Methods: We integrated single-cell full-length transcriptome sequencing and spatial transcriptomics to profile tumor—immune interactions in TNBC patients treated with neoadjuvant camrelizumab plus chemotherapy. Comparative analyses between pathological complete response (pCR) and non-pCR groups identified resistant subpopulations and candidate long noncoding RNAs (lncRNAs). A TNBC lung metastasis model was established to further investigate candidate lncRNAs. Functional studies and in vivo experiments, including loss-of-function assays, were conducted to validate candidate lncRNAs and define underlying mechanisms.

Results: The G-quadruplex—structured lncRNA CHROMR was identified as a critical regulator of immunotherapy resistance and lung metastasis. CHROMR was enriched in a proliferative Krt81+ tumor cell subpopulation from non-pCR cases. Spatial and ligand—receptor analyses revealed that these cells foster an immunosuppressive microenvironment by enhancing CSF1—CSF1R signaling with FOLR2+ macrophages and CD70—CD27 interactions with Treg cells. Silencing CHROMR alleviated suppression of macrophage antigen presentation, restored T cell activation, and reduced immune evasion. In vivo, CHROMR targeting significantly suppressed lung metastasis and improved therapeutic efficacy in TNBC.

Conclusions: This study uncovers CHROMR as a novel epigenetic driver of TNBC immune resistance through modulation of tumor—immune cell communication and microenvironmental remodeling. CHROMR expression marks resistant subpopulations, predicts poor immunotherapy response, and represents a promising therapeutic target to enhance the efficacy of immune checkpoint blockade in TNBC.

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399P From cold to responsive liposarcoma: An IFN-α—Collagen VI axis that enhances anti—PD-1 efficacy

A. Zhuang[1], C. Xu[2], Z. Xi[3], M. Xiao[4], C. Luo[4], W. Li[1]

[1]Department of Hepatobiliary Surgery, Xiang'an Hospital of Xiamen University, Xiamen, China; [2]State Key Laboratory of Cellular Stress Biology, School of Life Sciences, Xiamen University, Xiamen, China; [3]Zhongshan School of Medicine, Sun Yat-sen University - School of Medicine, Shenzhen, China; [4]Department of Retroperitoneal Tumor Surgery, Peking University People's Hospital, Beijing, China

Background: Given frequent post-surgical recurrence, poor cytotoxic activity, and ~7% ORR to immune checkpoint inhibitors, well-/dedifferentiated liposarcoma (WD/DD LPS) is an immune-cold disease with few responders, necessitating biomarker-guided selection and rational sensitisation strategies.

Methods: In discovery, we harmonised >400 bulk transcriptomes, deconvolved the tumour microenvironment to define immune classes, and derived a pathology-ready IHC panel. In mechanism/validation, we corroborated class biology with orthogonal whole-exome sequencing and quantitative proteomics; validated the IHC classifiers in independent pre-treatment WD/DD LPS cohorts with documented ICI responses; integrated single-cell RNA-seq to map cellular sources and pathways and functionally tested IFN-α, anti—PD-1, and their combination in vitro co-cultures and in humanised DDLPS xenografts.

Results: Across 403 WD/DD LPS transcriptomes, unsupervised profiling resolved two immune states—Immune-high (Hi) 63/403 (15.6%) and Immune-low (Lo) 340/403 (84.4%)—with comparable tumour mutational burden. A 5-marker (CD8A, CD27, AOAH, NCF1, LST1) IHC panel robustly reproduced this taxonomy and enriched for disease control in independent ICI—treated cohorts (n=10). Quantitative proteomics (n=71) established type VI collagen (COL6) as the dominant collagen, and scRNA-seq (n=46) with multiplex immunofluorescence localised COL6 production to tumour cells. IFN-α activity inversely associated with COL6 abundance, and recombinant IFN-α suppressed tumour-cell COL6A1 secretion in vitro. Across bulk, proteomic and single-cell layers, COL6 negatively correlated with $CD8^+$ T-cell abundance; Ligand—receptor analysis revealed tumour-derived COL6—CD44 signalling with increased $CD44^+CD68^+CD163^+$ M2-like macrophages in Lo. In PBMC-humanised DDLPS models, IFN-α plus anti—PD-1 outperformed monotherapies, inducing tumour regression accompanied by reduced intratumoural COL6A1.

Conclusions: We delineate an IFN-α-COL6 axis that structures the WD/DD LPS microenvironment. By suppressing tumour-cell COL6, IFN-α permits $CD8^+$ T-cell infiltration and limits M2 polarization, supporting IFN-α co-administration with PD-1 blockade in WD/DD LPS patients.

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400P Targeting immuno-metabolic pathways to overcome resistance to immune-check point inhibitors in obesity-associated breast cancer

C. Savva[1], J. Pang[2], A. Thommen[3], P. Nunes[2], A. Benedetti[2], K. Boukas[4], C. Birts[5], S. Beers[4], D. Anastasiou[6]

[1]Oncology Dept., University of Southampton, Southampton, United Kingdom; [2]Cancer Metabolism Lab, The Francis Crick Institute, London, United Kingdom; [3]Francis Crick Institute, London, United Kingdom; [4]Cancer Sciences, University of Southampton, Southampton, United Kingdom; [5]School of Biological Sciences, University of Southampton, Southampton, United Kingdom; [6]Cancer Metabolism, The Francis Crick Institute, London, United Kingdom

Background: Immune checkpoint inhibition (ICI) has improved clinical outcomes in breast cancer (BC), yet it often demonstrates variable response and resistance. New strategies are critically needed, given the rising prevalence of obesity in patients with triple-negative BC (TNBC). Obesity-driven adipose tissue dysfunction and systemic inflammation are known to promote tumour growth. Our previous research showed that body composition and crown-like structures (CLS) are associated with attenuated anti-tumour immune responses and poor survival in BC patients. Furthermore, the anti-diabetic drug metformin increased tumour-infiltrating immune cells in non-diabetic BC patients. We, therefore, hypothesize that metabolic modulators like metformin will improve ICI efficacy in obese TNBC patients by reversing obesity-driven metabolic and immune dysregulation.

Methods: E0771 cells were orthotopically implanted into C57BL/J6 mice fed obesogenic (OD) or control diets (CD) and treated with ICB, metformin, combination, or vehicle. Tumour, serum, and adipose tissue samples were collected for comprehensive analysis. Serum metabolites were quantified by gas chromatography-mass spectrometry (GC-MS) and enzymatic methods, and serum inflammatory cytokines by ELISAs. Immunological profiles of adipose tissue and tumours were assessed via whole transcriptome RNA sequencing and multiplex immunohistochemistry. Statistical analysis was performed using R and GraphPad Prism.

Results: Long-term consumption of OD promoted tumour growth. While ICB completely inhibited tumour growth in CD-fed mice, it was only partial in OD-fed mice, suggesting that obesity induces ICB resistance. Metformin alone had no effect, but when combined with anti-PD1 in OD-fed mice it fully restored tumour control. The combination synergistically decreased CLS and increased tumour-infiltrating CD8 +PD1+ T-cells, elicited enriched interferon-γ gene signature and prolonged survival ($P<0.05$). There was also a reduction in systemic inflammation markers and a normalisation of non-esterified fatty acid levels in OD-fed mice ($P<0.05$).

Conclusions: Metformin synergises with ICI to limit tumour growth by modulating the tumour-immune microenvironment and metabolism.

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402P TMEM33 loss enhances CD8+ T cell functionality and tumour control

M.T. Jackson[1], T. Zhao[1], G.B. Milotay[1], I. Pedroza-Pacheco[2], A. Grover[3], D. Gabrilovich[4], J. Rehwinkel[5], B.P. Fairfax[1], E. Honoré[6], D. Withers[2], E.E. Parkes[1]

[1]Oncology, University of Oxford, Oxford, United Kingdom; [2]Centre for Immuno-Oncology, University of Oxford, Oxford, United Kingdom; [3]Immuno-Oncology, AstraZeneca, Cambridge, United Kingdom; [4]Immuno-Oncology, AstraZeneca, Gaithersburg, United States of America; [5]MRC Translational Immune Discovery Unit, University of Oxford, Oxford, United Kingdom; [6]Molecular and Integrative Mechanobiology, Institute of Molecular and Cellular Pharmacology, Valbonne, France

Background: TMEM33 is an endoplasmic reticulum-resident transmembrane protein implicated in lipid metabolism, calcium homeostasis, and STING-dependent anti-viral immunity. Here we demonstrate that TMEM33 modulates anti-tumour $CD8^+$ T cell functionality.

Methods: Bulk RNA-seq was performed in peripheral $CD8^+$ T cells isolated from 236 metastatic melanoma patients (OxCITE cohort). Wildtype (WT) and $Tmem33^{-/-}$ mice were challenged with B16F10-OVA or YUMM1.7-OVA (melanoma) models followed by flow cytometric immune profiling of tumours and draining lymph nodes (DLNs). Naïve $CD8^+$ T cells from both genotypes were stimulated ex vivo, or adoptively transferred from OT-I ($Tmem33^{+/+}$/$Tmem33^{-/-}$) mice into tumour-bearing hosts. Antigen cross-presentation was examined in co-culture studies using OVA-pulsed bone marrow-derived dendritic cells (BMDCs) from WT and $Tmem33^{-/-}$ mice.

Results: Lower $CD8^+$ T cell-specific TMEM33 expression in metastatic melanoma patients significantly correlates with improved overall and progression-free survival. $Tmem33^{-/-}$ mice showed attenuated B16F10-OVA and YUMM1.7-OVA tumour growth, and enhanced tumour $CD8^+$ T cell frequency. Tumour control persisted in