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Paclitaxel, interferons and functional reprogramming of tumor-associated macrophages in optimized chemo-immunotherapy

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ABSTRACT

Immune checkpoint inhibition (ICI) targeting programmed cell death protein-1 (PD1) prevents the elimination of activated cytotoxic T lymphocytes (CTLs) by programmed death-ligand 1/2-expressing cancer and myeloid cells in the tumor microenvironment (TME). ICI has shown its effectiveness in many solid tumors, but it lacks activity against "cold" tumors which lack CTL infiltration, including most of the colon, prostate, lung and breast cancers. Metastatic triple-negative breast cancer (TNBC) responds to PD-1 blockade only in 5–20% cases. Chemotherapy has been shown to have a PD1-sensitizing effect in a fraction of patients with TNBC but the underlying mechanism and the reasoning behind its limitation to only a subset of patients are unknown. Recent data demonstrate the key roles played by paclitaxel-driven Toll-like receptor 4 (TLR4) signaling and the resulting activation of type-1 and type-2 interferon pathways in tumor-associated macrophages, resulting in local M2 to M1 transition and enhanced tumor antigen cross-presentation, in the paclitaxel-driven sensitization of "cold" tumors to ICI. These data and the known ability of the TLR4-activated MyD88-NFκB pathway to mobilize both antitumor and tumor-promoting events in the TME provide new tools to enhance the efficacy of chemo-immunotherapy for metastatic, and potentially early, TNBC and other taxane-sensitive cancers.

Programmed cell death protein-1 (PD1)-programmed death-ligand 1 (PDL1)/PDL2 immune checkpoint inhibition (ICI) therapies, which prevent the apoptotic death of activated effector T cells in the tumor microenvironments (TMEs) have been the game-changers in the clinical management of advanced (and increasingly early-stage) solid tumors, but their efficacy in several common cancers, such as lung, colon, prostate and breast cancers remain limited to patients with highly cytotoxic T lymphocyte (CTL)-infiltrated and more immunogenic tumors. Triple-negative breast cancer (TNBC), representing 10–20% of all breast cancers, lacks estrogen and progesterone receptors and HER2, showing a particularly aggressive character. However, TNBC has a limited yet significant sensitivity to PD-1-blocking ICIs, which led to their Food and Drug Administration approval based on KEYNOTE 355 findings.[1] The fraction of patients with metastatic TNBC benefitting from PD-1/PD-L1 blockade is limited to about 5% overall, which increases to 19–23% in patients with PD-L1-positive TME.[2] In TNBC, PD1-blockade is currently approved in combination with chemotherapy, including taxanes and gemcitabine–carboplatin, which enhances the overall population response rate to over 20%, but the mechanism of synergistic action between these agents remains unclear, making it difficult to target the relevant stimulatory and/or suppressive pathways to enhance the effectiveness of the paclitaxel-based and ICI-based chemo-immunotherapy.

KEY ROLE OF TLR4 IN PACLITAXEL-MOBILIZED CANCER IMMUNITY: A DOUBLE-EDGED SWORD

Paclitaxel is a tubulin-binding inhibitor of mitosis with complex positive and negative effects on the immune system. In addition to its direct killing of cancer cells, paclitaxel has been reported to be able to both enhance and suppress the killer function of T and natural killer (NK) cells, inhibit the antibody production by B cells, and enhance the expression of costimulatory molecules and cytokines in antigen-presenting cells, such as tumor-associated macrophages (TAMs) or dendritic cells (DCs).[3] The enhanced CTL function may result from the ability of paclitaxel to reduce the accumulation and function of myeloid-derived suppressor cells (MDSCs).[4] However, paclitaxel also induces MDSC attractants CXCL8/IL-8 and CXCL12/SDF-1, the chemokines correlated with poor outcomes.[5–7] These heterologous immunomodulatory effects, involve its ability

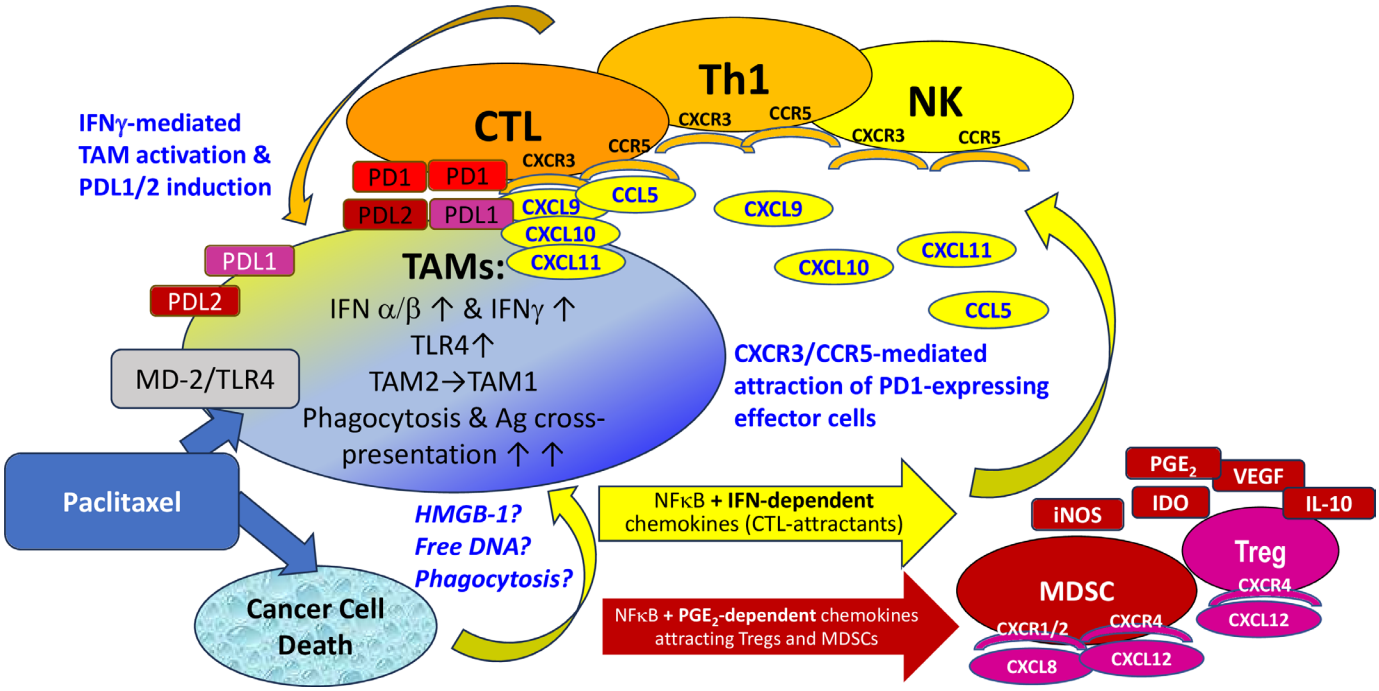

Figure 1 Paclitaxel binds to the MD-2 in an LPS-like manner, directly activating the TLR4/TRIF/IRF3 signaling pathway, leading to the activation of type-1 IFN pathway in intratumoral myeloid cells and induction of CTL, Th1, and NK cell-attracting chemokines (CXCL9/MIG, CXCL10/IP10 and CXCL11/ITAC; ligands for CXCR3; and CCL5/RANTES, ligand for CCR5) in the tumor microenvironment (TME). It also promotes local macrophage conversion from M2 to M1 phenotype (a process likely to include multiple intermediate forms of macrophages), enhancing antigen cross-presentation and CTL-mediated tumor-specific immunity. However, paclitaxel/TLR4-activated parallel MyD88 signaling also mobilizes the NFκB pathway, which activates the tumor-promoting COX2/PGE_2 pathway, which can enhance cancer cell survival, vascularization and metastatic potential. The COX2/PGE_2-dependent suppressive factors such as IL-10, IDO, or VEGF, and chemokines CXCL12/SDF1 and CCL22/MDC, which attract myeloid-derived suppressor cells (MDSC) and T-regulatory cells (Tregs), undermine the immunostimulatory effects of paclitaxel by promoting local immunosuppression. Paclitaxel-induced cancer cell death and release of additional activators of the TLR4/MyD88 and STING/IRF3/IFN pathways result in additional mobilization of both the immunostimulatory/antitumor and suppressive/tumor-promoting effects. The paper of Choi and colleagues in a recent issue of JITC[21] demonstrates the prognostic role of the intratumoral activation of type 1 (IFNα/β) and type-2 (IFNγ) pathways in paclitaxel-driven sensitization of TNBC to antitumor effectiveness of PD1 blockade and the key role of TLR4-dependent M2 and M1 reprogramming in this regard. These considerations provide direct rationale for recalibrating the balance between the TLR4/MyD88- and STING/IRF3/IFN pathways in paclitaxel-treated tumors, helping to design improved modalities of chemo-immunotherapy involving taxanes and potentially other chemotherapeutic agents. IFNγ, interferon-gamma; IL-10, interleukin 10; LPS, lipopolysaccharide; NK, natural killer; PD-L1, programmed death-ligand 1; TAM, tumor-associated macrophage; Th1, T helper 1 cells; TLR4, Toll-like receptor 4; TNBC, triple-negative breast cancer.

to promote IκB degradation and activation of a pleiotropic mediator of inflammation, NFκB.[8]

Toll-like receptor 4 (TLR4) is a pattern-recognition receptor expressed both on cancer cells as well as on stromal and immune cells, especially monocytes, macrophages, DCs and NK cells.[9–11] TLR4 is known to activate both the NFκB/general inflammatory pathway and the TRIF/IRF3-mediated type-1 interferon (IFN) induction pathway, in response to bacterial lipopolysaccharide (LPS),[12] but it has emerged as the central player in the immunomodulatory activities of paclitaxel. Paclitaxel binds to the TLR4-accessory molecule, MD-2 showing an LPS-like TLR4/MyD88-mediated impact on myeloid cells,[13] but its TLR4-mimetic activity may also involve additional indirect pathways, activated by immunogenic cell death (ICD) and factors released from dying cancer cells[14 15] (see figure 1).

The TLR4-driven inflammation can undermine paclitaxel's efficacy and contribute to disease progression and metastatic dissemination of TLR4-positive tumors,[16–18] in a mechanism involving NF-kB-mediated transcription of inflammatory and prosurvival genes.[17] However, TLR4 is also key to multiple proimmunogenic activities of paclitaxel, including the reprogramming of TAMs from the suppressive M2 to a stimulatory M1 status, essential for its overall antitumor effects.[19] Paclitaxel induces ICD in ovarian cancer cells via TLR4/IKK2/SNARE-dependent exocytosis.[14] TLR4 signaling has been shown to support the survival, proliferation, production of type-1 effector cytokines and cytotoxic function of NK cells as well as B cell proliferation and antibody production.[11 20] These divergent effects of the TLR4-mediated impact on cancer immunity appear to be driven by different signaling pathways (including NFκB and TRIF/IRF3)

and different cellular targets, but the molecular pathways mediating these separate effects have not been fully understood, limiting the feasibility of their therapeutic targeting.

The study by Choi and colleagues in a recent issue of JITC[21] helps to address this problem by highlighting the key role of type-1 and type-2 IFN signaling in the TME in identifying the patients with TNBC who benefit from the combination of paclitaxel and PD-1 blockade from those who do not, and showing the importance of the TLR4-dependent M2 to M1 conversion for the antitumor activity of paclitaxel/PD1 combination in mouse TNBC models.

The authors show the TLR4-dependent ability of paclitaxel to enhance the cross-presentation of tumor-derived antigens by macrophages. Paclitaxel activated the TLR4-dependent cross-presentation and T cell stimulatory function in the nominally immunosuppressive TAMs, improving the $CD8^+$ T-cell mediated responses. Within the TME, TLR4 expression was the highest among macrophages and the TLR4 expression and the IFNα and IFNγ signaling pathways were significantly upregulated in TAMs from patients with TNBC who responded to paclitaxel, compared with the patients who did not. Paclitaxel-driven mobilization of the major histocompatibility complex (MHC) class I antigen-loading machinery, phagocytosis and tumor antigen cross-presentation leading to higher IFNγ production in $CD8^+$ T cells, all required TLR4. Compared with TAMs, local DCs showed lower TLR4 expression and did not increase MHC class I and CD86 levels after paclitaxel administration, indicating that TAMs represent the key target. Paclitaxel enhanced the antitumor activity of PD-1 blockade, only in wild-type, but not TLR4-knockout animals.[16] These observations highlight the primary role of TAM modulation and the resulting enhancement of tumor-specific CTL responses as the main mechanism of PD-1-sensitizing activity of paclitaxel.

ACTIVATION OF THE TLR4/MYD88 PATHWAY BY PACLITAXEL: DIRECT AND INDIRECT MECHANISMS

Taxanes directly bind to MD-2/TLR4 complex,[22] resulting in their LPS-like TLR4/MyD88-mediated activation of myeloid cells.[13] However, it remains to be tested to what extent, endogenous TLR4 ligands released from paclitaxel-killed cancer cells, such as HMGB1, contribute to the TLR4-dependent immunomodulatory effects. HMGB, a ligand for TLR4 (and RAGE) released from chemotherapy-killed cancer cells is key to its effectiveness.[15 23–25] Paclitaxel-mobilized HMGB1, TLR4 and RAGE, are all involved in NFκB-mediated paclitaxel-triggered neuropathic pain,[5 25–28] suggesting a contribution of this pathway also to immune modulation. TLR4 and NFκB-inducible[29 30] cyclooxygenases and their key product, PGE2, a known pain mediator, are also likely to be involved.[31 32]

ENHANCING THE TRIF/IRF3/IFNα/β PATHWAY IN PACLITAXEL-TREATED TUMORS: OPPORTUNITIES TO ENHANCE THE EFFECTS OF PD1 BLOCKADE

Apart from the direct TLR4/TRIF/IRF3 pathway, paclitaxel can also (and more effectively) induce the IFNα/β-mediated response indirectly, acting by cGAS/STING/IRF3 pathway, activated by the DNA released from cancer cells.[33 34] In addition to the cGAS/STING/IRF3/IFNα/β pathway, which drives the induction of CTL/Th1/NK cell-attracting chemokines CXCL9/10/11 and CCL5, paclitaxel treatment involves the induction of the NFκB-dependent and PGE_2-dependent[30 35] chemokine SDF1/CXCL12.[5] Since intratumoral SDF1/CXCL12 attracts Tregs and MDSCs, promotes angiogenesis, TNBC progression, resistance to apoptosis,[36] and predicts failure of paclitaxel-based neoadjuvant chemotherapy,[7] these considerations provide rationale for rebalancing the ratio between IRF3/IFNα/β pathway and TLR4/MyD88/NFκB pathways in patients receiving paclitaxel/ICI therapies.

Similar to paclitaxel, both the IRF3-IFNα/β pathway and the NFκB/PGE_2 pathway are also triggered by double-stranded (ds) RNA viruses or stable forms of dsRNA, such as poly-IC.[29 30] While the NFκB pathway may enhance the IFNα/β-dependent induction of CXCL9, CXCL10 and CCL5, it is also the key factor in the PGE_2-dependent induction of Treg attractants CXCL12 and CCL22, and suppressive IL10, IDO and NOS2.[29 30] The use of non-NFκB-activating versions of dsRNA, such as rintatolimod, or blocking the NFκB-induced PGE_2 pathway, enhances the selective CTL attraction, without suppressive cells.[30]

Taxanes are known to induce COX2 expression and PGE_2 synthesis in breast and other cancers,[31] and many of these MDSC/Treg-attracting chemokines and suppressive factors are dependent on the COX2/PGE_2 induction in the TME and local myeloid cells.[30 35 37] Therefore, it remains to be tested if the effects of paclitaxel can be enhanced by interference with each of these factors individually, or potentially by targeting the COX2/PGE_2/EP2-EP4 pathway in NFκB signaling involved in COX2 induction and shown to interfere with taxanes' activities in other cancers.[38] We have recently shown that the combination of IFNα with poly-IC (or its destabilized analog, rintatolimod) selectively enhances intratumoral production of CTL/Th1/NK cell attractants while suppressing Treg attraction in vitro[29 30] and in the TME of patients with TNBC,[39] by targeting not only cancer cells, but also TME-associated fibroblasts and myeloid cells.[29] The additional inclusion of COX2 blockers further enhanced the selectivity of treatment by eliminating the residual production of Treg attractants.[29 30] In our phase I clinical trial (NCT04081389), paclitaxel was given concomitantly with the above combination to enrich the TME with T-cell attracting chemokines and decrease MDSC and Treg-favoring chemokines, resulting in selective increases in the desirable CTLs.[40]

POTENTIAL APPLICABILITY OF PACLITAXEL EFFECTS TO OTHER FORMS OF CHEMO AND CHEMO-IMMUNOTHERAPY

Another emerging question is whether the above results and their therapeutic implications can be extrapolated to other ICI treatments, such as TIM3-blockade, which have recently shown synergistic activity with paclitaxel in preclinical models through a mechanism involving release of extracellular DNA, HMGB1 and cGAS-STING pathway, leading to the release of IFN-dependent chemokines, such as CXCL9.[41] The immuno-potentiating effect of chemotherapy is likely to be particularly effective in stimulating anticancer immune responses when used at a low dose. In a phase 2 multi-arm TONIC trial (NCT02499367), PD-1/PD-L1 blockade was applied after short-term low-dose chemotherapy. Compared with nivolumab alone where the overall response rate (ORR) was 17%, cisplatin induction enhanced the ORR to 23% (95% CI: 5% to 53.8%) and doxorubicin induction enhanced the ORR to 35% (95% CI: 14.2% to 61.7%), in both cases associated with early increases in $CD8^+$ tumor-infiltrating lymphocytes (TILs) counts.[42] Our recent study involving the addition of IFNα/rintatolimod regimen to local (intraperitoneal) cisplatin regimen in ovarian cancer, demonstrated a selective enhancement of CTL attractants and activated CTL and NK cell markers, without enhancing Treg markers,[43] suggesting that recalibration of the IRF3 to NFκB activation ratios and blocking PGE_2 may also be beneficial in the context of other forms of chemotherapy and additional cancers.

Considering the importance of T cell migration into the TME in the antitumor effectiveness of adoptive T cell therapies of solid tumors; it remains to be tested if short-term chemotherapy or chemo-immunotherapy interventions can be used to enhance the clinical efficacy of chimeric antigen receptor T (CAR-T) cell therapies or TIL therapies.

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