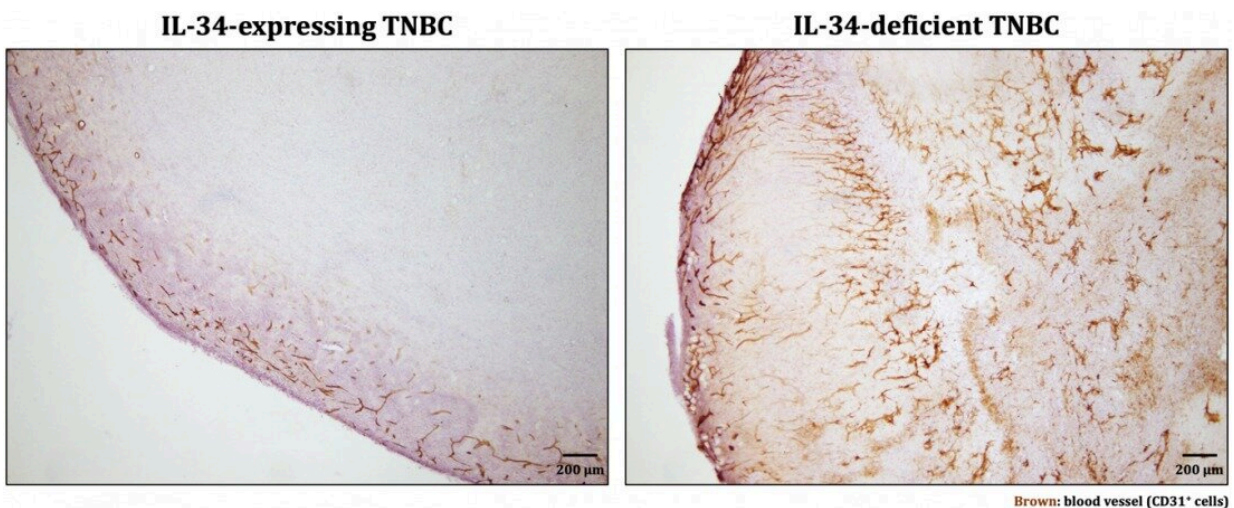


Study reveals root of triple negative breast cancer immunosuppression and chemoresistance

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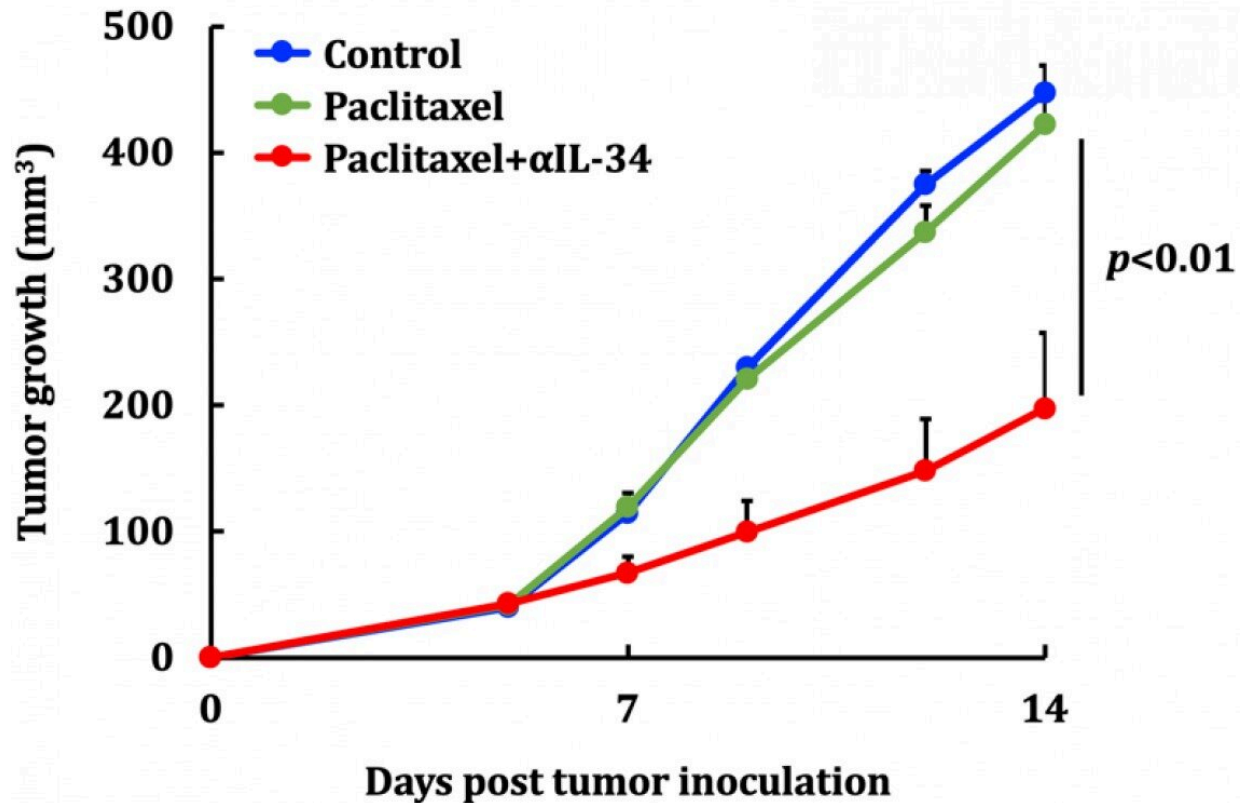
In IL-34-expressing tumors, blood vessels were observed only in the outer layer, whereas in IL-34-deficient tumors, blood vessels were observed in the whole area (modified from Nabeel Kajihara, et al. *Cancer Immunology, Immunotherapy*. September 14, 2022) Credit: Nabeel Kajihara, et al. *Cancer Immunology, Immunotherapy*. September 14, 2022

Triple-negative breast cancer (TNBC) tumors gain immunosuppression and chemoresistance through interactions between interleukin 34 and myeloid-derived suppressor cells, researchers find.

TNBC is a type of breast cancer characterized by the absence of any of the three typical cell surface receptors seen in other breast cancer types. TNBC accounts for 15–20% of all breast cancers; it is highly aggressive, and has a [poor prognosis](#) and a high relapse rate. Most troublingly, a large proportion of TNBC tumors develop resistance to chemotherapy.

A team of researchers from the Institute for Genetic Medicine (IGM) at Hokkaido University has identified a relationship between a cell signaling protein called interleukin 34 (IL-34) and the development of immunosuppression and chemoresistant in TNBC tumors. Their results, which identify a novel treatment target for TNBC, were published in the journal *Cancer Immunology, Immunotherapy*.

Prior work by the research team had demonstrated that IL-34 was an independent factor for poor prognosis in TNBC. The team decided to investigate the role of IL-34 in detail to determine how it induces poor prognosis in TNBC. For this purpose, they used an IL-34-expressing TNBC cell line, from which they established an IL-34-deficient cell line. They inoculated mice with these cell lines and compared the immune cell populations that infiltrated their tumors.



Growth of TNBC tumors without any treatment (blue line); it is unaffected by paclitaxel alone (green line) and dramatically suppressed by a combination of paclitaxel and anti-IL-34 antibody (α IL-34; red line) (modified from Nabeel Kajihara, et al. Cancer Immunology, Immunotherapy. September 14, 2022). Credit: Nabeel Kajihara, et al. Cancer Immunology, Immunotherapy. September 14, 2022

They found that IL-34 is key to modulating the balance between two myeloid-derived suppressor cell (MDSC) populations. Specifically, within the [tumor microenvironment](#), IL-34 caused a sharp increase in the population of monocytic-MDSCs (M-MDSCs) and a decrease in polymorphonuclear-MDSCs (PMN-MDSCs). M-MDSCs are especially important as they themselves have strong immunosuppressive effects and also differentiate into tumor-associated macrophages, which

suppress the anti-tumor immune response. Meanwhile, PMN-MDSCs have low immunosuppressive activity and powerful angiogenic ability. Based on these backgrounds, they hypothesized that the interaction between IL-34 and MDSCs is responsible for the chemoresistance in TNBC tumors.

They showed that a drug that neutralizes IL-34 reduces the growth rate of IL-34-expressing tumors and makes them susceptible to the chemotherapeutic drug paclitaxel, a standard treatment for TNBC. In particular, the IL-34–MDSC interaction causes chemoresistance by tilting the tumor interior towards an immunosuppressive condition and, at the same time, inhibiting angiogenesis, preventing chemotherapeutic agents from reaching the whole [tumor](#). Finally, they analyzed human data from The Cancer Genome Atlas (TCGA) and found a positive correlation between IL-34 and M-MDSCs and a negative correlation between IL-34 and PMN-MDSCs in TNBC tumors—showing that the results from mice models could be applied to humans.

"Our data demonstrated that the combination therapy of IL-34 blockade and chemotherapeutic agents was very effective and could be clinically significant," says first author Nabeel Kajihara.

More information: Nabeel Kajihara et al, Tumor-derived interleukin-34 creates an immunosuppressive and chemoresistant tumor microenvironment by modulating myeloid-derived suppressor cells in triple-negative breast cancer, *Cancer Immunology, Immunotherapy* (2022). [DOI: 10.1007/s00262-022-03293-3](https://doi.org/10.1007/s00262-022-03293-3)

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