

# Inhibiting macrophage MerTK signaling creates an innate immune response against cancer

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The tyrosine kinase MerTK plays a prominent role in the body's immune response. MerTK signaling helps "calm" the body's first line of immunity, the macrophage, while it performs the routine duties - clearing cells that die and healing damaged tissue.

New evidence by a University of North Carolina-led team published online on July 8 by the *Journal of Clinical Investigation* shows that MerTK macrophage action in the microenvironment that surrounds cancer cells blunts the immune response, allowing the tumor cell to grow and metastasize. The study, led by senior author Shelley Earp, MD, director of the UNC Lineberger Comprehensive Cancer Center, used mouse models bred without the gene for MerTK. Their work determined that MerTK absence increased the anti-tumor response and slowed the growth and spread of model breast, colon and skin cancers.

Several new drugs have recently been approved that effectively stimulate anti-tumor immunity. The evidence from the UNC researchers indicates that inhibiting MerTK in combination with these existing therapies may offer another avenue by which to activate the immune system in the fight against cancer.

Under normal circumstances, macrophages rid the body of normal debris while MerTK signaling evokes a wound healing, tissue repair response. With infection, the innate immune system, led by the macrophage, helps

create an "angry" response aimed at eliminating foreign material.

UNC researchers theorized that, in the case of cancer cells derived from the cells of the body, MerTK action in the microenvironment surrounding the tumor cells might suppress the anti-tumor response and keep the immune system's T lymphocytes from becoming active and killing tumor cells.

"In the first years of everyone's life, the immune system is 'educated' to tell the difference between 'self' and a foreign invader. Since tumor cells are part of our selves the immune system, unfortunately, becomes tolerant and fails to reject the tumor," said Dr. Earp.

Using model tumors, the research team examined the response of breast, skin and colon cancers growing in a mouse that lacked MerTK. They discovered that the tumors showed slower growth and a lower propensity to metastasize to other parts of the body. In the normal mouse, the MerTK macrophage signals were those of the wound healing type; whereas in the absence of MerTK, the entire immune system was activated, promoting inflammation.

"Our work strongly indicates that if you could inhibit MerTK signaling in the tumor bed, you could trigger a more active immune system leading to a stronger T-cell killing response against the tumor," said Dr. Earp.

While utilizing the immune system in the fight against cancer has been a goal of researchers for decades, the last four years have seen the development and approval of several drugs – including the monoclonal antibodies Ipilimumab and Tremelimumab – that prolong the anti-tumor T-cell response, resulting in clinical benefit particularly in melanoma. In some patients, these therapies have shown the ability not only to destroy cancer cells, but also to prevent the relapses that plague chemotherapy and even newer targeted agents.

The UNC Lineberger team is collaborating with the UNC Chemical Biology and Drug Discovery Center to discover, develop and test oral drugs that inhibit MerTK activity: compounds are currently being tested in animal models.

"We hope to create a new, more MerTK selective tool with which to stimulate the initial tumor response and combine this strategy with the existing drugs that extend the immune response. If we can initiate a stronger response and sustain that activity we may be more effective in treating metastatic cancer," said Dr Earp. "Tumor cells can move throughout the body thwarting some of our best therapeutic interventions. The immune system is mobile and may be able to help eliminate tumor cells even at distant sites."

**More information:** MerTK inhibition in tumor leukocytes decreases tumor growth and metastasis, *J Clin Invest.* [doi:10.1172/JCI67655](https://doi.org/10.1172/JCI67655)

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