20]. Therefore, in our experiments, one WG is used to expose two samples to 1.25 W/kg and two samples to 0.3 W/kg SAR, and the other WG is used to expose two samples to 0.6 W/kg and two samples to 0.15 W/kg SAR. The three WGs are placed inside the same cell culture incubator (Forma Scientific, model 311), that maintains the environmental conditions at 37 °C, 95% air and 5% CO_2 atmosphere. The PC drives the generator and the power sensors to control and adjust the incident and reflected power levels (P_i and P_r respectively) according to the desired SAR values (calculated as $(P_i\text{-}P_r)/m$, where m is the mass of the sample).

In separate experiments, the temperature of the sample exposed to the highest SAR was measured (fiber-optic thermometer, FISO Technologies, UMI4, equipped with fiber-optic temperature probe, FOT-M/2 m), to make sure that variations never exceeded accuracy range of the instrument (±0.3 °C) [16].

B. Signal Characteristics

In our experiments, specific settings of the RF generator were adopted to obtain CW, WCDMA and AWGN signals.

The CW was obtained by setting a frequency of 1950 MHz with no modulation applied. In the other two cases, the standard WCDMA or AWGN modulation schemes were applied to the carrier frequency.

The term WCDMA refers to a particular technology of multiple access to the radio channel for third-generation (3G) cellular networks. It is the transmission protocol used by 3G systems developed as an evolution of 2G GSM networks, spread almost all over the world. More technically, WCDMA is a broadband and expanded spectrum interface based on Code Division Multiple Access (CDMA). The channels at the radio interface have a bandwidth of 4.5–5 MHz, and the signals have a spectral composition characterized by a flat bandwidth, generally denoted as noise-like signals [21]. The choice to use WCDMA signals is due to the opportunity to consider RF signals of easy accessibility and reproducibility, thanks to the settled electronics and the high number of devices that use it.

In the AWGN signals, the noise is additive, it has uniform power across the whole frequency band (white), and the probability distribution function of noise samples is Gaussian. The use of AWGN signals is due to the desire to perform tests with

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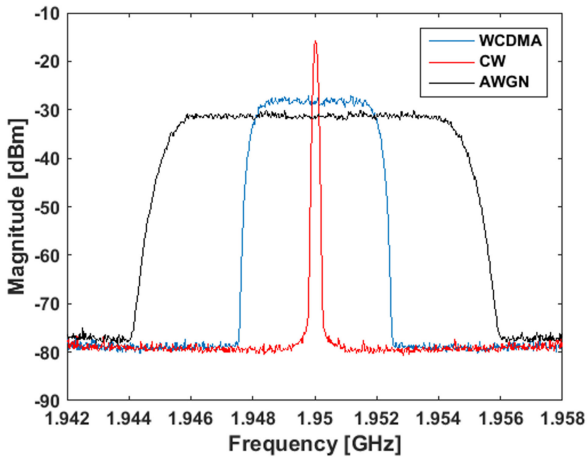


Fig. 2. Spectral power density of CW, WCDMA and AWGN signals adopted in the experiments.

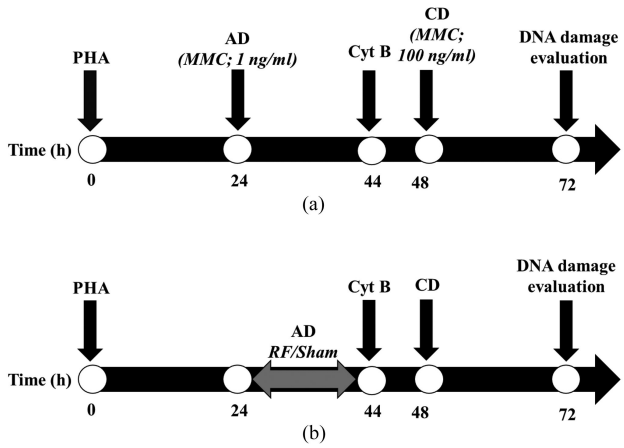


Fig. 3. Experimental procedures adopted to treat lymphocyte cultures with MMC as AD and CD (a) and with RF/Sham as AD and MMC as CD (b).

noise-like signals, and with higher bandwidth than the typical one of WCDMA. It is thus possible to operate with signals characterized by similar spectral conditions but different bandwidth, in order to verify the effect of the bandwidth on the observed biological response.

A picture of the spectral power density of signals adopted in our experiments is shown in Fig. 2, as acquired by a Rohde & Schwarz FSH4 spectrum analyzer. The 3 dB bandwidths of the three signals span 0.8 kHz (at a resolution bandwidth of the spectrum analyzer of 300 Hz), 4.5 MHz and 9 MHz for CW, WCDMA and AWGN, respectively.

C. Lymphocyte Cultures and Cytokinesis Block Micronucleus Assay

Peripheral blood samples from anonymized, healthy, non-smoking male donors were provided by the National Cancer Institute of Naples–G. Pascale Foundation (Italy), which also released the Ethical Committee approval. All donors were informed about the aim and experimental procedures of the study, and written consent form was obtained from all of them.

Lymphocyte cultures were set up by adding 0.3 mL whole blood to 2.7 mL RPMI 1640 culture medium containing 15% heat-inactivated foetal bovine serum (FBS), 1% L-glutamine, 1% penicillin/streptomycin, and 1% phytoemagglutinin (PHA) as mitogen to stimulate T-lymphocytes to enter the cell cycle [22].

Cytochalasin-B (6 μg/ml, dissolved in dimethylsulphoxide) was added to all cultures at 44 h, and at 72 h lymphocytes were harvested according to standard procedures [12]. Briefly, cells were collected by centrifugation and re-suspended in 3 mL of lysis buffer (10 mM EDTA, 155 mM NH_4Cl, 10 mM $KHCO_3$), for 7 min at room temperature, to lyse erythrocytes. Cells were centrifuged, washed in wash medium (RPMI 1640 + 2% FBS), treated with hypotonic solution (wash medium diluted 1:4 in distilled water) for 15 min at room temperature, followed by collection of cells on microscope slides using a cytospin centrifuge (Shandon, Thermo Scientific; 7 min at 1200 rpm). After fixation (80% methanol), and staining (10% Giemsa), coded slides were scored in blind at 1000x magnification. For each donor and for each exposure condition, a total of 2000 binucleate (BN) cells were examined to record the number of BN cells expressing MN.

D. Experimental Procedures

The response to adaptation protocol is characterized by a inter-individual variability. The adaptation grade is different among different donors, and some donors may not respond at all [12], [23]. Therefore, preliminary experiments were carried out to identify healthy donors responding to the adaptation protocol, in order to be enrolled in the study. To this purpose, lymphocyte cultures from four donors were pre-treated with 1 ng/mL MMC (Adaptive Dose, AD) dissolved in sterile distilled water and added 24 h after seeding, and then treated with 100 ng/mL MMC (Challenge Dose, CD) at 48 h from seeding. In addition, for each donor, a control culture, a culture treated with AD only, and one treated with CD only were also set up.

The induction of MN was evaluated after exposure to different RF conditions, alone and in combination with CD. In particular, for each signal, 11 cultures were set up: MMC (CD), sham, sham+MMC, RF at four SAR values alone and with MMC. A scheme of the experimental procedure is depicted in Fig. 3.

E. Statistical Analysis

To assess whether donors responded to the adaptation protocol, the Chi square (χ^2) test was applied to compare MN incidence in cultures treated with MMC as CD to those treated with MMC given as AD and CD (AD+CD). To assess the induction of protective effect, the two-tailed unpaired Student's *t*-test was applied to compare MN in cultures treated with MMC as CD to those pre-exposed to RF and then treated with MMC. The assumption of normal distribution was improved by the standard method of root square transformation [24] and examined by applying the Jarque-Bera test for normality. In all cases, Matlab (MathWorks) software was used for the analysis, and statistical significance was set for at least $P < 0.05$.

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TABLE I
INCIDENCE OF MICRONUCLEI IN LYMPHOCYTE CULTURES OF 4 DONORS TREATED WITH MITOMYCIN C AS ADAPTIVE DOSE (1 NG/ML), CHALLENGE DOSE (100 NG/ML), AND ADAPTIVE + CHALLENGE (1 + 100 NG/ML)

	MMC Treatment			
Donor	Control (0 ng/ml)	AD (1 ng/ml)	CD (100 ng/ml)	AD+CD (1+100 ng/ml)
1	8	9	$36^{\#\#}$	20^{*}
2	10	12	$58^{\#\#}$	24^{**}
3	14	18	$40^{\#\#}$	24^{*}
4	14	12	$36^{\#}$	20^{*}

Each data point is the number of BN cells with MN on 2000 BN cells scored. Data analyzed with the χ^2 test.
$^{\#}$P<0.05, $^{\#\#}$ P<0.01, 100 ng/ml vs Control.
* P<0.05, ** P<0.01, 1 + 100 ng/ml vs 100 ng/ml.

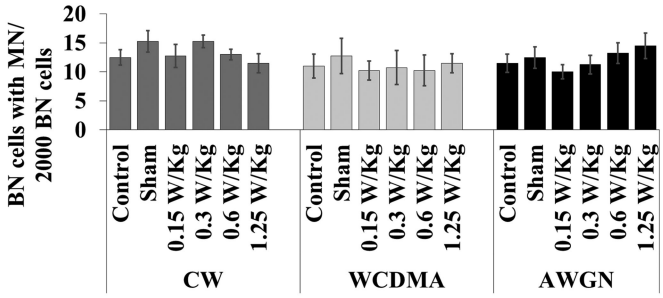


Fig. 4. Incidence of micronuclei in lymphocyte cultures exposed to RF under different conditions. The results are expressed as mean ± SE of four donors.

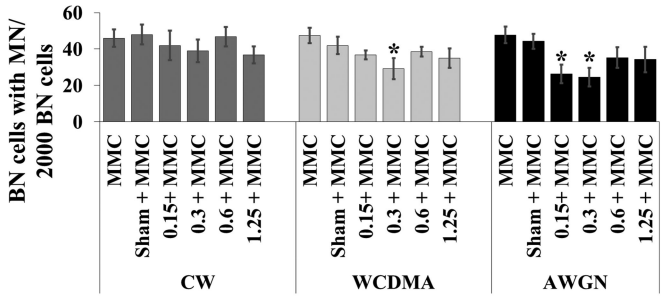


Fig. 5. Incidence of micronuclei in lymphocyte cultures exposed to RF under different conditions as adaptive dose and/or MMC as challenge dose (100 ng/ml). The results are expressed as mean ± SE of four donors. ∗P < 0.05 *vs.* MMC, two-tailed unpaired Student's t-test on root-square transformed data.

III. RESULTS

A. Donors Response to the Adaptation Protocol

The responsiveness of lymphocytes to the adaptation protocol was tested by using MMC as AD and CD. For each treatment/donor, the number of BN cells containing MN was recorded. Results are shown in Table I. Treatment with AD did not show MN increase (P > 0.05), while CD resulted in a statistically significant increase (P < 0.01) with respect to spontaneous MN incidence (Control). Lymphocyte cultures that received the MMC combined treatment (AD+CD) exhibited a decrease with respect to CD treated cultures (P < 0.05). Therefore, since all donors exhibited a significant reduction of MMC-induced MN, they were enrolled in the study.

B. Absence of DNA Damage Under RF Exposure Alone

The number of BN cells containing MN in lymphocyte cultures exposed to different RF conditions, is presented in Fig. 4. RF exposure at CW, WCDMA and AWGN signal never induced DNA damage, irrespective of the SAR level (P > 0.05 in all cases, one-way ANOVA for repeated measurements).

C. Protective Effect of RF Pre-Exposure Against Chemical Treatment

The incidence of MN in lymphocyte cultures pre-exposed to different RF conditions and challenged with 100 ng/ml MMC, is presented in Fig. 5.

CW-RF exposure never reduced the MMC-induced MN formation, irrespective of the SAR value (RF + MMC *vs.* MMC, P > 0.05).

Interestingly, the presence of modulation gave different results. In particular, exposure to WCDMA reduced MMC-induced MN formation only when 0.3 W/kg SAR was delivered (0.3 W/kg + MMC *vs*. MMC, P < 0.05). Similarly, exposure to AWGN reduced MMC-induced MN formation, but the effective SAR values were both 0.15 and 0.3 W/kg (RF + MMC *vs.* MMC, P< 0.05).

As expected, sham exposures never elicited the protective effect (sham + MMC *vs*. MMC, P > 0.05).

IV. DISCUSSION

Most of the RF sources available in the living environment are modulated, and different technologies like radars, ultra-wideband and mobile communications, including the forthcoming 5G technologies which will operate on larger bandwidths, employ different forms of modulation to deliver information. Studying the effects of modulation is not a trivial task, due to the difficulty of separating its contribution from that of carrier frequency. Only few studies on biological effects of exposure to RF fields, carried out to date, have been designed to disclose the possible influence of modulation, and the ones reporting modulation-dependent effects have not been independently confirmed [5], [6].

On the other hand, some papers addressed the intriguing hypothesis of non-linear responses in cells and tissues exposed to RF energy, or, in other words, whether these bio-systems could demodulate amplitude-modulated RF signals. According to this hypothesis, bio-systems would be exposed to low-frequency fields similar to those of biological processes and, therefore, with the potential for biological activity [25]–[27]. This hypothesis was challenged with a very sophisticated and accurate experimental procedure, but it was not proved [28], [29].

In this paper, we addressed, for the first time, the influence of signal modulation and bandwidth in affecting the biological response of human lymphocytes to RF electromagnetic fields, alone and in combination with a chemical agent. The effect of CW exposure was systematically compared to that of different modulation schemes and signal bandwidths. In particular,

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cell cultures exposed to either CW or modulated (WCDMA or AWGN) 1950 MHz electromagnetic field did not show DNA damage in the micronucleus test. When human lymphocyte cultures were pre-exposed to the same RF signals and then challenged with a well-known DNA damaging agent (MMC), different biological responses were detected depending on the signal characteristics in terms of modulation and bandwidth of the power spectrum. The CW signal did not alter the DNA damage induced by MMC treatment, while such damage was reduced when either signals WCDMA (4.5 MHz bandwidth) at 0.3 W/kg or AWGN (9 MHz bandwidth) at 0.15 and 0.3 W/kg were applied, indicating a protective effect.

It is well documented that the human population is heterogeneous in its ability to express AR, and that different genetic predisposition in the efficiency of DNA repair mechanisms, cellular redox status and overall intrinsic features of each individual do affect the biological response to different chemical and physical agents [30]. Therefore, in order to take into account the inter-individual variability of human lymphocytes response, cultures from each donor were exposed to all the electromagnetic conditions considered in the study.

These results confirm our previous findings on the induction of protective effect following pre-exposure to RF electromagnetic fields (900 MHz, GSM and 1950 MHz, WCDMA signals) against the damage induced by chemical and physical agents [12]–[16], as well as those reported by independent research groups and reviewed in [10]. Moreover, they add a further piece of information regarding the role of RF signal characteristics. The presence of a modulation scheme seems to be a crucial factor for the onset of a protective effect. To the best of our knowledge, the only study addressing the induction of a protective effect by CW or modulated RF exposure is the one by Gapeyev and Lukyanova, who detected, in mouse peripheral blood leukocytes, a protective effect of 42.2 GHz electromagnetic radiation exposure against the damaging action of X-rays, hydrogen peroxide, and the alkylating agent methyl methanesulfonate. The protective effect was observed only when the pre-exposure was given as pulse-modulated (1 or 16 Hz modulation frequency) but not as CW [7]. Our results are in agreement with the above and, furthermore, provide evidence that also the signal bandwidth is a factor in the occurrence of the protective effect. As a matter of fact, by doubling the signal bandwidth (AWGN 9 MHz, respect to WCDMA 4.5 MHz) the effect was induced not only at 0.3 W/kg, but also at 0.15 W/kg. In our previous studies, exposure to 900 MHz, GSM signal, 200 kHz bandwidth, resulted in an effective SAR value of 1.25 W/kg [12], [13]. Based on the overall results, it could be speculated that a relation (a compensation?) exists between the applied signal bandwidth and the power absorbed by the samples. This hypothesis cannot be generalized since, as an example, in the the case of WCDMA signal, the effect is not induced at the highest SAR levels. However, in the literature on biological effects of non-thermal RF exposure, "window" effects are postulated to explain several results that cannot be explained by a dose-response relationship [31].

Moreover, these findings suggest the existence of a non-thermal, complex interaction between modulated RF fields and biological systems whose effects become detectable when the latter are appropriately sensitized, as in combined exposure protocols. Therefore, although the interaction mechanisms between RF fields and biological systems have not yet been clarified [32], [33], a plausible hypothesis for the results here presented is the perturbation of the cell redox status and of DNA repair mechanisms after RF-modulated pre-exposures, as highlighted in the paper by Gapeyev and Lukyanova [7], and in our recent findings [34].

V. Conclusion

The results of the present investigation provide further evidence that RF exposure can prompt a protective effect in mammalian cells against subsequent genotoxic insults. Moreover, in the current experimental conditions, taking advantage of a systematic comparison with the CW exposure, our findings highlight the modulation scheme and the signal bandwidth as crucial factors for the occurrence of the protective effect.

Having said the above, if proved in *in vivo* models, a new research horizon lies ahead of us, as a potential, innovative clinical application of RF electromagnetic fields, exploiting the protective effect, could be proved. In radio-biology the AR phenomenon has been proposed as a way to protect healthy cells from side effects of chemo/radio-therapeutic treatments, by pre-treatments with low doses of ionizing radiation. However, such proposal never moved into clinical practice due to the risk of cellular transformation as a biological consequence of protracted, low-dose rate exposures to ionizing radiation [35]. The possibility of inducing AR by RF pre-treatments may overcome this issue, due to the non-ionizing nature of these fields. Moreover, RF-induced protection has been here proved to be a tunable phenomenon depending on the electromagnetic conditions adopted, which could be able to target different cell types located at different depths in the body. In addition, potential biomedical applications exploiting the protective effect of RF could benefit from the availability of commercially established, low-cost RF sources.

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