

Summary

Cancerous cells develop resistance to the immune system through various mechanisms, impairing its capacity to recognise and eliminate them. Immunotherapies, such as checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways, along with adoptive cell therapy (ACT), have shown potential in treating cancers like melanoma. However, a significant number of patients do not respond to these treatments. Overcoming immune suppression within the tumour microenvironment appears critical for improving therapeutic outcomes. To address this, we investigated how immune responses, particularly those involving T cells and macrophages, contribute to melanoma-induced immunosuppression.

Previous research identified Neuropilin-1 (NRP1) as a promising target for mitigating immunosuppressive effects. In our study, we demonstrated that blocking NRP1 in *in vitro*, *in vivo*, and *ex vivo* models effectively counteracted the immunosuppressive influence of melanoma on peripheral regulatory T cells (Tregs). This intervention led to significant tumour regression, reduced metastasis, and increased survival in murine models. These findings suggest that targeting NRP1 may hold considerable potential as a therapeutic strategy for melanoma immunotherapy.

Additionally, the role of inflammation in tumour progression was examined. Chronic inflammation is known to promote tumour growth and diminish treatment efficacy, while acute inflammation has been shown to bolster immune responses against tumours. Chikungunya virus (CHIKV) infection, characterised by sustained immune activation and the production of cytokines and chemokines, has the potential to enhance anti-tumour immunity. We explored how acute CHIKV infection influences melanoma-induced immunosuppression and vice versa.

Our findings revealed that CHIKV can infect the murine melanoma cell line B16-F10, significantly reducing the cancer cells' immunosuppressive effects on murine splenic T cells. Interestingly, CHIKV infection was more prominent in immunosuppressed macrophages, yet it did not trigger robust immune activation in these cells. This highlights the intricate interactions between acute

viral infections, immune modulation, and the tumour microenvironment.

In conclusion, our research underscores the necessity of understanding the differential roles of T cells and macrophages in managing cancer-associated immunosuppression. Gaining mechanistic insights into these processes can guide the development of more effective, targeted anti-cancer immunotherapies tailored to individual tumour contexts.