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Mostafa Ghanei, Majid Shohrati & Amin Saburi

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The new aspects of immunotherapy in prostate cancer

Mostafa Ghanei · Majid Shohrati · Amin Saburi

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Dear Editors,

We read with a great interest your recently published paper on immunotherapeutic approaches to prostate cancer treatment [1]. Rigamonti and Bellone discussed interactions between the immune system and the prostate tumor and mechanisms of tumor escape. They also discussed immune-based medications and reviewed immunosuppressive mechanisms of the neoplasm, but they did discuss one of the most interesting mechanisms which have been recently considered, namely Gc protein and Gc protein-derived macrophage activating factor (Gc-MAF).

Serum Gc protein is necessary for macrophage activation. It is also known as vitamin D (3)-binding protein and is deactivated by an enzyme produced by cancer cells. If this macrophage activating factor (MAF) is present in sufficient amounts, it can activate macrophages to attack cancerous tissue. Serum Gc protein, as a precursor of MAF, is activated via glycosylation by beta-galactosidase and sialidase produced by lymphocytes. Neoplastic cells and cells infected with HIV can also produce an enzyme, alpha-N-acetylgalactosaminidase (NaGalase), which can deglycosylate

macrophages [2]. Therefore, macrophages of patients with neoplasms such as prostate cancer cannot be activated, leading to immunosuppression. Gc protein can be activated by beta-galactosidase and sialidase synthetically (termed Gc-MAF) which has been effectively and safely used in cancer patients. Receptors which can recognize the malignant abnormality were present on macrophages activated by GcMAF and induce their tumoricidal activity.

In the only report on prostate cancer in this context, 16 patients received 100 ng of Gc-MAF weekly. After 14–25 weeks, all 16 patients had very low serum NaGalase levels reflecting the decreased tumor burden, and there was no recurrence for 7 years [3]. GC-MAF has also been used effectively for treating other neoplastic disorders such as colorectal and breast cancer [4, 5]. However, there are three challenging issues here:

1. How can we monitor the tumoricidal efficacy of Gc-MAF up? Previous reports evaluated the anti-neoplastic efficacy of chemotherapy via survival and quality of life, but it seems that this is not enough at least for low grade tumors. Serum levels of NaGalase could potentially be the best marker of tumor burden but in HIV-infected patients at least, it may present false-positive responses [5, 6].
2. How long should Gc-MAF be administered? Yamamoto et al. [7] demonstrated that “4 days after GcMAF-primed immunization of mice with heat-killed Ehrlich ascites tumour cells, the ascites tumour was no longer transplantable in these mice”. Regarding the half-life of the activated macrophages (about 6 days), interval of Gc-MAF administration should be a week. Duration of drug administration in patients with colon cancer was 50 weeks, prostate cancer 25 weeks, and breast cancer 22 weeks [5].

This Letter to the Editors comments on the review article *Prostate cancer, tumor immunity and a renewed sense of optimism in immunotherapy* by Nicolò Rigamonti and Matteo Bellone (Cancer Immunol Immunother. 61:453–468, 2012). The authors of the review article have responded to this letter (see Bellone and Rigamonti, Cancer Immunol Immunother. 2012).

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3. Which patients are the best candidates to receive Gc-MAF? Regarding the role of NaGalase in inactivating Gc protein, if Gc-MAF is administered when the serum NaGalase level is at its lowest, the drug would be more effective. Therefore, patients after radiotherapy, initial chemotherapy, or surgical debulking might benefit most [6]. Therefore, there is a necessary period of time (1 week) before administration of Gc-MAF for the generation of new macrophages after chemotherapy. Moreover, it was reported that “Heparin inhibited the stimulatory effect of GcMAF” and patients who receive heparin have a worse response to Gc-MAF therapy [8]. A Gc-MAF benefit not yet much considered is its effect on angiogenesis. Kanda et al. demonstrated that Gc-MAF can inhibit the process of chemotaxis, endothelial cell proliferation, and tube formation, all stimulated by fibroblast growth factor-2 (FGF-2), angiopoietin 2, and vascular endothelial growth factor-A (VEGF-A) [8–10].

Finally, it is known that “antiangiogenic activity of GcMAF was mediated through the CD36 receptor” [10]. C3 antigen generated by macrophages exposed to MAF shows tumoricidal activity [11]. Therefore, these biomarkers could be valuable predictors for monitoring the response to Gc-MAF treatment. It seems that Gc-MAF therapy might improve the treatment of cancer lacking other effective treatment as yet.

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