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Short Communication Open Access

Improving Anti-cancer Immunotherapy by Simultaneous Targeting Suppressive Tumor Microenvironment

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Abstract

Recent advances in immunotherapy led to a breakthrough in cancer treatment, changing the algorithms of clinical cancer management. Notwithstanding this success, numerous immune escape mechanisms significantly hamper the long-term efficacy of immunotherapy. A growing body of evidence recognizes immunosuppressive tumor microenvironment (TME) as a major obstacle for effective anti-cancer immunotherapy. It is therefore postulated that multiple pathways in TME need to be targeted in support to the induction of tumor-specific effector immune cells. Our lab has developed a novel mRNA vaccination platform allowing for induction of strong anti-tumor immune responses in the context of cervical cancer. In our recent study, using a variety of *in vivo* and *ex vivo* techniques, we observed the existence of organ-specific microenvironments that differed in their immunosuppressive capacity. We demonstrated that the particularly hostile nature of genital tract TME could be alleviated using cisplatin. This data indicated that the induction of tumor-specific T cells accompanied by a simultaneous targeting of TME is a prerequisite for the improvement of adaptive anti-cancer immunotherapies, thereby emphasizing the need for a TME-tailored immunotherapy.

Keywords: Tumor microenvironment; Personalized immunotherapy; mRNA vaccine; Cisplatin

Short Communication

The latest analyses of clinical success rates for drug development indicate a significant divergence between R&D expenses and new drug approvals. While anti-cancer drugs constitute a large majority of drug development paths, the 'Likelihood of Approval' rate for oncology (6.7%) is the lowest amongst all tested conditions [1]. One of the reasons for this *status quo* can be a limited predictive value of currently used animal models, particularly in the context of interactions between the host immune system and cancer cells. This can partly be due to the fact that traditionally the role of the host immune system was deemphasized giving the priority to the tumor cells [2]. As a consequence, for years the accurate recapitulation of the tumor microenvironment (TME) was underappreciated, disregarding the immune contexture as a powerful contributor to tumorigenesis [3]. Over decades, ectopically implanted tumor cell lines in syngeneic mice served as an universal model for anti-cancer drug evaluation [4]. Although such approach offered a unique possibility of *in vivo* therapy in the context of a fully functional immune system, the impact of the primary, orthotopic tumor location, and thus relevant microenvironment, was largely neglected. Only a few groups took the effort to compare the ectopic and orthotopic tumors side by side, but their groundbreaking findings did not reach the mainstream of anti-cancer research. For instance, it has been demonstrated that renal, colon and prostate tumors respond to immunotherapy to a much lesser extent in the orthotopic setting compared to the subcutaneous location [5]. In analogy, renal carcinoma cells were described to be more resistant to treatment with doxorubicin when inoculated into kidneys compared to subcutaneous tumors [6]. The even more detailed study by Wilmanns et al. demonstrated different drug sensitivity of murine colon carcinoma cells growing at different anatomical locations. The authors proved that these differences were due to organ-specific environmental factors and were not associated with obstacles in drug distribution [7]. It is now increasingly accepted that cancer cells come into a close interaction with surrounding extracellular matrix, stromal cells and immune cells. These interactions determine the susceptibility of tumors to therapies [8]. Therefore, acknowledging the influence of TME on the therapeutic response, the idea of a TME-tailored immunotherapy has been brought up in recent years [9,10].

Previous data from our laboratory demonstrated that intranodal immunization with TriMix mRNA accompanied by mRNA coding for tumor-associated antigens induces strong antigen-specific immune responses, leading to a complete rejection of subcutaneous tumors [11]. The goal of our current study was to verify to what extent TME affects the therapeutic outcomes of the mRNA-based immunotherapy against the TC-1 tumor model [12]. In our initial evaluation we screened the TME of differently located tumor lesions i.e. subcutaneous, in the genital tract and in the lungs. Using flow cytometry we observed major differences in the TME amongst the analyzed tumor locations, particularly with regard to myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). Paralleling our *ex vivo* flow cytometric data, we observed that the *in vivo* efficacy of the E7-TriMix vaccine was the most limited in the genital tract. As synergy between chemotherapy and cancer vaccination is being increasingly emphasized, we addressed the possibility of combinatory therapy with E7-TriMix mRNA and cisplatin [13]. We observed a dramatic improvement in the quality of life of the treated mice during the course of the experiment, followed by a complete rejection of genitally located tumor lesions. Flow cytometric analysis revealed a significant reduction in the numbers of tumor-infiltrating

immunosuppressive cells upon combinatory therapy. Importantly, we did not observe any effect of cisplatin on the numbers of splenic Tregs and MDSCs. Although its exact mode of action still remains to be elucidated, cisplatin is thought to modulate the immune system via several different mechanisms, including upregulation of MHC I, recruitment and proliferation of effector cells, improved lytic capacity of cytotoxic effector cells and elimination of suppressive immune cells [14]. More clinical studies will be needed to further address the question whether this holds true also for human setting.

Development of modern combination strategies will require a deep insight into the processes that promote tumor progression in individual patients. We postulate that it is of crucial importance, already at the level of pre-clinical research, to identify the tissue-specific signatures of tumor lesions in order to design appropriate multi-target therapies and maximize anti-tumor immune responses. Our findings suggest that defining tumor immune contexture may, besides its undoubtful predictive value, be a guide for a rational, personalized therapy design. To this aim serial tumor biopsies seem to be a necessity. The feasibility of such an approach has recently been demonstrated by several groups [15,16]. Our findings are in line with the revisited paradigm of personalized medicine postulating that therapy will not only be patient-tailored, but also organ-specific [17]. Lastly, none of the current cancer models is able to fully recapitulate the complexity of human disease. We believe that better knowledge of these limitations and cautious choosing of research models according to the fit-for-purpose rule will strengthen the credibility and improve the translational value of pre-clinical research.

References

1. Hay M, Thomas DW, Craighead JL, Economides C, Rosenthal J (2014) Clinical development success rates for investigational drugs. Nat Biotechnol 32: 40-51.
2. Sanmamed MF, Chester C, Melero I, Kohrt H (2016) Defining the optimal murine models to investigate immune checkpoint blockers and their combination with other immunotherapies. Ann Oncol mdw041.
3. Junttila MR, de Sauvage FJ (2013) Influence of tumour micro-environment heterogeneity on therapeutic response. Nature 501: 346-354.
4. Dranoff G (2011) Experimental mouse tumour models: what can be learnt about human cancer immunology? Nat Rev Immunol 12: 61-66.
5. Devaud C, Westwood JA, John LB, Flynn JK, Paquet-Fifield S, et al. (2014) Tissues in different anatomical sites can sculpt and vary the tumor microenvironment to affect responses to therapy. Mol Ther 22:18-27.
6. Ahn KS, Jung YS, Kim J, Lee H, Yoon SS (2001) Behavior of murine renal carcinoma cells grown in ectopic or orthotopic sites in syngeneic mice. Tumour Biol 22: 146-153.
7. Wilmanns C, Fan D, O'Brian CA, Bucana CD, Fidler IJ (1992) Orthotopic and ectopic organ environments differentially influence the sensitivity of murine colon carcinoma cells to doxorubicin and 5-fluorouracil. Int J Cancer 52: 98-104.
8. Meads MB, Gatenby RA, Dalton WS (2009) Environment-mediated drug resistance: a major contributor to minimal residual disease. Nat Rev Cancer 9: 665-674.
9. Smyth MJ, Ngiow SF, Ribas A, Teng MW (2016) Combination cancer immunotherapies tailored to the tumour microenvironment. Nat Rev Clin Oncol 13: 143-158.
10. Van der Jeught K, Bialkowski L, Daszkiewicz L, Broos K, Goyvaerts C, et al. (2015) Targeting the tumor microenvironment to enhance antitumor immune responses. Oncotarget 6: 1359-1381.
11. Van Lint S, Goyvaerts C, Maenhout S, Goethals L, Disy A, et al. (2012) Preclinical evaluation of TriMix and antigen mRNA-based antitumor therapy. Cancer Res 72: 1661-1671.
12. Bialkowski L, van Weijnen A, Van der Jeught K, Renmans D, Daszkiewicz L, et al. (2016) Intralymphatic mRNA vaccine induces CD8 T-cell responses that inhibit the growth of mucosally located tumours. Sci Rep 6: 22509.
13. van der Sluis TC, van der Burg SH, Melief CJ (2015) Synergy between chemotherapy and cancer vaccination. Aging (Albany NY) 7: 340-341.
14. de Biasi AR, Villena-Vargas J, Adusumilli PS (2014) Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. Clin Cancer Res 20: 5384-5391.
15. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, et al. (2011) Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 3: 75ra26.
16. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ et al. (2014) PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature 515: 568-571.
17. Klein-Goldberg A, Maman S, Witz IP (2014) The role played by the microenvironment in site-specific metastasis. Cancer Lett 352: 54-58.