Researchers discover new therapeutic target for non-small cell lung cancer

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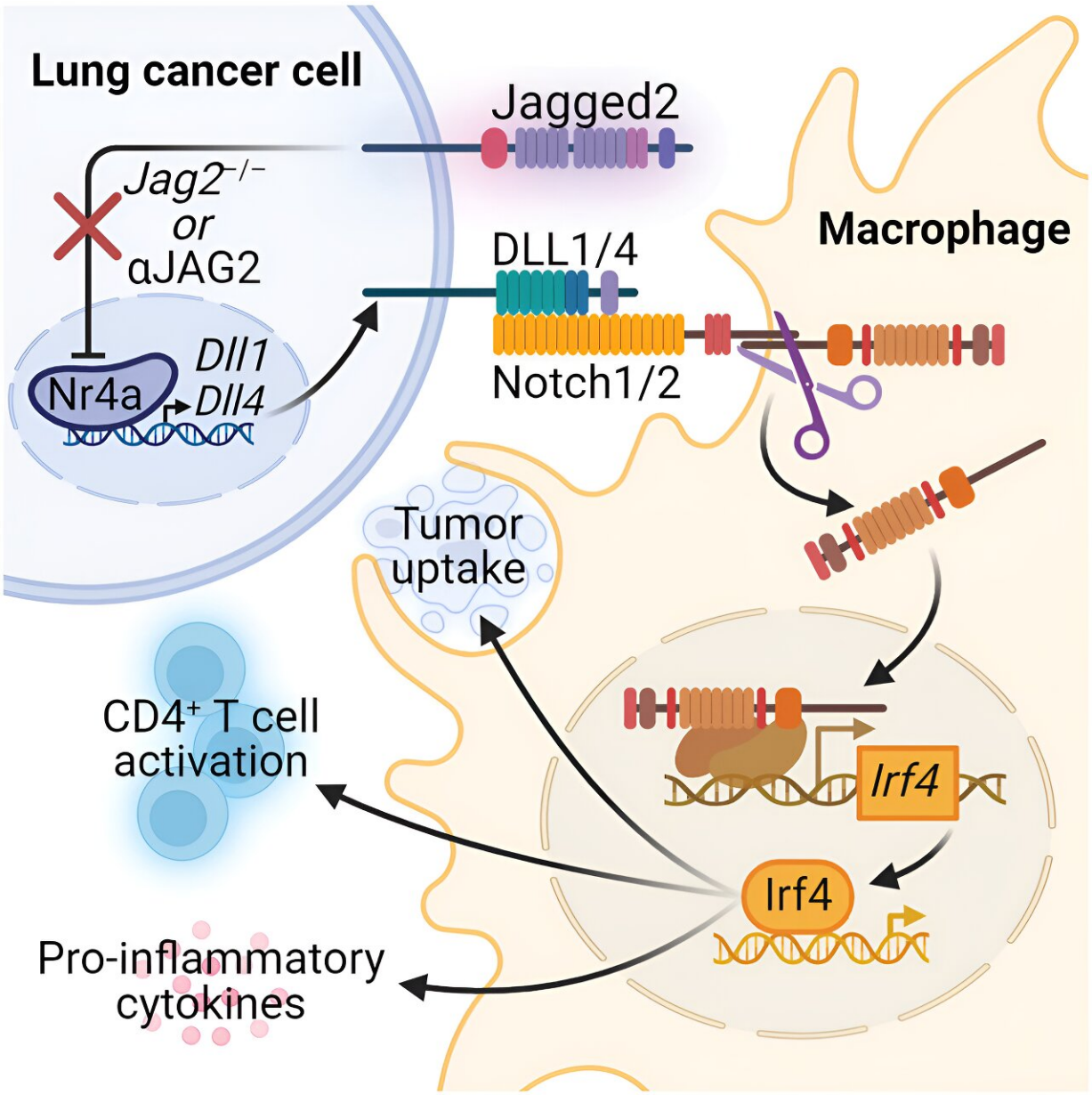

Graphical abstract. Credit: *Immunity* (2024). DOI: 10.1016/j.immuni.2024.03.020

Non-small cell lung cancer accounts for nearly 85% of all lung cancer cases. Targeted immunotherapy is a common treatment, but it does not work for everyone. However, a new Moffitt Cancer Center study

published in the journal *Immunity* offers insight into how lung cancer cells evade the protective immune system, potentially opening a door for novel antibody-based immunotherapies.

Their study centers on a molecule called Jagged2, which plays a primary role in fueling the aggressiveness and immune evasion capacity of lung cancer. Jagged2 elimination in lung tumors promotes the expansion of subgroups of immune cells called macrophages, with the ability to recognize the cancer cells and activate protective immune responses. This explains why tumors with higher levels of Jagged2 were associated with poorer outcomes and reduced immunity.

A research team led by Moffitt immunologist Paulo Rodriguez, Ph.D., found that removing Jagged2 from lung cancer cells or using antibodies recognizing Jagged2 led to slower tumor growth and increased protective immune cell activity mediated by macrophages.

"When we eliminated Jagged2, the lung cancer cells started expressing more of the molecules called DLL1 and DLL4. Unlike Jagged2, these molecules send an entirely different message to macrophages, telling them to fight back against the tumor cells," said Rodriguez, chair of the Department of Immunology.

He added that a key player in this reprogramming process is a molecule called IRF4. Blocking Jagged2 triggers macrophages to receive signals from the molecules DLL1 and DLL4 that, in turn, activate the Notch signaling pathway and drive IRF4; then, these macrophages target and eliminate cancer cells.

"This discovery could be a new opportunity for lung cancer treatment," Rodriguez said. "By dismantling the cancer's stealth mode and

empowering the immune system, we may be on the verge of a new era of effective and long-lasting therapies."

The research team is exploring the most effective methods to target Jagged2 in the clinical setting and in combination with immunotherapies.

More information: Jay K. Mandula et al, Jagged2 targeting in lung cancer activates anti-tumor immunity via Notch-induced functional reprogramming of tumor-associated macrophages, *Immunity* (2024). DOI: 10.1016/j.immuni.2024.03.020

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