TGFβ driven metabolic reprogramming of PDL1+ macrophages defines a targetable axis of immune evasion in diffuse large B cell lymphoma

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Experimental hematology / oncology

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INTRODUCTION

Diffuse large B cell lymphoma (DLBCL) remains a heterogeneous and refractory malignancy. Although immune checkpoint blockade benefits selected subtypes, most DLBCLs show limited clinical benefit, highlighting the need to identify alternative therapeutic intervention. We previously showed that macrophage PDL1 correlates with aggressive DLBCL and promotes lymphoma progression in EμMyc models, suggesting its role in shaping treatment response. However, the mechanisms maintaining PDL1+ TAMs and their role in immunotherapy resistance remain unclear. Here, we investigated the cytokine and metabolic signals driving PDL1+ macrophage function, aiming to uncover targetable mechanisms that could enhance immune and antibody based therapies in DLBCL.

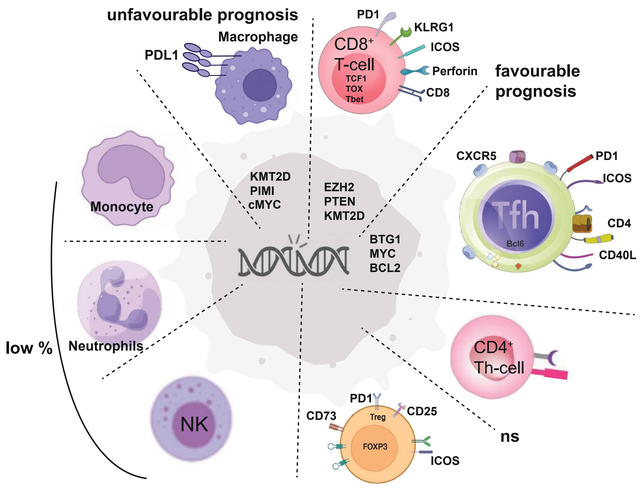
METHODS

Opal 7-color manual IHC kit was used for staining of TMAs; imaging of the slides was performed using the Vectra Polaris Automated Quantitative Pathology Imaging System. Spectrally unmixed images were generated using the inForm software package and further analyzed using machine learning algorithms built in the inForm software package. Single-cell–level data from inForm were exported for further processing using the R statistical programming language. Immunocompetent EμMyc lymphoma models that recapitulate aggressive human DLBCL were used. Mice with macrophage specific PDL1 deletion (Mrc1^CreERT2×Cd274^fl/fl) were analyzed. Spleen or lymph node tumours were collected for single cell RNA sequencing, high dimensional spectral flow cytometry. Cytokine blockade were performed to assess how TGFβ regulate PDL1 expression and macrophage phagocytic capacity.

RESULTS

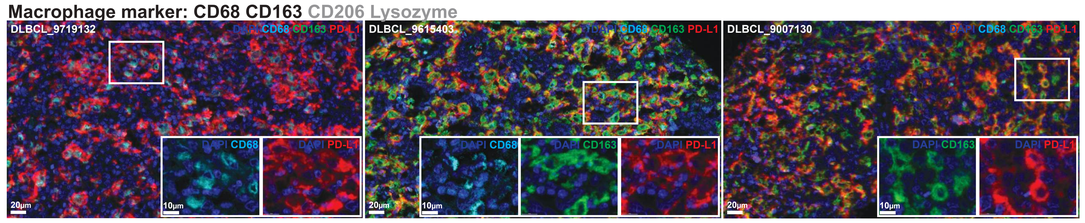
1. Multiplex IF results overview

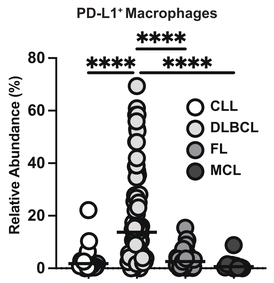
DLBCL patient: multiplex IF (n = 155); amplicon-sequenced (n = 78); survial follow-up (n = 77, CHOP therapy)

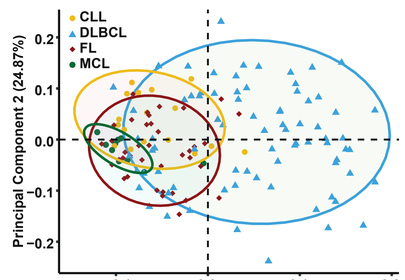


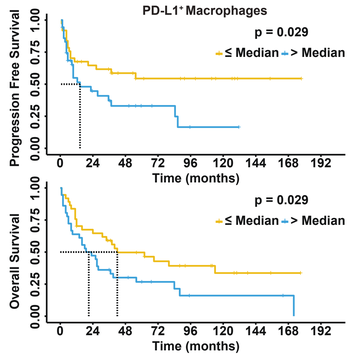
2. Macrophages PDL1 expression is a common feature of DLBCL and negatively prognostic

Macrophage marker: CD68 CD163 CD206 Lysozyme

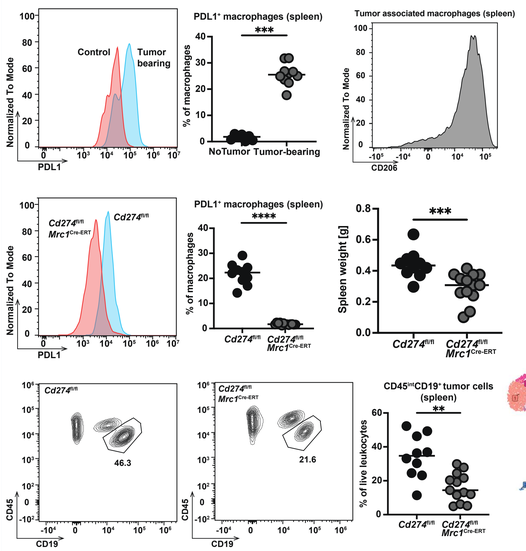


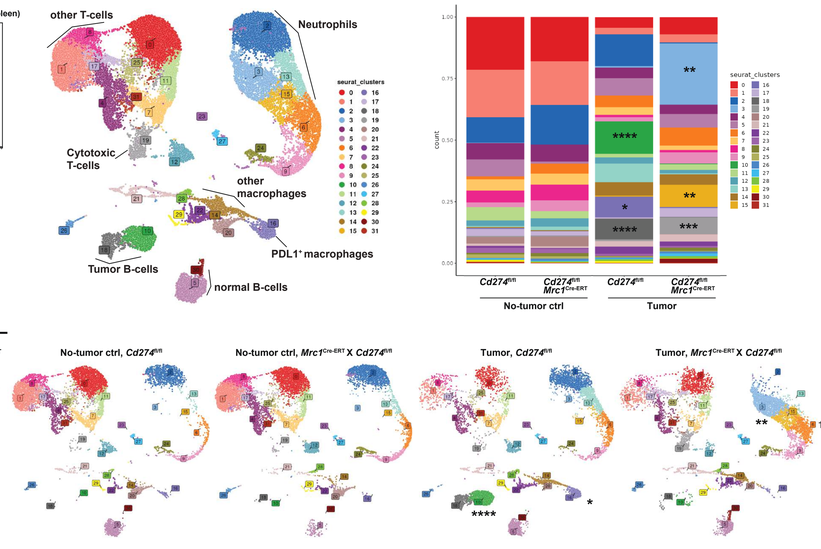


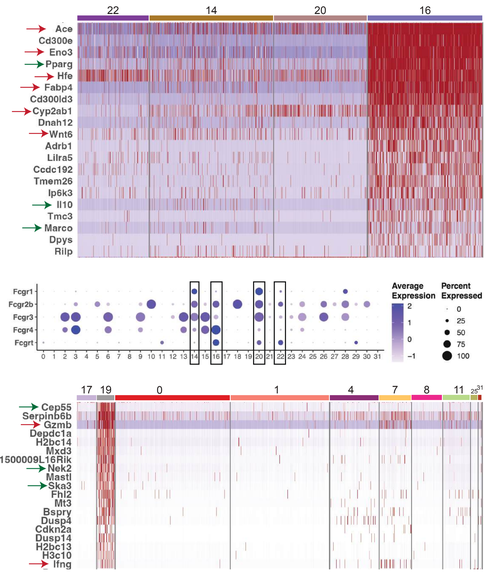




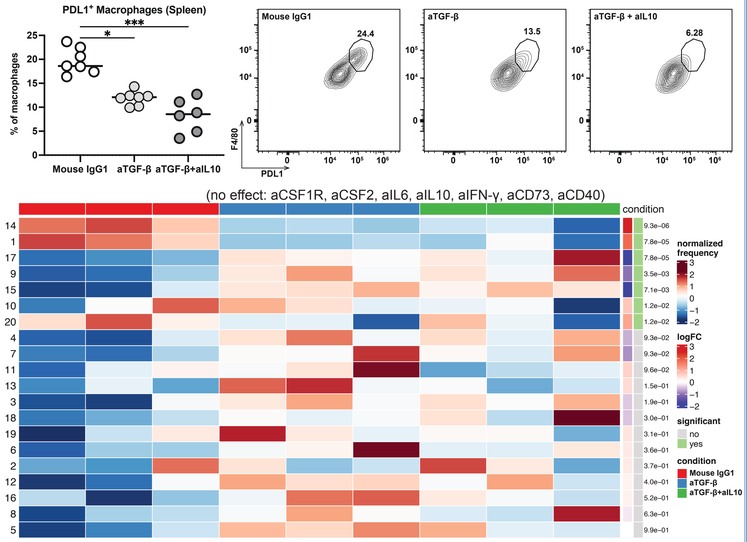
3. PDL1+ macrophage is metabolically adapted, immunosuppressive subset and suppresses cytotoxic effector CD8+ T cells

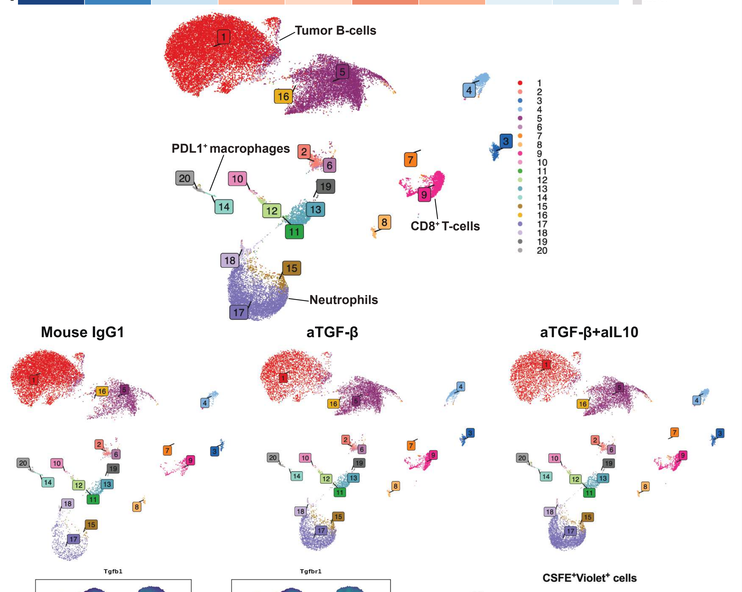






4. The blockade of TGF-β and IL10 decreases PDL1 expression on macrophages, facilitates lymphoma tumor control and increases CD8+ T cell infiltration





CONCLUSION

Our findings define a cytokine–metabolic checkpoint that maintains PDL1+ macrophages and limits both T cell and antibody mediated immunity. Targeting TGFβ signalling or restoring FcγR function may overcome macrophage driven resistance and improve the efficacy of PDL1 or anti-CD20 based therapies in DLBCL. These results provide a mechanistic basis for macrophage directed combination immunotherapy in B cell lymphomas.

REFERENCES

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