Signalling network map of innate immune response in cancer reveals signatures of cell heterogeneity and polarization in tumor microenvironment

SUMMARY (150 words) (now 190)

To describe the contribution of innate immune components to anti- and pro-tumor effect of tumor microenvironment (TME), we collected information on molecular mechanisms governing innate immune response in cancer and represented it in a form of network maps. The signalling maps of macrophages, dendritic cells, myeloid-derived suppressor cells, natural killers were constructed. These cell type-specific maps, integrated together and updated by intra-cellular interactions, gave rise to a seamless comprehensive meta-map of innate immune response in cancer. The meta-map depicts signalling of anti- and pro-tumor activities of innate immunity system as a whole. The cell type-specific maps and the meta-map were used for interpretation of single cell RNA-Seq data from natural killers and macrophages in metastatic melanoma. The analysis demonstrated existence of sub-populations within each cell type that possess different anti- and pro-tumor polarization status. In addition, we used the meta-map for interpretation of pan-cancer patient survival data to retrieve patient survival signature. The cell type-specific signalling maps together with the meta-map of innate immune response in cancer form an open source platform available online that can be applied by wide community for assessment of TME status in cancer and beyond.

Key words

Tumor immunology, tumor microenvironment, innate immunity signalling, cancer systems biology, comprehensive signalling network map, semantic zooming, single cell data analysis, bioinformatics, molecular pathways and networks, intercellular communication, cell reprogramming, polarization, heterogeneity

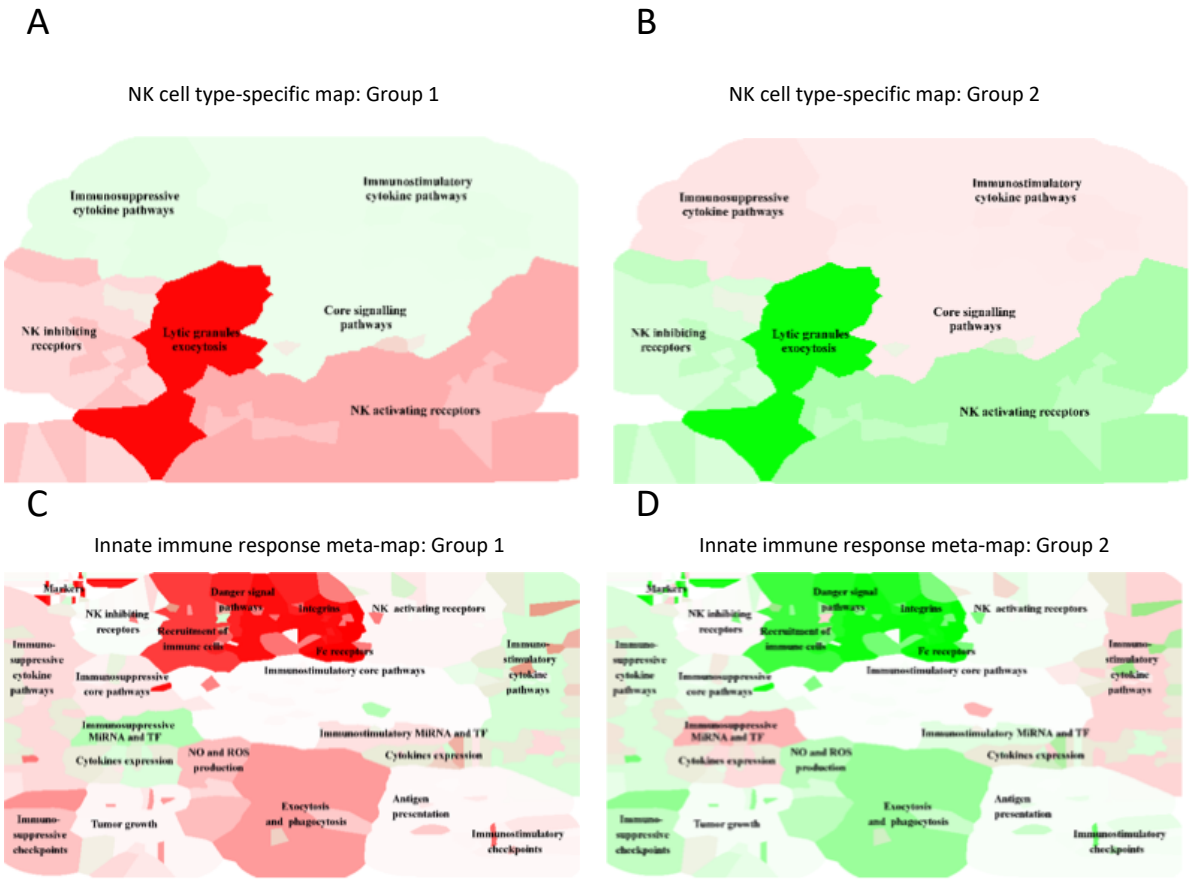


Figure 4. Visualization of modules activity scores using expression data from melanoma natural killers (NK) cells in the context of maps. Staining of the NK cell type-specific map with modules activity scores calculated from single cell RNAseq expression data for (A) NK Groups 1 and (B) NK Groups 2 cells. Staining of the innate immune response meta-map with modules activity scores for (C) NK Groups 1 and (D) NK Groups 2 cells. Red–upregulated, green- downregulated module activity.

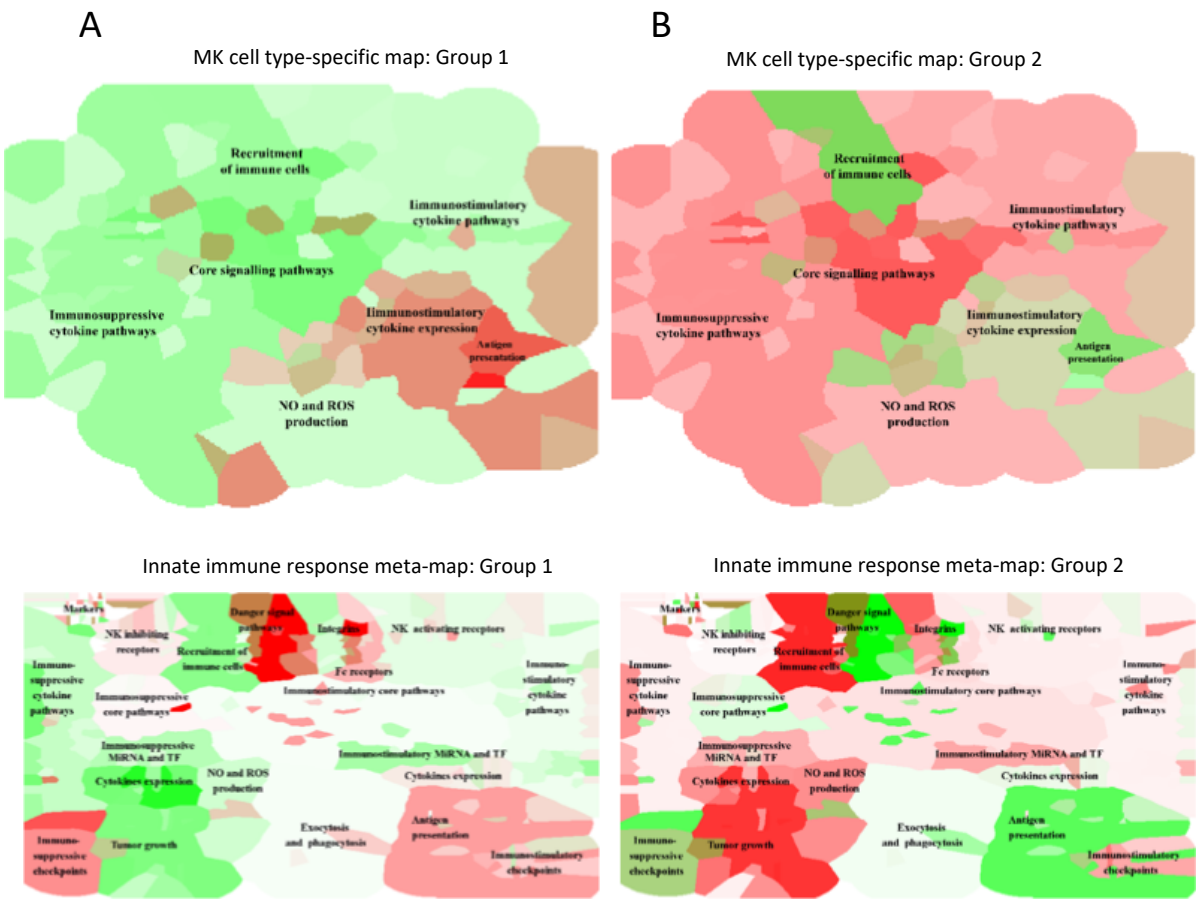
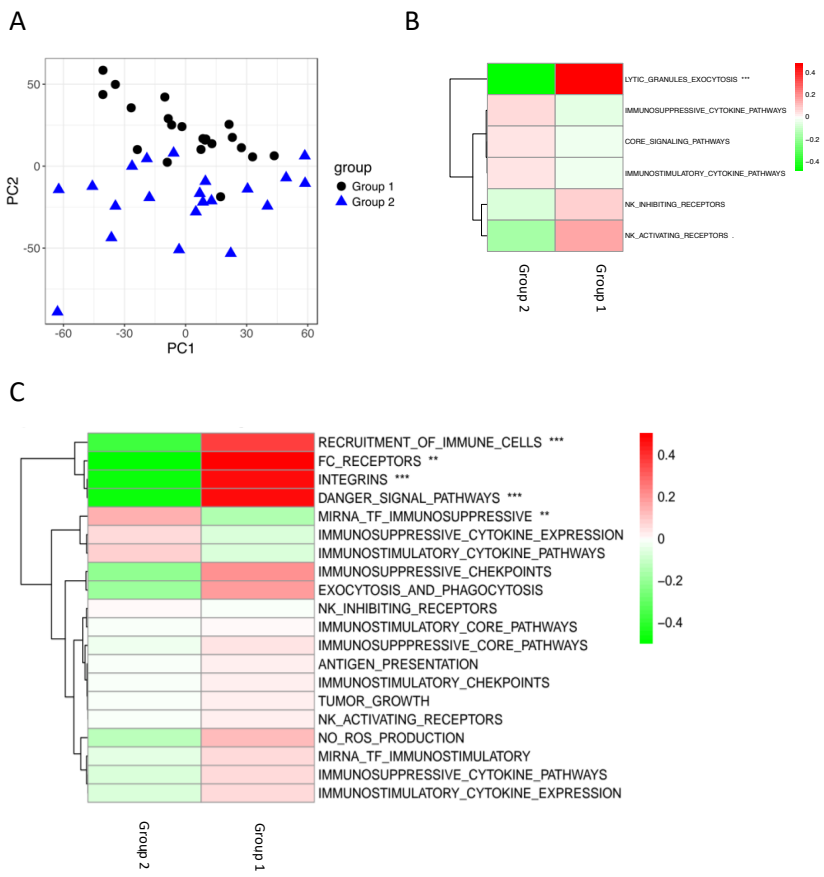
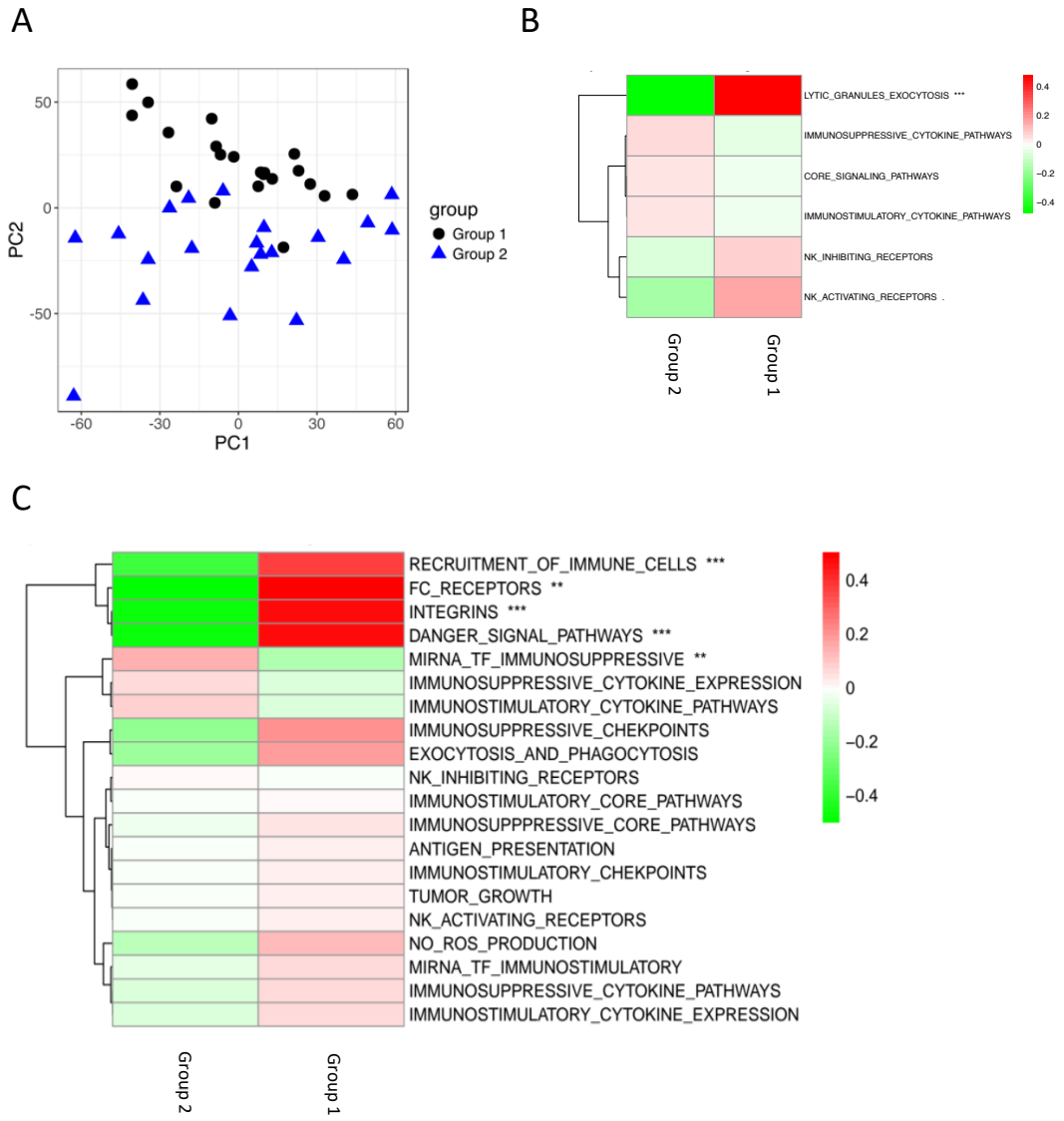


Figure 5. Visualization of modules activity scores using expression data from melanoma macrophages (Mph) cells in the context of maps. Staining of the Mph cell type-specific map with modules activity scores calculated from single cell RNAseq expression data for (A) Mph Groups 1 and (B) Mph Groups 2 cells. Staining of the innate immune response meta-map with modules activity scores for (C) Mph Groups 1 and (D) Mph Groups 2 cells. Red-upregulated, green-downregulated module activity.



Supplemental Figure 6. Sup-populations study and calculation of modules activity scores using expression data from melanoma natural killers (NK) cells. (A) NK single cells in PC1 and PC2 coordinates space. Two groups are colored distinctly in blue and black. Heatmap of mean values of 50% most variant genes divided by group of modules in (B) cell type-specific map and (C) meta-map. The p-value of the t-test between gene expression is reported following the code: *** < 0.001, ** < 0.01 , * < 0.05 , . < 0.1



Supplemental Figure 7. Sup-populations study and calculation of modules activity scores using expression data from melanoma macrophages (Mph) cells. (A) Mph single cells in PC1 and PC2 coordinates space. Two groups, the first and the fourth quartile of distribution along the IC1 axis, are colored distinctly in blue and black Heatmap of mean values of 50% most variant genes in groups in modules of (B) cell type-specific map and of(C) meta-map. The p-value of the t-test between gene expression is reported following the code: *** < 0.001, ** < 0.01 , * < 0.05 , . < 0.1