TITLE: Induction of adaptive response by non ionizing radiation

PROPOSERS: Maria Rosaria Scarfì (scarfi.mr@irea.cnr.it), Olga Zeni (zeni.o@irea.cnr.it), Rita Massa (massa@unina.it) – CNR, Institute for Electromagnetic Sensing of the Environment, Naples, Italy

Working Module description

It is known that chemical or physical-induced cell damage can be decreased if the biological system is pretreated with extremely low doses of such agents. This phenomenon, called adaptive response (AR), has been largely described for ionizing radiation, although the action mechanisms to explain such a protection are not yet clarified. The AR is of particular interest since it offer interesting perspectives in the field of radioprotection and biomedical applications.
When in '80s the phenomenon of AR induced by low doses ionizing radiation was reported, several researchers evaluated the possibility to employ such phenomenon to protect healthy tissues, but not cancer tissues, against cyto-toxicity of radio and chemo-therapy. However, still now the AR is not employed for therapeutic purposes since the long term effects of low doses ionizing radiation are not yet well known.
Recently, it has been reported in both in vitro and in vivo experiments that pre- exposures to non-ionizing radiation in the radiofrequency range (900 - 1950 MHz) are able to reduce the genotoxic effects induced by a subsequent treatment with chemical or physical mutagens, therefore to induce AR.
The WM aims to study and characterize the AR induced by electromagnetic fields in mammalian cell cultures treated with chemical or physical mutagens.
Experimental investigations on different cell types (healthy and cancer cells) will be carried out, and the efficacy of different RF signals in inducing protection from chemical or physical genotoxic treatments will be evaluated. Moreover, it will be also investigated if AR can be induced by other frequencies in non-ionizing electromagnetic spectrum (including static and magnetic fields).
The activity, within the WG1 (Cancer EMF interactions and applications) is in the framework of the development of technologies aimed to reduce the radio- or chemotherapy toxicity in healthy tissues. The results obtained will also contribute to explain the action mechanisms underlying the phenomenon.
Apart from the proposing researchers, two colleagues involved in the COST action have already declared their interest in this topic: Prof Myrtill Simko (AIT Austrian Institute of Technology, Department of Health & Environment , Austria) and Dr Gyorgy Thuroczy (National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary)

State-of-the-art

The phenomenon of Adaptive Response (AR), i.e. the resistance to a DNA damage induced by ionizing radiation following pre-treatments with very low-doses of the same agent, was described in 1984 (Olivieri et al., 1984). Ever since, AR has been demonstrated to occur in both human and animal cell cultures following pre-exposures to different chemical or physical genotoxic agents. Examples of AR have been also reported in environmental, occupational and clinical framework (Dimova et al., 2008).
Different action mechanisms have been proposed to explain AR induction (Stecca and Gerber, 1998), but none of them has been universally acknowledged so far. Several authors believe that enzymes involved in DNA repair play a key role, particularly the poly(ADP-ribosil)polymerase (PARP), which is involved in the repair of free radicals-induced DNA strand breaks (Dimova et al., 2008). Several investigations have demonstrated that many, but not all, cancer cell lines exhibit

AR. Such observations have suggested the possibility to exploit the different sensitivity to adaptation of cancer cells with respect to healthy ones, seeking to optimize the balance between the damage induced to cancer tissues and that induced to healthy ones in the framework of chemo and radiotherapy (Park et al., 1999, Schwarz et al., 2008). However, AR has not been used in therapeutic applications so far due to the lack of knowledge on potential long-term effects of low doses of genotoxic agents.

Recently, some components of the proposing group showed that pre-exposure to non-ionizing radiation (900 – 1950 MHz) are able of reducing the genotoxic damage induced in mammalian cell cultures by subsequent treatments with either chemical and physical mutagens, therefore indicating that non ionizing radiation are also capable of inducing AR (Sannino et al., 2009). The results obtained so far showed that this phenomenon is dependent on the phase of the cell cycle during which cell cultures are pre-exposed (Sannino et al., 2011). AR has been demonstrated with respect to chemotherapy treatment (mitomycin-C) in human peripheral blood lymphocytes pre-exposed for 20 hours to a GSM, 900 MHz signal, 1.25 W/kg average SAR (Sannino et al., 2009, Sannino et al., 2011). With a different signal (UMTS, 1950 MHz), a protective effect against MMC has been shown following 20 hour exposures to 0.3 W/kg SAR, but not to 0.15, 0.6 or 1.25 W/kg (Zeni et al., 2012). In the same experimental conditions, RF also induced protection against 1.5 Gy X rays (Sannino et al., 2014). Moreover, results obtained in rodents fibroblasts indicate that different SAR values, with the same signal, are needed to obtain a protective effect comparable to those induced in human lymphocytes (manuscript in preparation).
Other independent research groups confirmed, both in vitro and in vivo, that pre-exposures to 900 MHz protect from gamma rays-induced damage (Cao et al., 2010, Cao et al., 2011, Jiang et al., 2012, Jin et al., 2012, Jiang et al., 2013).
The main results on RF-induced AR have been reviewed by Vijayalaxmi and co-workers (Vijayalaxmi et al., 2014).
These findings are of particular interest since demonstrate that non genotoxic non-ionizing radiation is able to induce AR, by mimicking the effect of low dose ionizing radiation. They envisage interesting perspectives in the field of radio-protection and biomedical applications of non-ionizing radiations.

Gaps in knowledge, challenges and objectives to be achieved

Although results on RF-induced AR are very recent and require a deep and accurate characterization, the possibility of gaining different exposure conditions for healthy and cancer tissues, based on the differences in terms of electromagnetic properties, location (depth) and morphology, is particularly attractive for therapeutic applications.
However, a large amount of experimental work has to be done:
- replication/confirmation studies on RF-induced AR by other researchers in independent laboratories;
- assessment of the best exposure configuration, in terms of applied signal and duration, to maximize the protective effect of RF pre-exposure in healthy cell cultures;
- investigation of induction of AR by other frequencies in non-ionizing electromagnetic spectrum (including static and magnetic fields);
- evaluation of the ability of different genotoxic agents with different action mechanisms on DNA to induce AR in cells pre-exposed to non-ionizing EMFs;
- investigation of EMF-induced AR by evaluating several biological endpoints such as cell proliferation, apoptosis, oxidative stress;
- comparison of the effectiveness of the treatments in healthy and cancer cell cultures;

- investigation of the mechanisms of RF induced AR in a cell model.

Proposed research activity

The following main activities are foreseen:

1) characterization the EMF-induced AR by investigating the role a) of the employed electromagnetic parameters (duration, frequency, signal, specific absorption rate) and b) of the nature of the chemical or physical agent in the induction of the phenomenon with the aim of highlighting the action mechanisms and developing the possible biomedical applications;
2) measurement of AR in different cell types, in terms of DNA damage, proliferation, apoptosis and oxidative stress;
3) assessment of possible of therapeutic applications of EMF-induced AR by employing the same exposure conditions in healthy and cancer cell cultures with the aim to find the experimental procedure such that AR is induced in healthy cells but reduced or absent in cancer cells;
4) application of the more effective experimental conditions obtained in in vitro studies to animal models.

References

Cao Y, Xu Q, Jin ZD, Zhang J, Lu MX, Nie JH, Tong J (2010) Effects of 900-MHz microwave radiation on gamma-ray-induced damage to mouse hematopoietic system. Journal of toxicology and environmental health Part A 73:507-513.

Cao Y, Xu Q, Jin ZD, Zhou Z, Nie JH, Tong J (2011) Induction of adaptive response: pre-exposure of mice to 900 MHz radiofrequency fields reduces hematopoietic damage caused by subsequent exposure to ionising radiation. International journal of radiation biology 87:720-728.

Dimova EG, Bryant PE, Chankova SG (2008) "Adaptive response" - Some underlying mechanisms and open questions. Genet Mol Biol 31:396-408.

Jiang B, Nie J, Zhou Z, Zhang J, Tong J, Cao Y (2012) Adaptive response in mice exposed to 900 MHz radiofrequency fields: primary DNA damage. PloS one 7:e32040.

Jiang B, Zong C, Zhao H, Ji Y, Tong J, Cao Y (2013) Induction of adaptive response in mice exposed to 900MHz radiofrequency fields: application of micronucleus assay. Mutation research 751:127-129.

Jin Z, Zong C, Jiang B, Zhou Z, Tong J, Cao Y (2012) The effect of combined exposure of 900 MHz radiofrequency fields and doxorubicin in HL-60 cells. PloS one 7:e46102.

Olivieri G, Bodycote J, Wolff S (1984) Adaptive response of human lymphocytes to low concentrations of radioactive thymidine. Science 223:594-597.

Park SH, Lee Y, Jeong K, Yoo SY, Cho CK, Lee YS (1999) Different induction of adaptive response to ionizing radiation in normal and neoplastic cells. Cell biology and toxicology 15:111-119.

Sannino A, Sarti M, Reddy SB, Prihoda TJ, Vijayalaxmi, Scarfi MR (2009) Induction of adaptive response in human blood lymphocytes exposed to radiofrequency radiation. Radiation research 171:735-742.

Sannino A, Zeni O, Romeo S, Massa R, Gialanella G, Grossi G, Manti L, Vijayalaxmi, Scarfi MR (2014) Adaptive response in human blood lymphocytes exposed to non-ionizing radiofrequency fields: resistance to ionizing radiation-induced damage. Journal of radiation research 55:210-217.

Sannino A, Zeni O, Sarti M, Romeo S, Reddy SB, Belisario MA, Prihoda TJ, Vijayalaxmi, Scarfi MR (2011) Induction of adaptive response in human blood lymphocytes exposed to 900 MHz radiofrequency fields: influence of cell cycle. International journal of radiation biology 87:993-999.

Schwarz SB, Schaffer PM, Kulka U, Ertl-Wagner B, Hell R, Schaffer M (2008) The effect of radio-adaptive doses on HT29 and GM637 cells. Radiation oncology 3:12.

Stecca C, Gerber GB (1998) Adaptive response to DNA-damaging agents: a review of potential mechanisms. Biochemical pharmacology 55:941-951.

Vijayalaxmi, Cao Y, Scarfi MR (2014) Adaptive response in mammalian cells exposed to non-ionizing radiofrequency fields: A review and gaps in knowledge. Mutation research Reviews in mutation research 760:36-45.

Zeni O, Sannino A, Romeo S, Massa R, Sarti M, Reddy AB, Prihoda TJ, Vijayalaxmi, Scarfi MR (2012) Induction of an adaptive response in human blood lymphocytes exposed to radiofrequency fields: influence of the universal mobile telecommunication system (UMTS) signal and the specific absorption rate. Mutation research 747:29-35.