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Lytic CD8+ T cell responses to target antigens induced by sipuleucel-T in men with hormone-sensitive and castration-resistant prostate cancer

Background: Sipuleucel-T is an FDA-approved autologous cellular immunotherapy for patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC), manufactured from peripheral blood mononuclear cells (PBMCs) cultured with the immunogen PA2024, a fusion antigen of prostatic acid phosphatase (PAP) conjugated to granulocyte macrophage colony-stimulating factor. Treatment with sipuleucel-T induces cellular and humoral immune responses to both PA2024 and PAP (Antonarakis, ASCO 2015; Petrylak, ECC 2015). To further elucidate the mechanism of sipuleucel-T–induced immune responses, we evaluated the proliferative and lytic characteristics of PA2024- and PAP-specific CD8+ T cells.

Methods: Patient samples were assessed for antigen-specific cellular immune responses by IFN-γ ELISPOT (Enzyme-Linked ImmunoSpot) assays. Cell proliferation was measured with a flow cytometry assay; PBMCs labeled with the membrane dye carboxyfluorescein succinimidyl ester (CFSE) were cultured with PA2024 or PAP, and progressive dilution of CSFE indicated antigen-specific cellular proliferation. Phenotypic analyses were then performed to identify whether proliferating T cells were CD4+ (T helper [T_H]) or CD8+ (cytotoxic T lymphocytes [CTLs]). To assess whether CD8+ T cells were engaged in CTL activity, loss of intracellular granzyme B (GzB), indicating exocytosis of this apoptosis-mediating enzyme, was also measured. Patient samples were from 2 sipuleucel-T clinical trials (NCT01431391; NCT01981122) in hormone-sensitive prostate cancer and mCRPC patients.

Results: Sipuleucel-T generated PA2024 and PAP-specific IFN-γ ELISPOT responses (N=118), and both CTL and T_H subpopulations demonstrated proliferation responses to PAP and PA2024 (14 patients assessed) 6 weeks post–sipuleucel-T administration ($p<0.10$). CTL proliferative responses were greater against PA2024 compared with the magnitude of response against PAP, with most patients with CTL responses to PA2024 also having T_H responses. CTLs from patients who exhibited PA2024- and/or PAP-specific proliferative responses were assessed for lytic ability. After in vitro antigen stimulation and in all evaluated samples (PA2024, n=14; PAP, n=13), intracellular GzB was significantly decreased compared with a no-antigen control ($p<0.05$) at 6 weeks post–sipuleucel-T, demonstrating CTL activity.

Conclusions: Sipuleucel-T generated PA2024- and PAP-specific cellular responses, which consisted of both T_H and CTL responses. Moreover, the lytic activity observed by antigen-specific CTLs provides direct evidence that sipuleucel-T can induce tumor cell lysis against PAP-expressing tumor cells within 6 weeks of sipuleucel-T administration.

Conflict of Interest: ESA: Honoraria and consultancy/advisory role with Sanofi, Dendreon, Janssen, and Medivation, research funding from Sanofi, Dendreon, Johnson & Johnson, and Astellas; DIQ: consultancy/advisory role for Astellas Pharma, Dendreon, Novartis, Pfizer, Janssen Oncology, Bristol-Myers Squibb, Medivation, Genentech/Roche, Merck, EMD Serono, and Oncogenex, honoraria from Bayer, Dendreon, Medivation, Astellas Pharma, Novartis, Pfizer, Janssen Oncology, Bristol-Myers Squibb, Genentech/Roche, research funding from Millennium, Genentech/Roche, Sanofi, GlaxoSmithKline; ASK: consultancy/advisory role for Dendreon, Sanofi Aventis, MTG, Profound, Tokai, Janssen; DPP: stock from Bellicum Pharmaceuticals, and Tyme, Inc., honoraria from Bayer, Bellicum Pharmaceuticals, Sanofi,

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