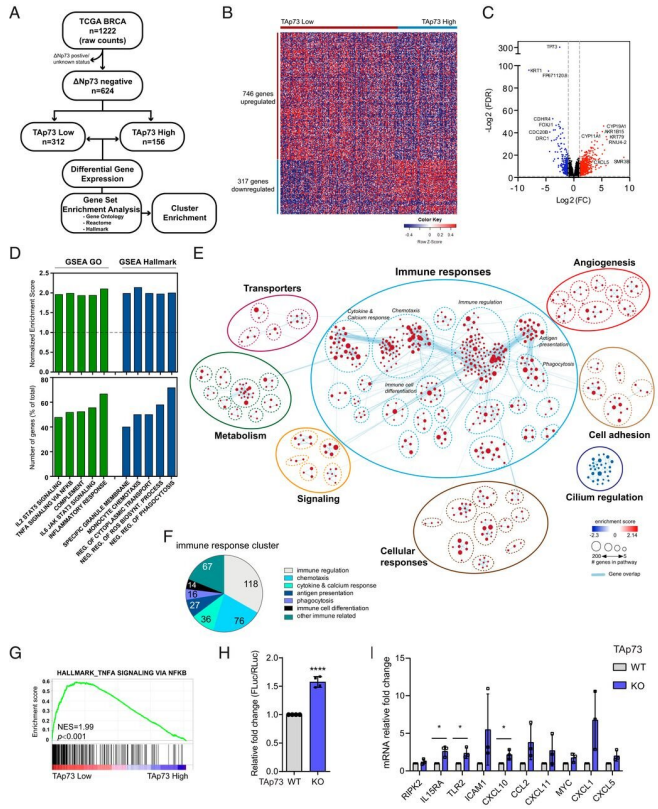
New insights on how immune cells are recruited and reprogrammed to drive tumor development

2 March 2021



Low levels of TAp73 correlate with an inflammatory signature and increased activity of the NF-?B pathway in breast cancer. (A) A flowchart of TCGA breast cancer data set analysis. (B) A heatmap based on differential gene set analysis comparing TAp73 low versus TAp73 high expressing samples (FC[Log2]>1, FDR > 0.05). (C) A volcano plot presenting differential gene expression as significance (FDR value) versus fold change. (D, Top) GO- and Hallmark-enriched gene sets in TAp73 Low tumors. (E) An enrichment map generated from GSEA results and visualized by Cytoscape EnrichmentMap and AutoAnnotate application, showing biological pathways enriched in TAp73 low versus TAp73 high. The red nodes represent up-regulated biological pathways, blue nodes represent down-regulated biological pathways, and blue lines represent gene overlap between pathways. (F) A cluster enrichment analysis within the immune response cluster showing number of significantly enriched gene sets/biological category. (G) An enrichment plot of a representative NF-?B gene set within the NF-?B gene set cluster. (H) NF-?B reporter assay was performed in TAp73 WT and KO MEFE1A/Ras (data shown as mean ± SD, n = 3, P

Researchers at Karolinska Institutet show how a certain type of immune cells, macrophages, can be recruited into breast cancer tumors, where they are reprogrammed to support and drive tumor growth. In a study published in the scientific journal *PNAS*, they describe that low levels of the tumor suppressor protein TAp73 lead to hyperactivation of NFkB signaling and an inflammatory condition in breast cancer as well as secretion of molecules that recruit tumor-promoting macrophages into the tumor.

Breast cancer is one of the most common cancers worldwide and understanding this complex disease is therefore of great importance.

"Previous studies have shown that infiltration of immune cells into tumors is of great importance for how the tumor develops and that there is a fine balance between infiltration of immune cells that attack the tumor cells and immune cells that can instead protect the tumor cells and help the tumor grow and spread," says Margareta Wilhelm, researcher at the Department of Microbiology, Tumor and Cell Biology, and corresponding author of the article.

"In the study we report that decreased levels of the protein TAp73 correlate with more aggressive types of breast cancer and that TAp73 acts as an inhibitor of NFkB activation. NFkB activates a variety of functions in the cell including the secretion of chemokines that attract immune cells into the tumor," she continues.

"Downregulation or lack of TAp73 leads to a condition in which NFkB is hyperactivated and upregulates secretion of the chemokine CCL2 which attracts circulating monocytes into the tumor where they differentiate into a special type of macrophage that supports tumor growth and leads to a more aggressive disease."

The published study increases the understanding of the mechanisms that drive the development of breast cancer and identifies TAp73 as an important factor in regulating how immune cells are recruited to the tumor.

More information: Johanna Wolfsberger et al. TAp73 represses NF-?B–mediated recruitment of tumor-associated macrophages in breast cancer, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2017089118

Provided by Karolinska Institutet