Predicting immunotherapy success via biomarkers

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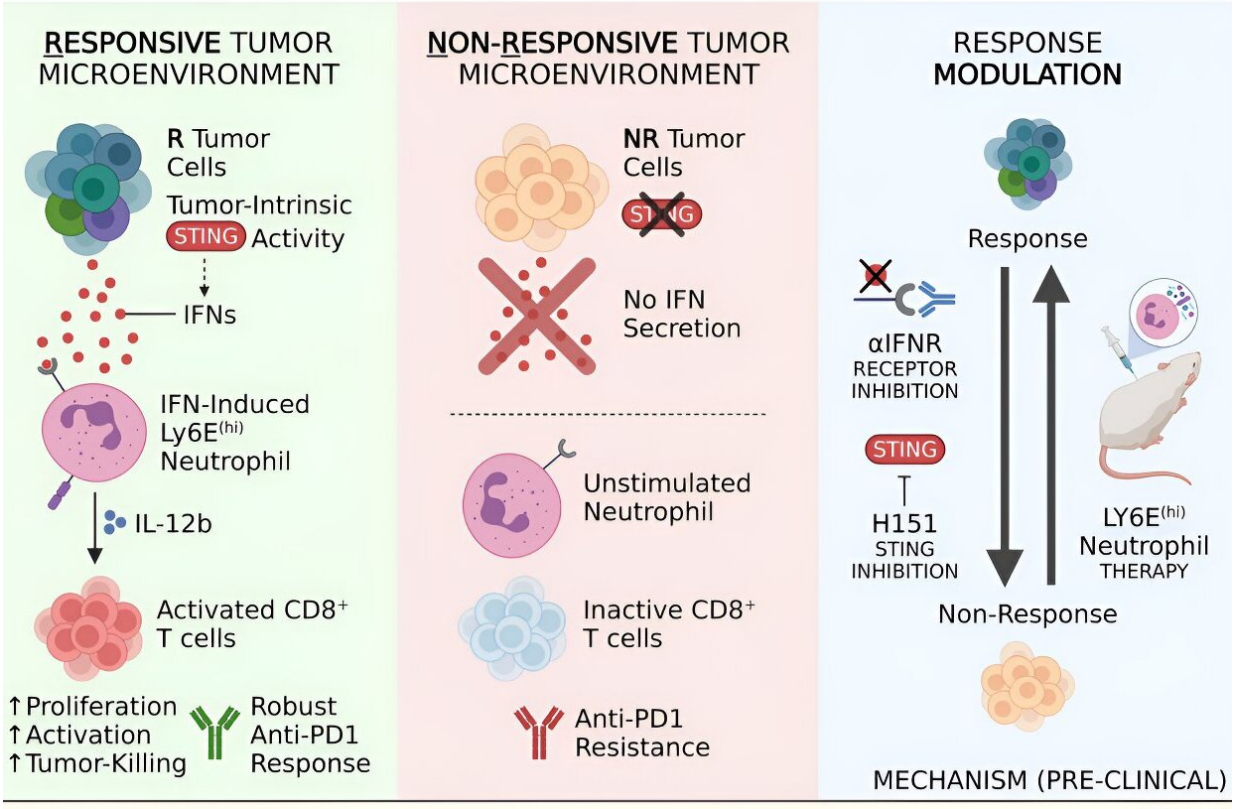

Graphical abstract. Credit: *Cancer Cell* (2024). DOI: 10.1016/j.ccell.2023.12.005

Researchers at the Technion's Ruth and Bruce Rappaport Faculty of Medicine and the Rappaport Family Institute for Research in the Medical Sciences have discovered a subset of blood cells that predict the

success of immunotherapy treatment. These findings are expected to streamline the process of matching an immunotherapy treatment to a specific patient, since it is very important to identify in advance those patients who will react to a given treatment.

The research published in *Cancer Cell* was led by doctoral student Madeleine Benguigui and post-doctoral fellow Dr. Tim J. Cooper, under the supervision of Professor Yuval Shaked of the Rappaport Faculty of Medicine. They contributed equally to the research and to the article. The translational research is based on RNA sequencing (scRNA-seq), analysis of existing data, pre-clinical models of cancer, and the corroboration of the findings in humans.

Immunotherapy, which is considered one of the most important breakthroughs in the treatment of cancer, is based on the understanding that the natural immune system excels at attacking cancer cells in a selective and precise manner.

The problem is that in many cases, the cancerous tumor tricks the immune system and prevents it from identifying the cells as enemies. Immunotherapy is based on the concept that instead of attacking cancer with chemotherapy drugs that also harm healthy tissue, it is preferable to boost the immune system with the goal of identifying cancer cells as enemies and letting it do the rest of the work on its own.

Despite the remarkable success of the immunotherapy approach for treating cancer, its effectiveness is still limited to around 40% of all patients. This means that many patients receive this harsh treatment without positive results. Consequently, it is crucial to attain a deep understanding of biological reactions to these treatments and to identify biomarkers that can predict the treatment's future success.

Biomarkers are an important component of personalized medicine,

which helps physicians make educated medical decisions and formulate optimal treatment protocols adapted to the specific patient and their medical profile.

Biomarkers are already being used for immunotherapy treatments, but they are obtained through biopsies—an invasive procedure that can endanger the patient. Moreover, this approach fails to sufficiently take into account the specific patient's immune profile, and its predictive capability is limited. For this reason, a great deal of research in this field—both in industry and in academia—strives to find new ways to predict which patients will respond to immunotherapy treatments.

The Technion researchers who focused on antibody-based immunotherapy discovered biomarkers that predict a specific patient's response to the treatment. Since these biomarkers are in the bloodstream, they don't require taking biopsies from the tumor—an invasive procedure that is not always feasible, and as mentioned, can sometimes endanger the patient.

In brief, the researchers discovered that a protein called STING, which activates the immune system, is triggered by cancerous growths and is especially pronounced in cancer cells that will respond to immunotherapy treatment. This protein is manifested in interferon protein, which in turn stimulates neutrophils to be differentiated into a specific type (which expresses the protein Ly6Ehi).

These neutrophils act directly on the immune system and stimulate it to target the cancerous tumor. Indeed, the researchers discovered that these neutrophils may help the actual treatment, as their presence in the tumor prompts greater sensitivity to immunotherapy treatment.

The team inferred that testing the levels of Ly6Ehi neutrophils in the patient's blood could serve as an efficient biomarker for predicting the

response to immunotherapy treatment. The researchers tested these findings, which were based on pre-clinical studies, on patients with lung cancer and melanoma.

These findings are consistent with the analysis of existing data on 1,237 cancer patients who underwent antibody-based immunotherapy treatments. Therefore, they demonstrated the neutrophils' ability to predict, with a high degree of precision, response to immunotherapy in humans.

The technology developed by Prof. Yuval Shaked's research group has been registered as a patent, and it is currently in the midst of a tech transfer process with the company OncoHost in order to continue its development. Prof. Shaked points out that the technology can be used with the ubiquitous flow cytometry device, which can be found in almost every hospital and is approved by regulatory agencies.

More information: Madeleine Benguigui et al, Interferon-stimulated neutrophils as a predictor of immunotherapy response, *Cancer Cell* (2024). DOI: 10.1016/j.ccell.2023.12.005

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