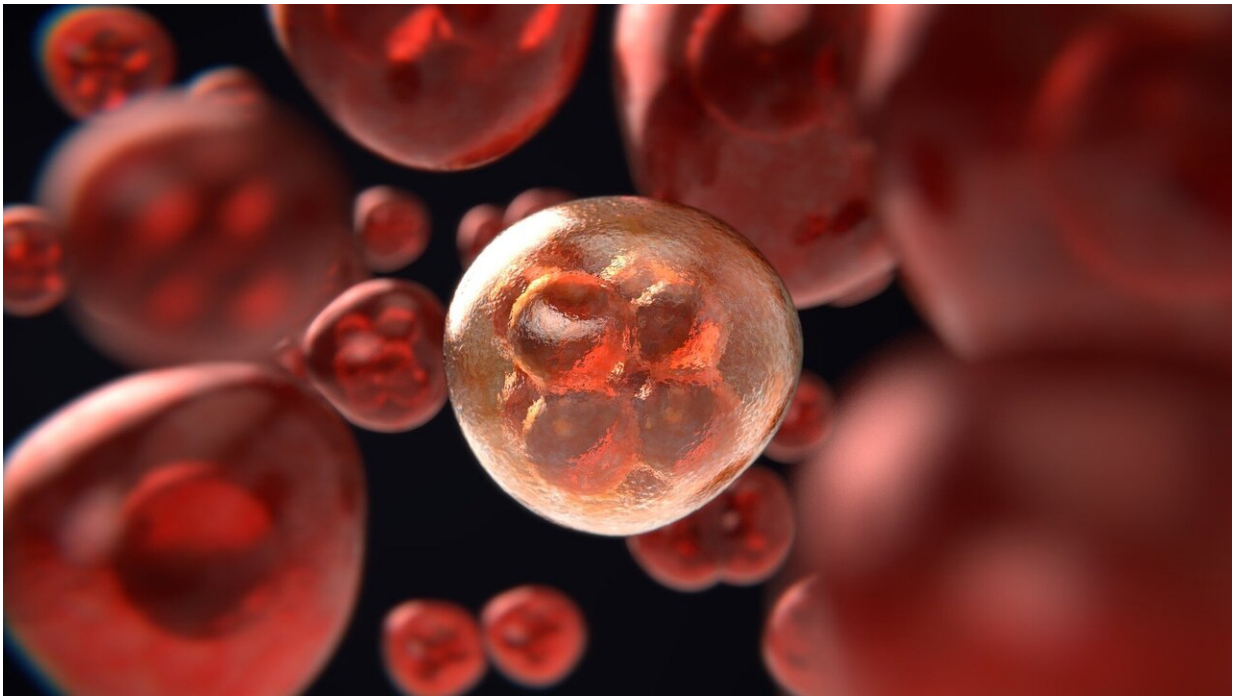
MedicalXpress

Scientists identify protein crucial to tumor cells' metabolism and immune evasion

February 14 2023, by Katie Marquedant



Credit: CC0 Public Domain

Tumor cells typically alter their energy metabolism and increase glucose uptake to support their rapid division and spread. This limits glucose availability for immune cells and therefore dampens the body's anti-cancer immune response.

By searching for proteins that both regulate the metabolism of cancer

cells and affect immune cells in tumors, a team led by investigators at Massachusetts General Hospital (MGH) recently identified a potential target for therapies that could simultaneously drain tumors of energy and boost the immune response against them.

For the research, which is published in *Cancer Discovery*, Keith T. Flaherty, MD, the director of Clinical Research at the MGH Cancer Center and a professor of medicine at Harvard Medical School, and his colleagues developed a new computational tool called BipotentR that can identify targets that block immune activation and also stimulate a second user-defined pathway (in this case, metabolism).

When applied to gene expression data from patients with cancer who were treated with immunotherapy, as well as from cell lines and animal models, the tool identified 38 cancer cell–specific immune-metabolic regulators.

Artificial intelligence techniques showed that the activity level of these regulators in tumors predicted patients' outcomes after receiving immunotherapy.

The topmost identified regulator, ESRRA (Estrogen Related Receptor Alpha), was activated in immunotherapy-resistant tumors of many types. Inhibiting ESRRA killed tumors by suppressing energy metabolism and activating two immune mechanisms involving different types of immune cells.

ESRRA inhibition was safe when tested in mice, and its effects on energy metabolism were focused on cancer cells.

The scientists also demonstrated that BipotentR can be applied to other survival mechanisms used by cancer cells, such as their ability to promote blood vessel formation to increase their blood supply.

Therefore, the BipotentR tool, available here, provides a resource for discovering single drugs that can act through one cancer-related pathway while simultaneously stimulating an immune response.

"These findings provide a simple biomarker to predict response/non-response to immunotherapy, and they support ERRA as a therapeutic target," says Flaherty.

Additional MGH co-authors include Phillip Munson, Dejan Juric, and David E. Fisher.

More information: Avinash Sahu et al, Discovery of Targets for Immune–Metabolic Antitumor Drugs Identifies Estrogen-Related Receptor Alpha, *Cancer Discovery* (2023). DOI: 10.1158/2159-8290.CD-22-0244

Provided by Massachusetts General Hospital