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Commentary

Hepatocellular carcinoma therapy finds a channel on the radio

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Hugo Jimenez et al. [1] report in this article of *EBioMedicine* that the voltage-gated calcium channel $Ca_v3.2$ (CACNA1H) is significantly involved in the amplitude-modulated radiofrequency electromagnetic fields (AM RF EMF) anti-cancer therapy specific for hepatocellular carcinoma (HCC). In a companion paper of this issue, they also show that AM RF EMF suppresses breast cancer brain metastasis via calcium ions and CACNA1H channels [2].

HCC is the main type of liver cancer which has very poor prognosis. Worldwide, liver cancer is the fourth most common cause of cancer-related death, and in some countries the number of deaths practically equals the number of new cases reported [3]. Most of the patients with advanced HCC either do not respond to first- or second- line therapy, or develop resistance and relapse [3]. Then, finding alternative therapeutic approaches for these patients is imperative. In this direction, a plethora of ion channels including voltage-gated T-type calcium channels have gained enormous interest in cancer as potential diagnostic and prognostic markers, as well as novel therapeutic targets [4,5]. Previous studies suggested the involvement of T-type channels in the anti-proliferative effect of EMF on melanoma cells [6]; and alternating electric fields were shown to exert antitumor effects on glioblastoma cells through activation of the voltage-gated calcium channels $Ca_v1.2$ [7].

The research group of the new investigation previously showed that several HCC patients had very good response when treated with AM RF EMF, and that the response was tumour-specific [8]. The corresponding medical device received European approval in 2018 and is indicated for patients with advanced HCC who have failed or are intolerant to first-line and second-line therapies [9]. Now, they report that the whole body averaged specific absorption rate (SAR) in a HCC patient treated with AM RF EMF is below the international standards for safety exposure. Then, the authors performed experiments in animals at SAR levels like those generated in HCC patients treated with AM RF EMF, and in HCC cultured cells treated with tumor-specific frequencies to study the potential anti-cancer molecular mechanism of action of AM RF EMF. By using genomic approaches and gene silencing, they demonstrate that the T-type calcium channels $Ca_v3.2$ are the specific calcium entry proteins responsible for the anti-HCC effects. Interestingly, they also observed that calcium influx through $Ca_v3.2$ channels initiates the down-regulation of HCC cancer stem cells. Beneficially, they show that normal hepatocytes are not affected by AM RF EMF, and that this therapy is effective on several HCC cell lines independently of hepatitis B virus status or ethnicity.

Many questions arise whit these important contributions. Does this molecular mechanism is really taking place in the body of the treated patient? Which tissue and cancer properties allow AM RF EMF to be tissue- and cancer- specific? How does AM RF EMF selectively affect CACNA1H channels? Is this via special properties of its voltage sensor? Are single-channel properties affected by AM RF EMF? Which signaling pathways are activated/inhibited or which protein-protein interactions occur after CACNA1H channel activation by AM RF EMF in HCC cells? Is any of such pathways druggable in order to synergize the anti-cancer effect of AM RF EMF and propose novel anti-cancer agents?

The authors recommend that the use of calcium channel blockers should be avoided in patients receiving treatment with tumour-specific-AM RF EMF, as they are likely to block the anticancer effects. Then, drug substitutes for patients using calcium channel blockers submitted to AM RF EMF would be necessary. Some epidemiological studies suggest that calcium channel blocker use may be associated to the chemotherapy response, therefore, specific epidemiological studies on T-type-channel blocker use associated to HCC are also needed.

The results presented by Jimenez *et al.* [1] add very special value to the basic and clinical research fighting HCC, as well as to the ion channel and cancer stem cell fields. It will be very interesting to investigate the potential use of AM RF EMF as a diagnostic tool. Are SAR levels different in healthy volunteers in comparison with patients with liver cirrhosis or HCC at different stages? Some animal models resembling the sequence from liver cirrhosis to HCC and metastasis (as it occurs in humans) may be used to this purpose. Actually, the expression of several ion channels during rat HCC development has been reported [10]. The authors prompt the investigation of concomitant treatment of HCC with AM RF EMF and sorafenib. The same co-treatment approach could be made with second-line therapy for HCC and with chemotherapeutic agents for other cancers. Moreover, AM RF EMF basic and clinical research may be extended to other cancers and many other pathologies where calcium influx and ion channels play an important role including central nervous system, cardiac, lung and bone diseases.

Definitely, the identification of CACNA1H channels as the biosensors mediating the anti-cancer-specific effects of AM RF EMF presented by Jimenez *et al.* [1] is an important trigger for future basic and clinical research in the benefit of HCC patients.

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Author contribution

Dr. Camacho wrote the commentary.

Conflict of interests

Dr. Camacho has nothing to disclose.

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References

[1] Jimenez H, Wang M, Zimmerman JW, et al. Tumour specific amplitude-modulated radiofrequency electromagnetic fields induce differentiation of hepatocellular carcinoma via targeting Cav3.2 T-type voltage-gated calcium channels and Ca2+ influx. EBioMedicine 2019;44:209–24.
[2] Sharma S, Wu S-Y, Jimenez H, et al. Ca^{2+} and CACNA1H mediate targeted suppression of breast cancer brain metastasis by AM RF EMF. EBioMedicine 2019;44:194–208.
[3] Villanueva A. Hepatocellular carcinoma. N Engl J Med 2019;380:1450–62.
[4] Pardo LA, Stühmer W. The roles of K(+) channels in cancer. Nat Rev Cancer 2014;14:39–48.
[5] Lauren A, Martin-Caraballo M. T-type calcium channels in cancer. Cancers 2019;11:134.
[6] Buckner CA, Buckner AL, Koren SA, Persinger MA, Lafrenie RM. Inhibition of cancer cell growth by exposure to a specific time-varying electromagnetic field involves T-type calcium channels. PLoS One 2015:1–16. https://doi.org/10.1371/journal.pone.0124136.
[7] Neuhaus E, Zirjacks L, Ganser K. Alternating electric fields (TTFields) activate Cav1.2 channels in human glioblastoma cells. Cancers 2019;11:110.
[8] Jimenez H, Blackman C, Lesser G, et al. Use of non-ionizing electromagnetic fields for the treatment of cancer. Front Biosci 2018;23:284–97.
[9] Goldberg P. TheraBionic P1 device receives European regulatory approval. Cancer Lett 2018;44:19.
[10] Zuñiga-García V, Chávez-López MdG, Quintanar-Jurado V, et al. Differential expression of ion channels and transporters during hepatocellular carcinoma development. Dig Dis Sci 2015;60(8):2373–83.