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Radiofrequency ablation for the treatment of HCC – Maybe much more than simple tumor destruction?

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COMMENTARY ON:
Radiofrequency thermal ablation for hepatocellular carcinoma stimulates autologous NK-cell response. Zerbini A, Pilli M, Laccabue D, Pelosi G, Molinari A, Negri E, Cerioni S, Fagnoni F, Soliani P, Ferrari C, Missale G. Gastroenterology, 2010 May;138(5):1931–1942. Eup 2010 Jan 11. Copyright 2010. Abstract reprinted with permission from Elsevier Inc.
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Abstract: Background & Aims: *Radiofrequency thermal ablation (RFA) is a minimally invasive technique used as standard local therapy of hepatocellular carcinoma and second-line treatment for metastatic liver tumors. Studies in preclinical models and in patients have shown that thermal destruction of tumor tissue can enhance anti-tumor cellular responses, but our knowledge of its impact on natural killer (NK) cells is still very limited.*
Methods: *Thirty-seven patients undergoing RFA for hepatocellular carcinoma were studied for peripheral blood lymphocytes counts followed by phenotypic and functional characterization of NK-cell population.*
Results: *Peripheral blood lymphocytes kinetics revealed an increased frequency and absolute number of NK-cells expressing higher levels of activatory along with reduced levels of inhibitory NK receptors, and increased functional NK-cell activity. A prevalent expansion of the CD3(−)CD56(dim) NK subset was observed compared to the CD3(−)CD56(bright) counterpart. Interferon-gamma production, anti-K562 cell-cytotoxicity, and antibody-dependent cell-cytotoxicity, appeared consistently increased in terms of both absolute activity and killing efficiency at 4 weeks after RFA, as compared to baseline. Interestingly, when recurrence-free survival was assessed in two groups of patients separated according to higher vs lower enhancement of cytotoxicity and/or interferon-gamma production, a significant difference was observed, thus suggesting a potential predictive role of NK functional assays on efficacy of RFA.*
Conclusions: *RFA can lead to stimulation of NK-cells with a more differentiated and proactivatory phenotypic profile with general increase of functional activities. This observation may be relevant for development of adjuvant immunotherapeutic strategies aimed at enhancing NK-cell responses against primary and metastatic liver tumors. Copyright 2010 AGA Institute.*

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Radiofrequency thermoablation (RFTA) has become a possible standard of care treatment option for patients with early HCC according to Barcelona Clinic Liver Cancer (BCLC). Recently, much focus has been put on its efficacy and safety in comparison to surgical resection. In a recent report published in Gastroenterology [1], Missale and colleagues describe a new potential mechanism of action occurring in HCC patients undergoing RFTA.

Thirty-seven patients with HCC were treated with RFTA. Phenotype, number, and function of natural killer (NK) cells were analyzed one week before and one and four weeks after ablative therapy. Follow up included three monthly contrast-enhanced ultrasound examinations and six monthly CT scans. In contrast to CD3+, CD4+, CD8+ T cells, and CD19+ B cells, the absolute and relative frequency of CD16+ CD56+ NK-cells increased upon RFTA in HCC patients. Apart from an increase in expression of the activating receptors (NKG2D, CD16, NKp44, and NKp30) as well as a decrease in expression of the inhibitory receptor NKG2A on NK-cells, an enhanced NK mediated cell-cytotoxicity and IFN-γ production was documented in HCC patients four weeks after RFTA. Interestingly, RFTA also increased the capacity of antibody-dependent cell mediated cytotoxicity (ADCC), supporting the idea of a new treatment modality, in which RFTA might be combined with monoclonal antibody based therapies. Finally, the authors present preliminary data suggesting that enhanced NK-cell function after RFTA treatment is associated with improved disease-free survival.

The study by Zerbini et al. touches three very relevant areas, which have increasingly become the focus of mainly preclinical investigations in HCC as well as in tumor immunology in general.

First, this report adds on to the list of different studies demonstrating the relevance of NK-cells in the context of HCC. Previous work has shown that NK-cell function is already impaired in patients with liver cirrhosis supporting the development of progression of HCC. In addition, we have recently shown that frequency and function of NK-cells in HCC patients is impaired

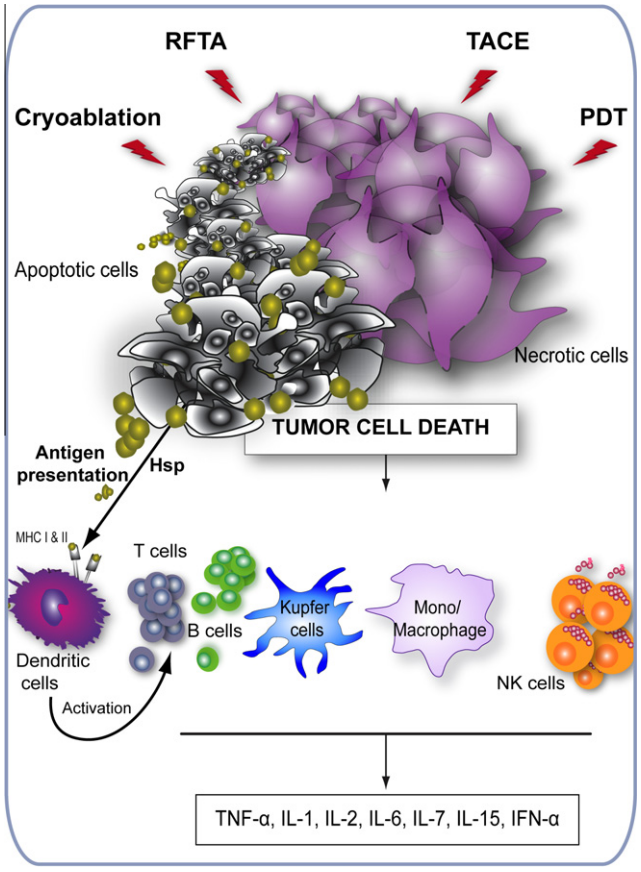

Fig. 1. Local ablative treatment caused by RFTA, cryoablation, TACE, and PDT can cause different types of tumor death. Dying tumor cells lead to the release of antigens, which are presented by heat shock protein-activated dendritic cells, and at the same time different types of immune cells (macrophages/monocytes, T, and NK-cells) become activated in the local environment of the dying tumor.

possibly through an increase of a suppressor cell population called myeloid derived suppressor cells [2]. Moreover, preclinical studies suggest a potential efficacy of NK-cell based immunotherapy for the treatment of HCC.

Most importantly, this study adds to the already existing and currently upcoming literature on the effect of tumor cell death on tumor-specific immune responses [3]. While it was generally believed that apoptotic tumor cell death induces anergy whereas necrotic cells augment inflammation, others and we have shown that not only necrotic tumor cell death can dampen immune responses, but also that apoptotic tumor cell death can mount tumor-specific immune responses *in vivo* [4]. In HCC, tumor destruction can be induced through different mechanisms including RFTA, cryoablation, photodynamic therapy, and transarterial chemoembolization. All these ablative therapies have been shown to have potent effects either directly or indirectly on the adaptive as well as innate immune response. Apart from activation of NK-cell function as shown in the study by Zerbini et al., there is strong preclinical data demonstrating that RFTA leads to release of tumor antigens and attracts dendritic cells into tumor draining lymph nodes. It should be noted that others have also reported RFTA dependent changes in the function of antigen-presentation as well as T cell responses (Fig. 1).

Currently, it is not clear what type of ablative therapy induces the most potent immune responses *in vivo*. Induction of anti-tumor immune responses have been observed in preclinical mouse models after RFTA, PDT, and cryotherapy [5,6]. Sporadic remission of tumor metastasis distant from ablated tumors has also been observed in preclinical models after RFTA treatment of patients with prostate cancer, cryoablative therapy (colon cancer), and HCC patients treated with PDT and TACE. However, more work is clearly needed in this area to understand the exact mechanisms involved in the induction and enhancement of immune responses upon different types of ablative therapies.

Finally, this study has addressed the interesting area of combining immune based therapies with other types of HCC treatment. Targeted therapies have shown limited success in patients with advanced disease and relapse rates are still too high in patients with potential curable disease. Therefore, new treatment strategies are needed and the combination of interventional therapies with immune based therapies represents one choice. While progress has already been achieved in preclinical murine studies using dendritic cell based approaches [7], there is currently one clinical trial investigating the effect of the adoptive transfer of *ex vivo* activated PBMC in combination with TACE. Well-designed future clinical trials in HCC patients will help broaden our understanding of immunological mechanisms in HCC, which include the interplay between the tumor and the immune system. This will also help in identifying the effects of non-immune based therapies on tumor-specific immune responses as well immune suppressor mechanisms in HCC.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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