Study shows Meteorin-like protein drains energy from T cells, limiting immune system's power to fight cancer

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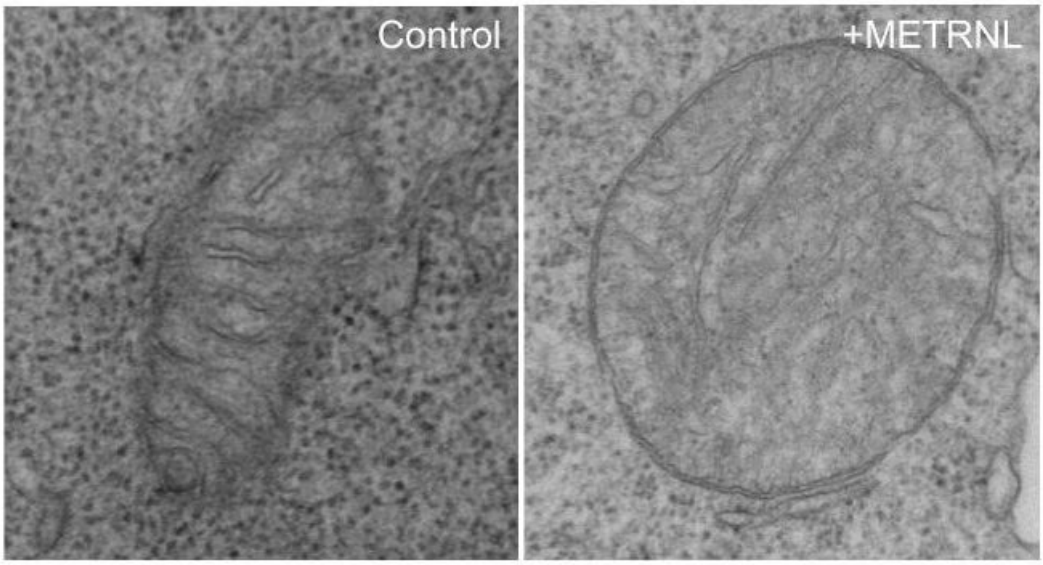

The image on the right shows an unhealthy mitochondrion in a T cell exposed to METRNL. Credit: Christopher Jackson, M.D.

A protein called Meteorin-like (METRNL) in the tumor microenvironment saps energy from T cells, thereby severely limiting their ability to fight cancer, according to new research directed by

investigators at the Johns Hopkins University School of Medicine and the Johns Hopkins Kimmel Cancer Center and its Bloomberg~Kimmel Institute for Cancer Immunotherapy.

Finding ways to block the effects of METRNL signaling on tumor-infiltrating T cells may allow these immune cells to regain the energy necessary to eliminate tumors.

A report about the work was published Aug. 6 in the journal *Immunity*.

METRNL has been described in the medical literature before—initially as playing a role in helping keep cold or exercising animals (and people) warm by poking holes in the mitochondria (energy factory) of fat cells so they produce heat. However, it had not previously been known to be active in cancer or in T cells, says lead study author Christopher Jackson, M.D., an assistant professor of neurosurgery at Johns Hopkins.

When T cells try to eliminate a tumor, the state of chronic stimulation/stress causes them to secrete METRNL, Jackson explains. Once METRNL is secreted, it interacts with the mitochondria and pokes holes in the electron transport chain, a cluster of proteins participating in a process to create energy.

When T cells can no longer keep up with their energy requirements, they stop trying to kill cancer cells, which enables cancer cells to multiply and spread.

"Others have shown that metabolic dysfunction limits T cells' ability to fight cancer, but we are among the first to describe a discrete signaling pathway that causes that to happen," Jackson says.

"Most of the previous work has looked at how the lack of specific nutrients in tumors limits a T cell's ability to function. The problem is

this is difficult to modify because it's hard to get the right nutrients into a tumor and direct them to T cells.

"We potentially can do much better by targeting a signaling pathway because we can block it or turn it on or off, but until now, nobody had identified such a pathway that restores the metabolic health of T cells in tumors."

In a series of laboratory investigations, researchers first studied T cells from the tumor tissue and blood of patients with previously untreated brain tumors (glioblastomas), prostate cancer, bladder cancer and renal cell/kidney cancer, and performed RNA sequencing to try to identify genes responsible for dysfunction in the tumor. METRNL was the gene most highly expressed.

Next, they wanted to find out what makes T cells secrete METRNL in the first place, discovering that the reason was chronic stimulation. Normally, the immune system activates when stimulated to fight an infection and then diminishes when that illness resolves. But in the setting of cancer, T cells are chronically stimulated, which causes them to become dysfunctional.

METRNL was also found to be secreted by other immune cells in tumors such as macrophages and dendritic cells, but it acts specifically on T cells.

Additional research determined that METRNL acts directly on the mitochondria, and decouples the electron transport chain. As T cells lose energy and start to fail, they increase their attempts to use glucose (natural sugar) as a backup source of energy.

But, because the tumor environment is low in glucose, they continue to flounder and eventually die. This is one of the ways that tumors can

continue to grow. Deleting METRNL in models of different cancer types in the researchers' investigations universally delayed tumor growth.

Finally, researchers observed that METRNL is activated through a family of transcription factors (proteins that control the rate of transcription of genetic information from DNA to RNA) called E2F, that it is dependent on signaling by a receptor called PPAR delta, and that modulating these factors downstream can block the effects of METRNL.

The next steps are to determine how this can help patients, Jackson says. He and his colleagues are actively working on different means to target the METRNL-E2F-PPAR delta pathway or to combine targeted treatment with other immunotherapies.

"We think that one of the reasons that some current immunotherapies fail is they require more energy from immune cells that already are functioning at decreased capacity," he says. "Blocking the pathway may allow these immunotherapies that maybe have not been effective in the past to be more effective because there will be enough fuel for the T cells to meet that increased demand."

More information: The cytokine Meteorin-like inhibits anti-tumor CD8+ T cell responses by disrupting mitochondrial function, *Immunity* (2024). DOI: 10.1016/j.immuni.2024.07.003.
www.cell.com/immunity/fulltext … 1074-7613(24)00352-2

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