Single-Cell Co-Expression Networks reveal Actionable Resistance Mechanisms to Targeted and Immunotherapy treatments in Melanoma

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Eva Camarillo-Retamosa[1,2], Lars Bosshard[3], Parisa Rahimzadeh[2], Lukas Klein[1,4] , Benedict Gosztonyi[1], Zsolt Balázs[1,5], Nicola Miglino[1,2], Franziska Singer[3], Tumor Profiler consortium[6], Michael Prummer[3], Andreas Wicki[1,2]

[1]Medical Oncology and Hematology, University Hospital Zurich, CH; [2]Faculty of Medicine, University of Zurich, CH ; [3]Nexus Personalized Health, ETH Zurich and SIB Swiss Institute of Bioinformatics, Zurich, CH; [4]Institute of Computer and Communication Sciences, EPFL, Lausanne, CH.; [5]Department of Quantitative Biomedicine, University of Zurich, CH.; [6]Tumor Profiler consortium, CH.

Background and Methods

- Resistance to targeted therapy (BRAF/MEKi, TT) and immune checkpoint inhibitors (ICI) remains a significant challenge in advanced melanoma (**Fig.1**).
- scRNA-seq reveals cell heterogeneity but misses the dynamics of gene interactions driving treatment escape.
- We used scRNA-seq analysis from Tumor Profiler and assessed the Single-Cell Co-Expression Network (SCENE) (**Fig.2**) in both melanoma and T cells to uncover the dynamics of co-expression links between genes before and after treatment.

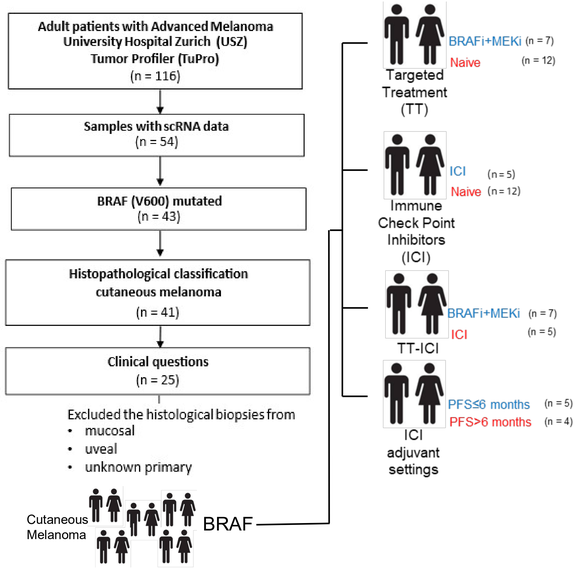

Figure 1. Cohort Selection and Clinical Subgroups. BRAF-mutated cases of advanced melanoma with single-cell RNA sequencing data (scRNA-seq) within the TuPro cohort were filtered by clinical scenarios: escape to TT or ICI to compare with untreated cases, treatment comparison (TT vs. ICI) and progression-free survival (PFS), long and short (six months) with ICI as adjuvant. Treatment administration within 8 weeks of the biopsy.

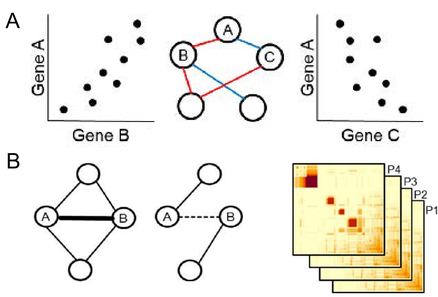

Figure 2. Single-cell Co-Expression Network (SCENE).
(A) Pairwise gene co-expression scatters and network construction using network topology and weighted distance matrix (WGCNA) [1].
(B) Examples of Strong (bold line) and Weak (dotted line) network connections and the aggregate similarity matrices across patients (heatmaps) summarising gene co-expression profiles to identify shared and private co-expression modules.

[1] Langfelder, Horvath 2008

Results

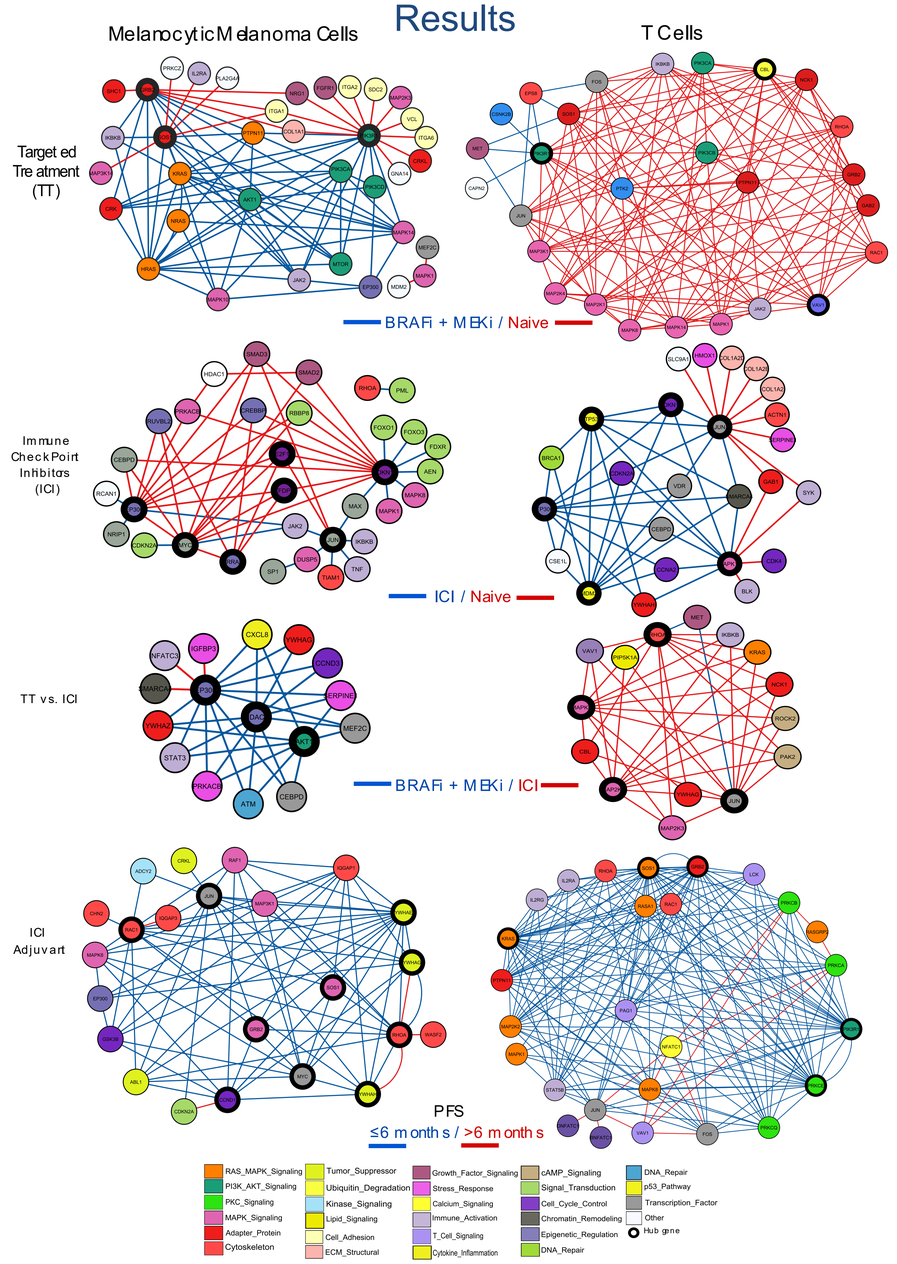

Figure 3. Connectivity dynamics of top targeted genes emerging upon therapy escape in BRAF-mutated melanoma.
Visualisation in Cytoscape of the gene wiring patterns in tumour (melanocytic melanoma cells) and T cells from patients escaping targeted therapy (BRAFi + MEKi) or immune checkpoint inhibition (ICI) (both in blue lines), compared to treatment-naïve cases (red lines), and between TT (blue lines) and ICI escape (red lines). Connectivity was also assessed in patients who progressed after ICI in an adjuvant setting, with extended (>6 months) (red lines) or short (≤6 months) (blue lines) progression-free survival. Targeted genes are shown in coloured circles, with the biological process/pathway involved indicated. The thicker circle lines highlight the hub genes.

Discussion

Using SCENE, we identified pathways that were differentially connected, selected the recurrent genes connected with more than five other genes, revealing private and novel co-expression network signatures specific to the treatment that escape. (**Fig. 3**)

- **TT escape:** Tumour cells rewired *PI3K–AKT–mTOR* and *MAPK* signalling to sustain growth, while T cells become hyperconnected yet transcriptionally exhausted (*PIK3R1, SOS1, JUN, MET, CAPN2, FOS, EPS8*), losing tumour control. *AP-1* factors (*FOS/JUN*) and *MAPK* suggest stress signalling and reduced cytotoxicity.
- **ICI escape:** epigenetic regulators (*EP300, HDAC1, MYC, JUN*) drove stress tolerance in tumour cells. T cells showed exhaustion and dysregulated activation (*TP53, MDM2, EP300, JUN, MAPK14*). Shared regulators revealed coordinated tumour-immune adaptation and potential vulnerabilities.
- **TT vs. ICI:** Hub genes (*HDAC1, AKT1, EP300*) in tumour cells drove growth and survival by chromatin remodelling and inflammatory signalling (*STAT3, CXCL8*). Modulators *YWHAG/Z* suggested evading immune destruction. *JUN-MET* connection supports T cell function. ICI network (*RHOA, MAPK8, MAP2K4, VAV1*) boosted anti-tumour immunity.
- **Long vs. short PFS - ICI adjuvant:** Tumour cells exhibited a co-expression signature of dysregulated proliferation (*MYC, JUN, CCND1*) in poor prognosis (blue) and cytoskeleton regulation (*RAC1, RHOA*) in long-PFS (red). T cells showed immune activation dysregulation (*IL-2–STAT5*) in poor prognosis, while transcription factors (*JUN, FOS*) supported immune memory (*NFAT1/B, D, VAV1*) in long-PFS.

Conclusions

- SCENE captures hidden network-level mechanisms in expression-only analyses by identifying actionable rewiring targets, some of which are already in clinical testing, highlighting the rapid translational potential.
- Treatment-specific network maps identified functional resistance circuits beyond genetic mutations. This information can guide personalized therapy strategies that target resistance mechanisms driving tumour growth and restore immune function.
- Our work supports a shift from mutation-based to functional network-based stratification for precision oncology.

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