PDL1 shapes the classical Hodgkin lymphoma microenvironment without inducing T-cell exhaustion

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Abstract

Classical Hodgkin lymphoma (CHL) is unusually sensitive to PD1 inhibition and PDL1 is highly expressed on CHL cells and in the tumor microenvironment. This could be interpreted as evidence of exhaustion, but paradoxically, PD1$^+$ lymphocyte infiltration does not predict response to PD1 inhibitors and no increase in cytotoxic markers is seen after PD1 therapy as might be expected with reversal of exhaustion. In contrast to PD1, elevated PDL1 does predict response to PD1 inhibitors and recent data associate both retained CHL MHC-II expression and increased T helper (T_H) T-cell receptor diversity with response, suggesting a connection to the T_H compartment. We performed a phenotypic, spatial and functional assessment of T-cell exhaustion in CHL and found co-expression of an exhaustion marker and lower PD1 expression in CHL than in reactive nodes whereas the proliferative and cytokine production capacity were similar in CHL and the reactive nodes. We found no correlation between PDL1 expression and exhaustion signatures. Instead, we identified a strong association between PDL1 expression and CHL MHC-II expression, T_H recruitment, and enrichment of T_H1 regulatory cells. These data suggest that a dominant effect of PDL1 expression in CHL may be T_H engagement and promotion of a regulatory microenvironment rather than maintenance of exhaustion.

Introduction

Classical Hodgkin lymphoma (CHL) is the only licensed indication for CD279 (PD1, programmed cell death protein 1) inhibitors in hematologic malignancies and is unusually sensitive to this therapy.[1,2] PD1 inhibitors are classically thought to act by reversing T-cell exhaustion, a state which limits the effectiveness of anti-tumor immune responses.[3] Effector T cells become exhausted when they are chronically stimulated by low levels of antigen.[4] Exhausted cells have sustained high expression of PD1, alongside other exhaustion markers, including CD223 (LAG3), TIM3, TBC21 (TBET) and EOMES, and progressively lose their effector functions.[4,5] Exhaustion is partially reversible and PD1 inhibition can reinvigorate the T-cell response leading to improved tumor clearance.

CHL cells express high levels of ligand 1 for PD1 (PDL1) and polysomy, copy gains and amplifications of the *PDL1* locus are seen in upwards of 95% of cases.[6,7] PDL1 expression is also prominent within other cells in the tumor microenvironment.[8] However, functional data demonstrating exhaustion in CHL are limited and most studies, including studies from our own laboratory, report only low PD1 expression in the CHL microenvironment.[9] Furthermore, PD1$^+$ cell infiltration does not predict response to PD1 inhibitors in CHL.[9,10] Recent studies demonstrate that during PD1 inhibitor therapy the CHL microenvironment is characterized by a rapid reduction in PDL1$^+$ macrophages and type 1 regulatory cells (T_R1) rather than cytotoxic T-cell expansion that might be expected with reversal of T-cell exhaustion.[11] Another study found that expansion of singleton (putatively newly immigrant) T helper (T_H) clones is associated with PD1 inhibitor response.[12] This is in line with data from solid tumors and suggests that during PD1 therapy activated tumor-specific T cells are in fact newly immigrant and not derived from exhausted populations that were present before therapy.[13] These studies run counter to the traditional model of PD1 inhibitors acting by reversing exhaustion and highlight a need to better understand the function of PDL1 within the CHL microenvironment.

In this study we phenotypically and functionally assessed exhaustion in CHL and its relationship to PDL1 ex-