# Study uncovers drug target in a protein complex required for activation of NF-κB

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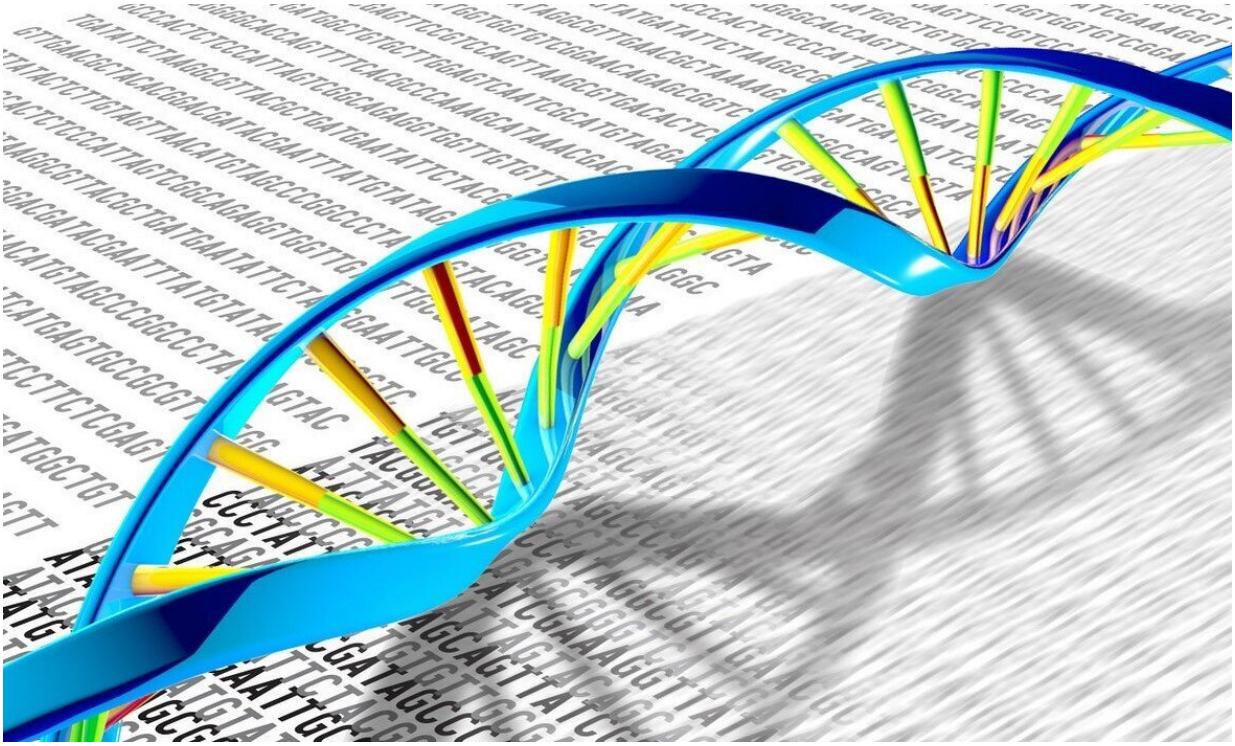

DNA, which has a double-helix structure, can have many genetic mutations and variations. Credit: NIH

A new paper by Dana-Farber Cancer Institute scientists lays the foundation for targeted therapies to inhibit the activation of nuclear factor kappa B (NF-κB), a transcription factor that plays a role in various autoimmune and inflammatory diseases and cancers.

The study tracks the mechanism of NF-κB activation to identify a key point of vulnerability. NF-κB is activated by circulating lipopolysaccharides (LPS) that bind to the cell surface receptor TLR4. Using CRISPR/Cas9, researchers showed that this LPS receptor TLR4 depends on OST-A—an oligosaccharyltransferase complex—to function properly. OST complexes can be inhibited with a compound called NGI-1, but the molecular mechanism of its action has been unclear.

By performing a CRISPR screen and cryo-electron microscopy studies, researchers found that NGI-1 binds to OST-A at the complex's catalytic subunit, STT3A. There, NGI-1 traps the complex in an inactive state, preventing TLR4 from getting to the cell surface. This, in turn, prevents the activation of NF-κB.

The development of agents capable of inhibiting STT3A represents a promising strategy for blocking the activation of NF-κB in response to LPS. The involvement of NF-κB in a range of autoimmune conditions, inflammatory diseases, and cancers suggests that this approach could have broad utility.

The findings are published in the journal *Cell*.

**More information:** Benjamin L. Lampson et al, Positive selection CRISPR screens reveal a druggable pocket in an oligosaccharyltransferase required for inflammatory signaling to NF-κB, *Cell* (2024). DOI: 10.1016/j.cell.2024.03.022

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