



ELF- magnetic field and immune response modulation

WM proposal as an umbrella activity

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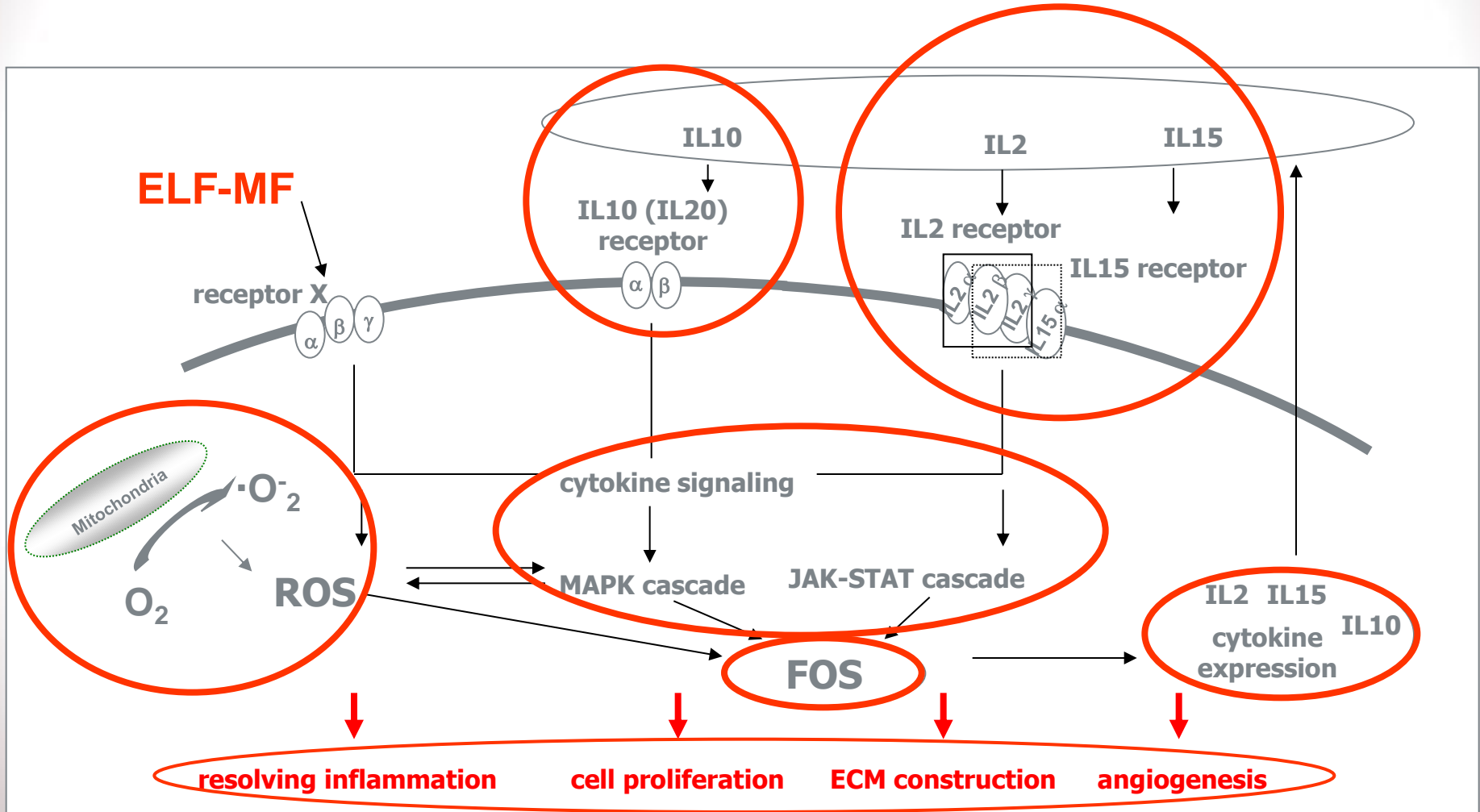
Situation: **ELF-EMF interacts with biological systems!**

Fact: **Different cell types react differently since they have different homeostatic capacity!**

Hypothesis 1: **ELF-EMF modulates oxidative response(s) dose (flux density and time) dependently**

Hypothesis 2: **This modulation can be used positively.**

Monocyte / Macrophage activation



Alternative activation pathway



Antigen-presenting phagocytes, secrete pro-inflammatory and antimicrobial mediators

Classically activated macrophages:

PROMOTES:

inflammation
extracellular matrix (ECM) destruction
apoptosis

phagocytosis → oxidative burst
tends to **elicit** chronic inflammation and **tissue injury**

Alternatively activated macrophages:

PROMOTES:

cell proliferation
ECM construction
angiogenesis

pinocytosis → free radical release
tends to **resolve** inflammation and facilitate **wound healing**

Lectine dependent activation

Summary of own results

- 👍 EMF induce immune cell activation: ROS, IL-1 β , phagocytosis, HSP70
- 👍 Seems to be cell type specific responses (different redox status, specific physiologic function), not in a general way
- 👍 ROS and HSP70 production: dose independency (flux density, time)
- 👍 Radical scavengers inhibit ROS and HSP70
- 👍 Modulation of the redox homeostasis leads to the activation of the alternative pathway in immune relevant cells

Summary and objectives

- The interface between physics and biology is still unclear
- It might be on the membrane, on receptor(s) or at other cell organell(s), and/or in parallel
- MF modulation of cell specific oxidative responses may be depending on the cell´s metabolic state and redox potential state
- It is known that MF influence different medical related processes such as transcranial stimulation by MF, wound and bone healing, etc.
- There is a need to identify **new areas** of application (dental area: gingiva) and
- to specify **targeted** (optimization of exposure parameters) **applications**

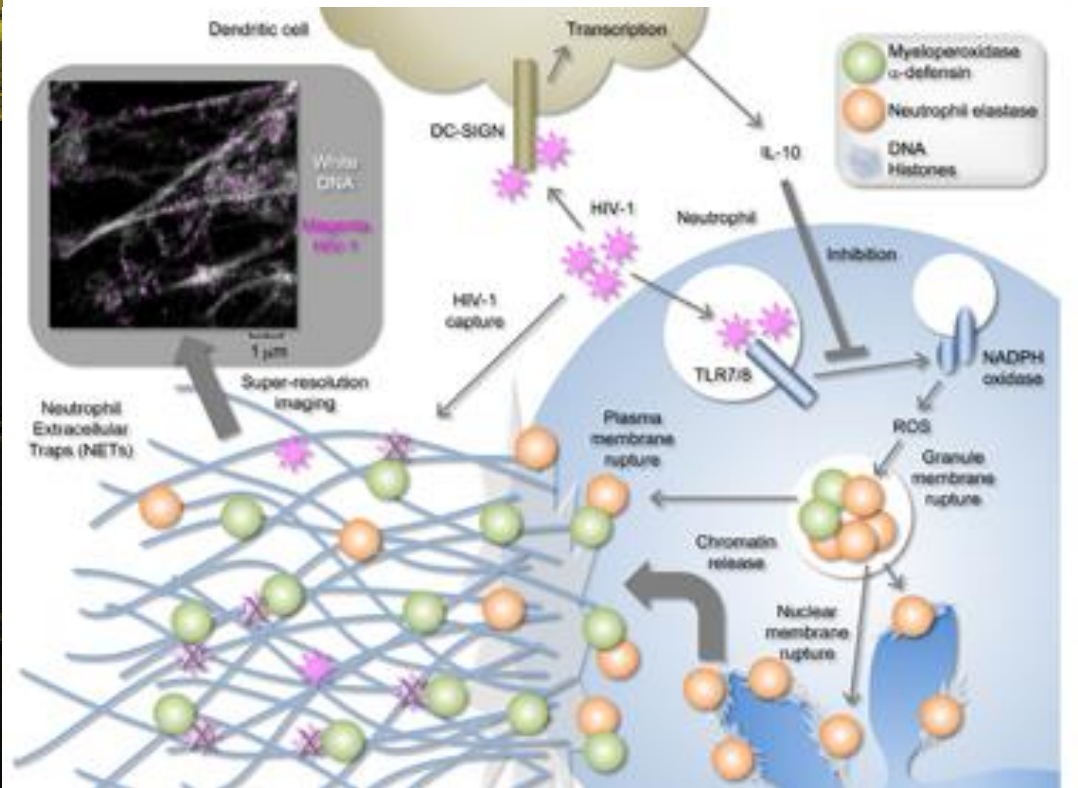
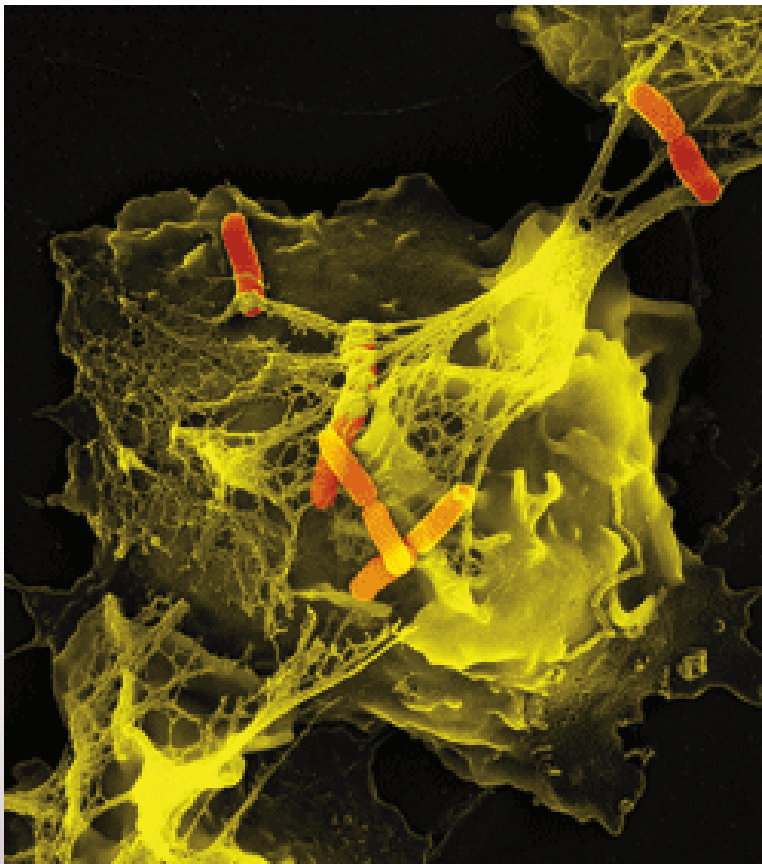
The module goal

..is to focus on beneficial effects related to oxidative responses and modulation of immune system functions of EMF MF in order to

- 1) provide a better understanding of underlying physical and biological modes of action and
- 2) to contribute to the development of innovative EMF-based medical treatment.

Low-frequency electromagnetic field exposure enhances extracellular trap formation by human neutrophils through the NADPH-pathway (accepted)

Golbach LA, Scheer MH, Cuppen JJM, Savelkoul HFJ, Verburg-Van Kemenade BML



Low-frequency electromagnetic field exposure enhances extracellular trap formation by human neutrophils through the NADPH-pathway (accepted)

Conclusion

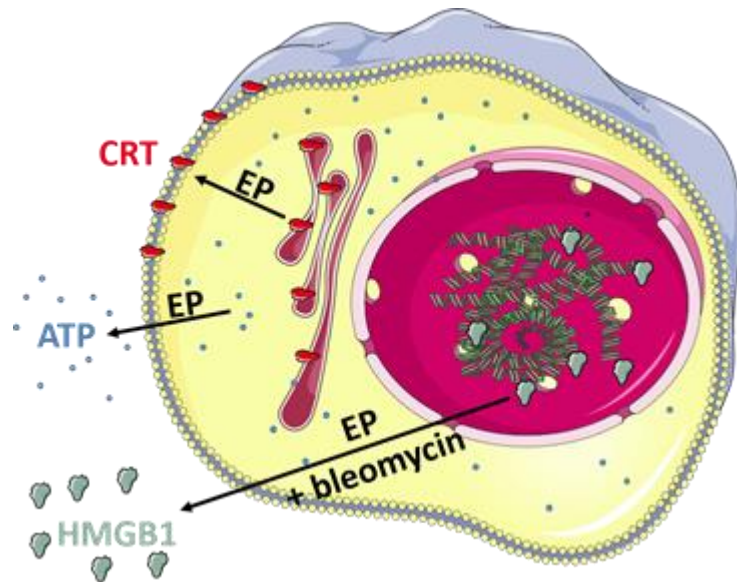
This is the first study to show that LF EMF exposure is able to enhance NET formation *ex vivo*. An increased NET formation of ~25% could be measured at four hours after stimulation with PMA. Cellular activation was needed, since LF EMF exposure alone was not able to promote NET formation. The pathways involved in PMA stimulated NET formation are partly known [29] and with the use of a selective pharmacological inhibitor we demonstrated that the NADPH-pathway is crucial for LF EMF enhanced NET formation, possibly by upregulated ROS production. These data provide a basic mechanism of action on immune cells to explain potential health effects of LF EMFs generated by household appliances and power lines.

In vivo electroporation and immune response

C. Y. Calvet, F. M. André and L. M. Mir

In vivo electroporation: not only an enhancer of gene transfer but also an adjuvant for DNA vaccination

Oncoimmunology 2014; 3:e28540; <http://dx.doi.org/10.4161/onci.28540> (Point of View)



- **ATP release:** autophagy
« find me » signal for dendritic cells
IL-1 β production → activation of IL-17+ $\gamma\delta$ T cells and CD8+ T cells
Favors DC differentiation and maturation
- **Exposure of Calreticuline (CRT):** ER stress
« eat-me » signal for dendritic cells
- **HMGB1 release:** membrane disruption
Pro-inflammatory cytokine
Favors cross-presentation of tumor antigens by DCs (Kroemer, 2013)

C. Y. Calvet, D. Famin, F. M. André and L. M. Mir - Electrochemotherapy with bleomycin induces hallmarks of immunogenic cell death in murine colon cancer cells.

Oncoimmunology 2014; 3:e28131; <http://dx.doi.org/10.4161/onci.28131>

However, no electroporation with EMF



No cell electroporation has been detected when cells are exposed to EMF

HOWEVER:

- No cell electroporation so far proved with classical electroporation markers does not mean that nothing happens (ongoing molecular dynamics studies)
- ATP is a very small molecule: is it released?
- Moreover we already showed that there is an increase in endocytosis rate that we consider (M. Breton, A. Silve and L.M. Mir, in preparation) as a late consequence of the membrane changes occurring during cell membrane electropermeabilization (whatever the level of electropermeabilization) => exposure of calreticulin?

N. Mahrour, R. Pologea-Moraru, M. G. Moiescu, S. Orłowski P. Lévêque and L. M. Mir
In-vitro increase of the fluid phase endocytosis induced by pulsed radiofrequency electromagnetic fields : importance of the electric field component.

Biochimica Biophysica Acta – Biomembranes, 1668, 126-137, 2005

M. G. Moiescu, P. Leveque, M.-A. Verjus, E. Kovacs and L. M. Mir
900MHz modulated electromagnetic fields accelerates the clathrin-mediated endocytosis pathway

Bioelectromagnetics 30, 222-230, 2009.

Moreover, besides potential calreticulin exposure and potential ATP release, other avenues can be explored:

Indeed, it has been found by several groups (Teissié's group, 1998, Pakhomov's group, 2012) that ROS appear in the vicinity of the cells exposed to electric pulses...

=> the links to Myrtil's hypothesis #1 and own data, as well as to Jan's data must be explored !

An overall consistency seems to emerge from our three groups data and ideas

Join us in a WM



or in several WMs



“Umbrella” activity for many WMs

Mode of action:

- Modulation of free radical homeostasis
- Different endpoints with modest effects
- Results from medical processes (wound and bone healing, etc.)
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-
-

Development of targeted (E)MF application:

- WG1
- WG2
- WG3