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EDITORIAL

STING-targeted PET imaging: unveiling tumor immunogenicity post-chemotherapy in colorectal cancer

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Colorectal cancer (CRC) stands as a formidable global health challenge, necessitating innovative approaches to augment treatment efficacy. As the third leading cause of cancer death globally, CRC brings about 1.85 million cases and 850,000 deaths per year [1]. The landscape of cancer treatment has been revolutionized by the advent of immunotherapy over the past decades. However, the success of immunotherapy is not universal, particularly in colorectal cancer (CRC), where the objective clinical efficiency of anti-PD-1/PD-L1 therapy remains under 20% [2]. The central predicament is limited responsiveness to immunotherapies. Specifically, CRC tumors include large numbers of immunosuppressive leukocytes (e.g. regulatory T cells, tumor-associated macrophages) and significant production of immune-dampening signals (e.g. IL-10, TGF-β, IDO-1), which restrains the immune responses [3]. By increasing tumor immunogenicity, several combined therapies such as cytokine or targeted therapies show promise in promoting anti-cancer efficiency [4].

Notably, chemotherapy has been a mainstay in CRC treatment. More importantly, chemotherapy has been shown to enhance tumor immunogenicity by promoting tumor-associated antigen expression and releasing damage-associated molecular patterns [5, 6]. However, the effectiveness of chemotherapy in converting "cold" tumors into "hot" ones, which are more responsive to immunotherapy, varies widely [7]. The strategies to predict and assess this conversion at the early stage of immunity are of paramount importance. Currently, several activated T-cell biomarkers (e.g., OX40, T cell inducible co-stimulatory molecules) have been applied to assess changes of tumor immunogenicity [8, 9] via PET-CT imaging. Nevertheless, the T-cell activation generally happens at the late stage, as it fails to detect the initiation or conversion of the immune response.

STING (Stimulator of Interferon Genes) agonists can activate the STING signaling pathway, promoting the body's immune response against cancer [10]. The STING pathway is a critical component of the body's innate immune system, responsible for recognizing and responding to viral infections and cellular damage. Activation of the STING pathway triggers an inflammatory response and prompts the immune system to attack tumor cells, thereby inhibiting tumor growth and metastasis. Therefore, STING agonists are considered promising anti-cancer drugs and may serve as a key component of cancer immunotherapy [11]. With targeted and sensitive probes, PET imaging is able to detect changes of tumor immunogenicity over a certain period. Hence, STING-targeted PET imaging shows great potential for monitoring the early variation of tumor immunogenicity. In a groundbreaking study published in the "European Journal of Nuclear Medicine and Molecular Imaging", Dan Li and co-investigates developed a novel methodology for

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monitoring early alterations in tumor immunogenicity post-chemotherapy [12]. Employing a state-of-the-art PET tracer targeting the stimulator of interferon genes (STING) protein [^{18}F]FBTA, this research holds the potential to revolutionize the optimization of chemotherapy regimens and enhances the effectiveness of combined chemotherapy and immunotherapy in CRC.

This study aims to assess the potential application of a novel PET tracer [^{18}F]FBTA, in evaluating the immunogenicity of colorectal cancer (CRC) patients after chemotherapy. Compared to conventional [^{18}F]FDG, [^{18}F]FBTA exhibits higher specificity and sensitivity, enabling the earlier detection of changes in tumor immune activity. The research findings indicate that [^{18}F]FBTA accurately reflects the impact of different chemotherapeutic agents (oxaliplatin and cisplatin) and doses of chemotherapy on the immune activity of CRC tumors. Particularly, CRC patients treated with cisplatin show higher tumor uptake. Furthermore, the selective uptake of [^{18}F]FBTA by immune cells provides a significant advantage in assessing tumor immune activity after chemotherapy. In conclusion, [^{18}F]FBTA holds promise as a reliable clinical tool for guiding treatment decisions in CRC patients and facilitating the combination of immunotherapy with chemotherapy.

In this work, the [^{18}F]FBTA tracer has been evaluated to monitor the effects of oxaliplatin (OXA) and cisplatin (CDDP) on colorectal cancer (CRC). The uptake of [^{18}F]FBTA in CRC tumors treated with CDDP was significantly higher than that in tumors treated with OXA, indicating the differential effects of chemotherapy drugs on tumor immunogenicity. Specifically, the tumor uptake at 1 h post-injection was 3.09 ± 0.25%ID/g and 4.01 ± 0.18%ID/g for the OXA and CDDP groups, respectively, and [^{18}F]FBTA uptake reached 3.29 ± 0.15%ID/g and 4.08 ± 0.11%ID/g at 2 h post-injection. These results showed that the CDDP group exhibited significantly higher uptake than the OXA group at both time points. Immunohistochemical staining further confirmed this, demonstrating a significant increase in STING expression in tumors treated with both OXA and CDDP, with the most pronounced increase observed in tumors treated with CDDP. The PET-derived tumor uptake values were closely correlated with STING immunohistochemical scores, with correlation coefficients of 0.8827 and 0.9064, respectively. Additionally, biodistribution studies showed no significant uptake changes in major organs between the OXA and CDDP groups compared to the control group, indicating the specific targeting of [^{18}F]FBTA to tumor tissue. Importantly, [^{18}F]FBTA PET imaging detected changes in tumor immunogenicity before visible changes in tumor size, highlighting its potential for early detection and monitoring of treatment response.

Moreover, the study further validated the specificity of the STING-targeted radiotracer by co-injecting [^{18}F]FBTA (11.1–14.8 MBP) with or without [^{19}F]FBTA (50 μg per animal) to CT26 tumor-bearing mice in the CDDP-treated group (2.5 mg/kg). The CDDP@Block group (1 h: 1.04 ± 0.05%ID/g; 2 h: 0.79 ± 0.02%ID/g) demonstrated a significantly lower tumor uptake and tumor-to-muscle ratio (1 h: 1.44 ± 0.69; 2 h: 1.01 ± 0.35) 1 and 2 h after injection. The PET imaging results were in good agreement with the biodistribution data, which revealed no appreciable changes in uptake in the main organs and tissue. Tumor uptakes at 3 h after injection were 3.72 ± 0.40%ID/g for the CDDP group and [^{19}F]FBTA blocked CDDP group. This is mostly because STING-targeted cells are absorbed when treated with CDDP, which increases the number of DCs and macrophages. The findings above are consistent with the possible use of [^{18}F]FBTA to evaluate variations in tumor immunogenicity brought forth by different chemotherapy treatments.

Previous studies aimed to develop a novel ^{18}F-labeled agonist, dimeric amidobenzimidazole (diABZI), and firstly evaluate the feasibility of non-invasive positron emission tomography (PET) imaging of STING expression in tumor microenvironments [13]. These strategies have demonstrated potential in preclinical and clinical contexts through increased patient survival rates [14]. In the current study, Dan Li's featurely investigates the impact of CDDP dosages on immunogenicity, revealing the importance of dose selection in chemotherapeutic regimens. The comparison between medium-dose (CDDP-MD) and low-dose (CDDP-LD) therapies highlights the subtle effects of different dosages on immune cell recruitment. Both CDDP-LD and CDDP-MD treatments significantly increased dendritic cell (DC) and macrophage infiltration in tumors compared to controls. Notably, CDDP-MD induced higher DC and macrophage infiltration than CDDP-LD. The quantitative analysis of MFI showed elevated STING, CD11c, and F4/80 levels post-treatment, especially in the CDDP-MD group. The ramifications of this study go beyond the fields of imaging and diagnosis. They explore the area of therapeutic decision-making and provide a possible framework for doctors to customize chemotherapy treatments. Opportunities to improve treatment outcomes arise from the capacity to select drugs and doses according to their immunogenic influence.

[^{18}F]FDG is the most commonly used PET tracer for cancer imaging and is essential to clinical practice. In order to fully assess the potential clinical usefulness of the novel tracer, it is imperative to compare [^{18}F]FBTA and [^{18}F]FDG while imaging the immunogenicity of CRC patients. Clinically, it takes a few weeks following treatment to notice a decrease in [^{18}F]FDG uptake. Lower expression of GLUT-1 was associated with decreased absorption of [^{18}F]FDG [15].

GLUT-1 expression, however, did not change throughout the early stages of chemotherapy [16]. Immune cells are brought into the tumor by chemotherapy, and these cells have a high [^{18}F]FDG absorption rate. The complex changes in the early stages of chemotherapy may result in a mutual counteraction between tumor cells and immune cells regarding the uptake of [^{18}F]FDG, making it difficult to distinguish between them in a clinical setting. In contrast, [^{18}F]FBTA is primarily taken up by immune cells, with a notable increase in uptake rates corresponding to the augmented presence of immune cells. Given that the uptake of [^{18}F]FDG in normal organs and non-target tissues is significantly higher than that of [^{18}F]FBTA, this further underscores the promising clinical translational potential of [^{18}F]FBTA. Additionally, no significant correlation was observed between [^{18}F]FDG uptake and the use of oxaliplatin/cisplatin treatment; conversely, [^{18}F]FBTA demonstrated specificity for tumor immunogenicity. Clearly, [^{18}F]FBTA exhibits higher specificity than [^{18}F]FDG in tracing tumor immunogenicity. This research signifies a substantial stride towards advancing precision oncology for CRC. The [^{18}F]FBTA PET tracer introduces a new era of early immunogenicity monitoring, offering clinicians a valuable tool to navigate the complexities of treatment selection and optimization. As we stand on the cusp of a new frontier in cancer care, the integration of STING-targeted imaging.

In conclusion, the [^{18}F]FBTA tracer represents a significant advancement in precision oncology for CRC. It offers a valuable tool for early immunogenicity monitoring and could lead to a paradigm shift in chemotherapy and immunotherapy for colorectal cancer.

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Declarations

Conflict of interest Weibo Cai declares conflict of interest with the following corporations: Actithera, Inc., Rad Source Technologies, Inc., Portrai, Inc., rTR Technovation Corporation, and Four Health Global Pharmaceuticals Inc. All other authors declare no conflict of interest.

Studies with human participants or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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