Journal Club

PREPRINT WATCH

THE CD58–CD2 AXIS IN CANCER IMMUNE EVASION

Cancer immune evasion following treatment is a major issue for immunotherapies such as immune checkpoint blockade (ICB), whereby adaptive resistance to treatment can occur following an initial response, leading to poor prognosis.

Previous work has found that downregulation of CD58, the co-stimulatory ligand for CD2, is associated with immune evasion in melanoma tumours and that ICB treatment of renal cell carcinoma is associated with decreased CD58 expression. However, the mechanism is poorly understood. In this preprint (not peer-reviewed), Ho et al. investigate both the role of CD58 expression in cancer cell immune evasion and the protein interactions of CD58.

The authors found that *CD58* knockout in human melanoma cell lines resulted in significantly reduced tumour lysis and interferon-γ production by T cells, whereas these features were significantly increased following overexpression of *CD58* compared with wild-type cells. The CD58 phenotype was shown to be mediated by T cell receptor (TCR)–epitope interactions and they confirmed that CD58–CD2 interactions between cancer cells and T cells, respectively, are essential for cell lysis. Killing of tumour cells was enhanced by pre-stimulation of tumour-infiltrating lymphocytes (TILs) through the TCR and this effect was multiplied by co-stimulation of TILs through CD2.

Tumours in partly humanized mouse models produced by implanting wild-type, *CD58*-knockout or *CD58*-overexpressing human cells were treated using adoptive cell transfer of TILs. *CD58*-knockout tumours were more resistant to TILs and had significantly lower rates of T cell infiltration and proliferation compared with wild-type tumours. Rescue with *CD58* overexpression reversed these effects.

The authors also identified that CD58 is co-regulated with the immune checkpoint protein PDL1 such that loss of CD58 expression leads to upregulation of PDL1. This was found to be mediated by CMTM6 — with which CD58 and PDL1 compete for binding, which prevents their degradation — and they identified the N-terminus of PDL1 as the region that binds to CMTM6.

This study highlights the importance of the CD58–CD2 axis in T cell responses to cancer cells and how disruption of this axis can lead to immune evasion not only through lack of T cell co-stimulation through CD2 but also through increased inhibition of T cells through PDL1–PD1 signalling. The work also suggests potential approaches to improve cancer immunotherapies, such as using CD2-expressing T cells or targeting the interactions between CMTM6 and PDL1.

Max Quastel and Michael Dustin
Preprint Club, University of Oxford, Oxford, UK.
e-mail: highlights@preprintclub.com

ORIGINAL ARTICLE Ho, P et al. The CD58:CD2 axis is co-regulated with PD-L1 via CMTM6 and governs anti-tumor immunity. Preprint at *bioRxiv* https://doi.org/10.1101/2022.03.21.485049 (2022)
RELATED ARTICLE Quastel, M. Preprint Journal Club. *PreprintClub* https://www.preprintclub.com/2022-apr-ho (2022)