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CD4 T Cells: the complicated key to unlocking the immune environment of classical Hodgkin Lymphoma

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Immune checkpoint inhibition has revolutionised the treatment landscape of relapsed classical Hodgkin lymphoma (cHL). Remarkably, 60-70\% of patients with relapsed disease will have a response to anti-PD1 therapy\textsuperscript{(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 Reed Sternberg cell (\textasciitilde{}5\%) that sit within a large inflammatory immune cell rich tumour milieu. These Reed Sternberg cells (HRS) in most cases possess copy number gains in the locus of PD-L1/-L2\textsuperscript{(2)}. Epstein Barr Virus expression is also found in 30-40\% of cases, and this acts 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 tumour, with the majority emanating from the macrophages in the supporting tumour microenvironment (TME)\textsuperscript{(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 tumours that have a high mutational burden such as melanoma, particularly if accompanied by CD8 T cell intratumoural 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 TME expression of PD1 axis molecules 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 MHC Class I and II expression on the malignant RS cells in many cases (particularly EBV-negative cHL), challenging the conventionally accepted understanding of immune checkpoint response.

In the current issue, Taylor et. al. provides an insight into the cHL TME and an alternative explanation for anti-PD1 response in classical Hodgkin lymphoma that may be quite distinct from that postulated in solid cancers\textsuperscript{(4)}. They confirm that HRS cells do possess high levels of PD-L1 and are associated with high PD-L1 expression on surrounding macrophages supporting previous work. They 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 exhaustion markers on T cells from cHL, compared to those obtained from reactive nodes. It appears 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 the cHL may have its greatest impact on specific subsets of helper and regulatory T cells rather than effector T cells. Th\textsubscript{1} reg cells were more common in PD-L1 rich environments and appeared to contribute to 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\textsubscript{reg}/immunosuppressive environment to one in which the resident effector T cells
can break through this immunosuppressive barrier and contribute to immune removal of tumour cells. Further functional work is required to test this hypothesis in models or patient cohorts treated with anti-PD1 therapy.

This work is consistent with previous work where CD4 T cells appear to play critical roles in the TME of cHL. Aoki et al. showed that Treg cells expressing LAG3 significantly contributed to an immunosuppressive TME in cHL particularly where MHC Class II was lost. This work showed the likely benefit of targeting multiple immune checkpoints in cHL given the different mechanisms that the HRS employs under different genetic and TME conditions. CD4 Tregs were directly targeted in a recent phase I study that included a large number of cHL patients utilising an anti-CD25 antibody that effectively depletes Treg cells. This study showed remarkable efficacy in patients with relapsed cHL likely confirming the importance of Treg manipulation in the treatment of cHL.

Emerging data from anti-PD1 treated clinical cohorts appears to possibly show differing mechanisms of response at diagnosis and relapse. Updated results from this correlative work on the NIVAHL study appears to show that peripheral T cell exhaustion markers are predictors of response to anti-PD1 therapy and that specific tumour associated antigen immune responses could be detected in a large number of treatment naive patients receiving front line anti-PD1 therapy. Responses at relapse appear to be related to more diverse CD4 T cell populations and innate immune cell expansions.

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 tumour cells, and that other immune cells such as NK cells may also have critical roles in the cHL illustrating that the TME in cHL is an unique and complex with likely multiple PD-1 pathways involved in disease propagation.

In conclusion, despite the widespread adoption of anti-PD1 therapy in cHL, important correlative work has lagged and this needs to be addressed in future studies to tease out the complexity of the TME in cHL. It would appear, as suggested by Taylor, that the dynamic changes of CD4 T cells in cHL appears to be critical in response to immune based therapies. Clinical studies that combine immune checkpoints therapies using anti-PD1 therapy as a backbone are emerging and will provide insights into how the targeting of T regulatory cells may be critical in cHL. The current paper provides important findings that could influence the design of the next phase of immune based therapies in cHL.

References:


