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Summary

TARGETED PLATELET INHIBITION OVERCOMES IMMUNOTHERAPY RESISTANCE IN LIVER CANCER

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Platelet activation drives immunotherapy resistance in hepatocellular carcinoma by promoting immunosuppressive myeloid cells that inhibit stem-like T cells, and pharmacological blockade of platelet GPIbα or genetic depletion of platelet α-granules significantly enhances immunotherapy response and prolongs survival in preclinical models.

KEY POINTS

- HCC patients with immunotherapy resistance showed enriched intrahepatic platelet transcriptomic signatures, while responders had lower platelet abundance.
- Pharmacological blockade of platelet GPIbα receptor or genetic silencing of Nbeal2 to deplete α-granules significantly enhanced immunotherapy response across multiple murine liver cancer models including cHCC-ICC, HCC, and MASH-HCC, and prolonged overall survival.
- Immunotherapy increased platelet presence and activation in the liver microenvironment, resulting in enrichment and immunosuppressive function of Trem2+ tumor-associated macrophages and myeloid-derived suppressor cells.
- Platelet-primed myeloid cells inhibit CD8+ PD1+ TCF1+ stem-like T cells, undermining adaptive immune response.
- Targeted platelet inhibition restored the stem-like T cell population, increased intratumoral CD4+ and CD8+ T cell quantity, enhanced T cell proliferation (Ki67+) and cytokine production (IFN-γ+ Gzm-A+), and reduced terminal exhaustion (TIM3+).
- In MASH-HCC models, platelet inhibition markedly decreased auto-aggressive CXCR6+ PD1+ CD8+ T cells, suggesting potential to overcome immunotherapy resistance in this non-responsive subtype.

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