

Medical/biological Study (experimental study)**Electromagnetic fields at mobile phone frequency induce apoptosis and inactivation of the multi-chaperone complex in human epidermoid cancer cells.**

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Aim of study (according to author)

A previous study showed that the exposure to non-thermal microwave electromagnetic field at 1.95 GHz, a frequency used in mobile communication, affects the refolding kinetics of eukaryotic proteins (see [publication 11255](#)).

On these basis the authors have evaluated the *in vivo* non-thermal effect of microwave electromagnetic field on the apoptosis of human epidermoid cancer cells.

Background/further details:

Modulation of the expression, activity, and proteasome-dependent degradation of the components of Ras --> Erk- and Akt-dependent survival signaling induced by electromagnetic field were studied.

Ras --> extracellular signal regulated kinase (Erk)-dependent signal transduction pathway: involved in regulation of both proliferation and apoptosis. Akt: another important anti-apoptotic pathway (Akt can be activated concomitantly or independently from Ras --> Erk-1/-2 signaling).

Finally the role of HSP90/multi-chaperone-dependent multi-chaperone complex in the regulation of expression and activity of anti-apoptotic signaling Ras and Raf-1 and of their relative survival signaling induced by microwave electromagnetic fields were investigated.

Many HSPs form complexes that act as chaperones and bind other proteins (so called client proteins). These complexes play a regulatory role in the fate of proteins. HSP90 acts in concert with other chaperones to provide maturation and folding, as well as trafficking and function of their client proteins (e.g. c-Raf, Ras, Mek) through the formation of the HSP90/multi-chaperone complex.

Several protein kinases (including Raf-1) depend upon the HSP90/multi-chaperone for function and stability. This is likely the way by which HSP90/multi-chaperone is involved in the regulation of apoptotic processes. The HSP90 client proteins Raf-1 and Mek are components of the Ras --> Erk-dependent signal transduction pathway.

Endpoint

- cell viability/cell division/proliferation: apoptosis

Exposure

General category: mobile phone/mobile communication system, microwaves

Field characteristics	Parameters
1.95 GHz exposure duration: continuous for 1, 2 and 3 h or for 48 h	SAR: 3.6 mW/g average over mass (± 0.2 mW/g)

Exposed system:

intact cell/cell culture (in vitro)

human oropharyngeal epidermoid carcinoma KB cancer cell line (depend from the Ras --> Erk-mediated survival signaling that protect them from apoptotic stimuli)

Methods

Endpoint/Measurement parameters/Methodology

- molecular biosynthesis: expression of Ras protein and Akt; expression of Raf-1, Erk-1 and -2; expression of PI3K (Western blot analysis using specific antibodies)
- cell function: ubiquitination of signaling proteins (Ras, Raf-1, Erk; immunoprecipitation)/ubiquitin-dependent degradation by proteasome complex; Akt kinase assay (immunoprecipitation; chemiluminescence)
- cell viability/cell division/proliferation: apoptosis evaluation (DNA fragmentation; gel electrophoresis); apoptotic cell death (flow cytometry and fluorescence microscopy)
- others: Ras activity (affinity precipitation); phosphorylation of Erk-1/-2; Akt activity; inactivation of multi-chaperone complex (expression & activity of different components (HSP27, HSP70, HSP90, p38K, JNK-1) of stress-activated pathways)

investigated material: DNA/RNA (in vitro), intact cell/cell culture (in vitro), cell supernatants/cell lysates

time of investigation: after exposure

Main outcome of study (according to author)

The authors revealed that exposure induces time-dependent apoptosis (45% after 3 h) that is paralleled by an about 2.5-fold decrease of the expression of Ras and Raf-1 and of the activity of Ras and Erk-1/2. Although also the expression of Akt was decreased, its activity was unchanged likely as a consequence of the increased expression of its upstream activator PI3K.

An about 2.5-fold increase of the ubiquitination of Ras and Raf-1 was also revealed. The addition of proteasome inhibitor lactacystin caused an accumulation of the ubiquitinated isoforms of Ras and Raf-1 and counteracted the effects of exposure on Ras and Raf-1 expression suggesting an increased proteasome-dependent degradation induced by the irradiation.

The irradiation induced a differential activation of stress-dependent pathway with an increase of JNK-1 activity and HSP70 and HSP27 expression and with a reduction of p38 kinase activity and HSP90 expression.

The overexpression of HSP90 (induced by transfection of the cells) completely antagonized the apoptosis and the inactivation of the Ras --> Erk-dependent survival signal induced by electromagnetic field. Conversely, the inhibition of Erk activity induced by 12 h exposure to Mek-1 inhibitor U0126 antagonized the effects induced by HSP90 transfection on apoptosis caused by irradiation.

In conclusion, these data demonstrate for the first time that microwave electromagnetic fields induce apoptosis through the inactivation of the Ras --> Erk survival signaling due to enhanced degradation of Ras and Raf-1 (determined by decreased expression of HSP90 and the consequent increase of proteasome dependent degradation).

(Study character: medical/biological study, experimental study, full/main study)

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