Medical Xpress

Researchers reveal key LAG3 mechanisms that could enhance cancer immunotherapy

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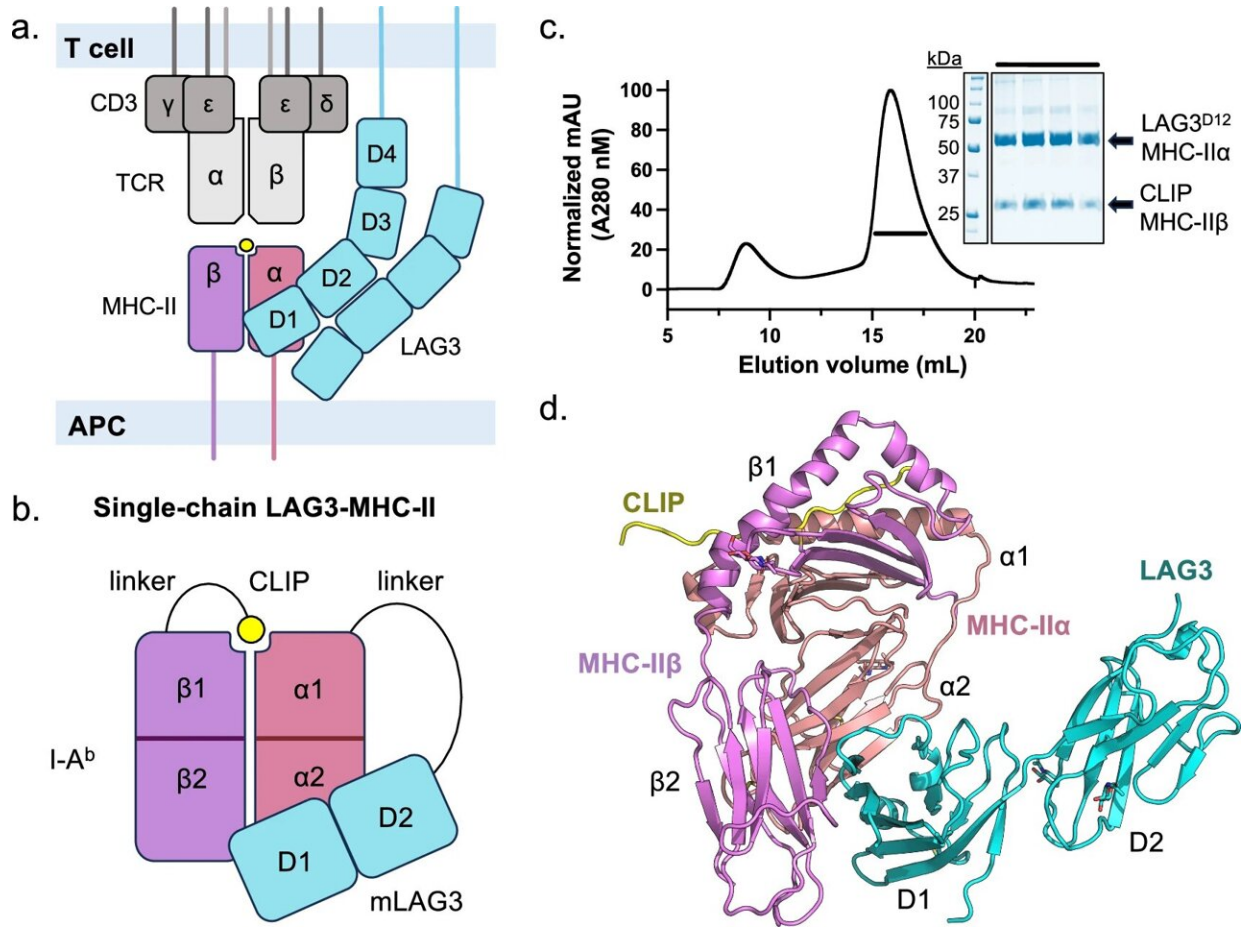

Structure of LAG3 bound to MHC class II. **a** Cartoon depicting LAG3 (cyan) in the context of an MHC-II (violet/pink) bound to the TCR-CD3 complex (grey). D1 of LAG3 binds to MHC-II, and D2 mediates LAG3 dimerization. **b** Schematic of the scLAG3-MHC-II construct used for structure determination. **c** A size-exclusion chromatogram from purification of scLAG3-MHC-II indicates that the construct elutes as a monodisperse peak. The inset SDS-PAGE gel shows

the purified LAG3^{D12}-MHC-IIα and CLIP-MHC-II β single-chain fusion proteins. This data is representative from one of at least three independent scLAG3-MHC-II purifications. Source data are provided as a Source Data file. **d** Crystal structure of the scLAG3-MHC-II construct consisting of the LAG3 D1 and D2 domains (teal) bound to I-A^{b} (violet/salmon) loaded with CLIP (yellow). Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-51930-5

Immune checkpoint inhibitors are a type of cancer treatment that helps the immune system attack cancer cells more effectively. One of the key proteins involved in this process is lymphocyte activation gene-3 (LAG3), which suppresses the antitumor immune response. Moffitt Cancer Center researchers have made an important discovery about LAG3, revealing how it interacts with other proteins to control immune activity. Their study, published in *Nature Communications*, could lead to better cancer treatments by enhancing the effectiveness of immune checkpoint inhibitors.

Led by Vince Luca, Ph.D., the Moffitt study provides a detailed blueprint of how LAG3 interacts with a molecule known as MHC class II. These interactions are critical because they help the immune system differentiate between healthy cells and cancer cells. By blocking LAG3, immune checkpoint inhibitors can allow the immune system to target and destroy cancer cells. Key findings include:

- Visualization of a LAG3 interaction network: The study reveals a detailed network of interactions between MHC class II and LAG3, uncovering multiple novel drug targets and signaling mechanisms. This comprehensive "molecular blueprint" provides a deeper understanding of how LAG3 modulates immune responses and its potential impact on therapeutic interventions.

- Mechanistic insights: The research sheds light on how LAG3 influences T cell activation and immune tolerance. These insights are crucial for designing targeted therapies that can control LAG3 activity with greater precision.

- Therapeutic implications: By revealing specific interactions between LAG3 and other immune regulators, the study opens new avenues for developing inhibitors and activators. These new molecules could enhance the effectiveness of existing immunotherapies and offer new treatment options for patients with cancer and autoimmune disorders.

"This study represents a significant breakthrough in our understanding of LAG3," said Luca, associate member of the Immunology Department. "The detailed molecular structure and mechanistic insights we've uncovered will help guide the development of next-generation immunotherapies. We're excited to translate these discoveries into innovative therapies that could transform patient care."

More information: Qianqian Ming et al, Structural basis for mouse LAG3 interactions with the MHC class II molecule I-Ab, *Nature Communications* (2024). DOI: 10.1038/s41467-024-51930-5

Provided by H. Lee Moffitt Cancer Center & Research Institute