CD4 T cells: the complicated key to unlocking the immune environment of classical Hodgkin lymphoma

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Immune checkpoint inhibition has revolutionized the treatment landscape of relapsed classical Hodgkin lymphoma (cHL). Remarkably, 60-70% of patients with relapsed disease will have a response to therapy with anti-programmed cell death 1 (PD1) therapy.[1] Despite its effectiveness, it is unclear why cHL is so responsive to this treatment approach. Clues may lie in the relatively small number of malignant Hodgkin and Reed-Sternberg (HRS) cells (approximately 5%) that sit within a large inflammatory immune cell-rich tumor milieu. In most cases these HRS cells have copy number gains in the locus of ligand 1 or ligand 2 for PD1 (PD-L1/-L2).[2] Epstein-Barr virus expression is also found in 30-40% of cases, and this acts as a further driver of PD-L1 and PD-L2 expression within the malignant cell.

Despite this, the malignant cell still only contributes a small proportion of total PD-L1 within the tumor, with the majority emanating from the macrophages in the supporting tumor microenvironment (TME).[3] This unique TME makes deciphering the role of the PD-1 axis in cHL extremely complex and challenging.

PD-1 blockade is an effective therapy in solid tumors that have a high mutational burden such as melanoma, particularly if accompanied by CD8 T-cell intratumoral infiltration. This indicates that the mechanism of action is in part related to reinvigoration of neoantigen-specific T cells. However, despite the clear genetic amplification and expression of PD1 axis molecules in the TME in cHL, there is a relative paucity of data to explain the excellent responses to anti-PD1 therapy. Indeed, understanding the excellent responses to anti-PD1 blockade is further complicated by the loss of major histocompatibility complex (MHC) class I and II expression on the malignant HRS cells in many cases (particularly Epstein-Barr virus-negative cHL), challenging the conventionally accepted understanding of immune checkpoint response.

In the current issue of *Haematologica*, Taylor *et al.* provide an insight into the cHL TME and an alternative explanation for anti-PD1 response in cHL which is quite distinct from that postulated in solid cancers.[4] In support of previous work, they confirm that HRS cells do possess high levels of PD-L1 and are associated with high PD-L1 expression on surrounding macrophages. They do, however, demonstrate that T-cell exhaustion in the cHL microenvironment is not a predominant feature. They use various techniques to assess the level of T-cell exhaustion within the cHL microenvironment, and consistently show lower expression of PD1 and other markers of exhaustion on T cells from cHL samples, compared to those obtained from reactive lymph nodes. It appears that most of these T cells are functionally active rather than exhausted. In addition, high levels of PD-L1 in the cHL TME did not correlate with increasing T-cell exhaustion and in fact PD-L1 expression in the TME was not associated with PD-1 expression. It appears that the influence of PD-L1 expression in cHL may have its greatest impact on specific subsets of helper and regulatory T cells rather than effector T cells. T_H1_{Reg} cells were more common in PD-L1-rich environments and appeared to contribute to the exclusion of CD8 effector T cells. Thus, the authors speculate that a key mechanism for anti-PD1 response in cHL is the manipulation of the immune response away from a T_{Reg}/immunosuppressive environment to one in which the resident effector T cells can break through this immunosuppressive barrier and contribute to immune removal of tumor cells. Further functional work is required to test this hypothesis in models or cohorts of patients treated with anti-PD1 therapy.

The work by Taylor *et al.* is consistent with previous work in which CD4 T cells appear to play critical roles in the TME of cHL.[5,6] Aoki *et al.* showed that T_{Reg} cells expressing LAG3 contributed significantly to an immunosuppressive TME in cHL, particularly where MHC class II molecules were lost. This work showed the likely benefit of targeting multiple immune checkpoints in cHL given the different mechanisms that the HRS employ under different genetic and TME conditions.

CD4 T_{Reg} were directly targeted in a recent phase I study that included a large number of cHL patients and utilized

an anti-CD25 antibody that effectively depletes T_{Reg} cells. This study showed remarkable efficacy in patients with relapsed cHL, seemingly confirming the importance of T_{Reg} manipulation in the treatment of cHL.[7]

Emerging data from clinical cohorts treated with anti-PD1 agents appear to show possibly differing mechanisms of response at diagnosis and relapse. Updated results from the correlative work on the NIVAHL study seems to show that markers of peripheral T-cell exhaustion are predictors of response to anti-PD1 therapy and that specific tumor-associated antigen immune responses could be detected in a large number of treatment-naïve patients receiving frontline anti-PD1 therapy.[8] Responses at relapse appear to be related to more diverse CD4 T-cell populations and innate immune cell expansions.[9]

In addition, it should be remembered that there is evidence of direct HRS cell survival with binding of PD-1 to its ligands on the tumor cells, and that other immune cells such as natural killer cells may also play critical roles in cHL, illustrating that the TME in cHL is unique and complex with likely multiple PD-1 pathways involved in disease propagation.[10,11]

In conclusion, despite the widespread adoption of anti-PD1 therapy in cHL, important correlative work has lagged and this shortcoming needs to be addressed in future studies aimed at teasing out the complexity of the TME in cHL. It would appear, as suggested by Taylor *et al.*, that dynamic changes of CD4 T cells in cHL are critical in the response to immune-based therapies.

Clinical studies that combine immune checkpoint therapies using anti-PD1 therapy as a backbone are emerging and will provide insights into how targeting T_{Reg} may be critical in cHL. The paper by Taylor *et al.* provides important findings that could influence the design of the next phase of immune-based therapies in cHL.

Disclosures

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Contributions

The authors contributed equally.

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